9 November 2023
EMA/539700/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mounjaro

International non-proprietary name: Tirzepatide

Procedure No. EMEA/H/C/005620//II/0007

Note

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

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List of abbreviations

Term	Definition
ABPM	ambulatory blood pressure monitoring
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AOM	anti-obesity medication
AS	analysis set
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BMI	body mass index
BP	blood pressure
Cmax	maximum observed drug plasma concentration
CI	confidence interval
CL/F	apparent total body clearance of drug calculated after extravascular administration
Cmax	maximum observed drug concentration
COVID-19	coronavirus disease 2019
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
Css	steady-state concentration
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
CWM	chronic weight management
EAS	efficacy analysis set
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FSG	fasting serum glucose
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide

Term	Definition
GIPR	glucose-dependent insulinotropic polypeptide receptor
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin A1c
HDL	high-density lipoprotein
HR	heart rate
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
ITT	intent to treat
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite-Clinical trials
LSM	least squares mean
MACE	major adverse cardiovascular event
MACE-4	composite endpoint comprised of death from CV or undetermined causes, myocardial infarction, stroke, and hospitalization for unstable angina
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMO	morbidity and mortality in adults with obesity
MMRM	mixed model for repeated measures
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
Nab	neutralizing antibody
OC	oral contraceptive
PD	pharmacodynamic(s)
PGIS	Patient Global Impression of Status for physical activity
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	preferred term
QW	once weekly
SAE	serious adverse event
SF-36v2	Short-Form 36, Version 2
SMQ	Standardised MedDRA Query

Term	Definition
SOC	system organ class
SURMOUNT-1	Study I8F-MC-GPHK
SURMOUNT-2	Study I8F-MC-GPHL
SURMOUNT-3	Study I8F-MC-GPHM
SURMOUNT-4	Study I8F-MC-GPHN
SURPASS-1	Study I8F-MC-GPGK
SURPASS-2	Study I8F-MC-GPGL
SURPASS-3	Study I8F-MC-GPGH
SURPASS-4	Study I8F-MC-GPGM
SURPASS-5	Study I8F-MC-GPGI
SURPASS-AP-Combo	Study I8F-MC-GPHO
SURPASS J-mono	Study I8F-MC-GPGO
SURPASS J-combo	Study I8F-MC-GPGP
T2DM	type 2 diabetes mellitus
TE	treatment-emergent
TEAE	treatment-emergent adverse event
tmax	time to maximum observed drug concentration
TZP	tirzepatide
TZP_ALL	all tirzepatide doses are pooled
UACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal
X-ray	energetic high-frequency electromagnetic radiation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 8 March 2023 an application for a variation.

The following variation was requested:

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

Extension of indication to include chronic weight management, including weight loss and weight maintenance, for MOUNJARO, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial body mass index (BMI) of ≥ 30 kg/m2 (obesity), or ≥ 27 kg/m2 to < 30 kg/m2 (overweight) in the presence of at least one weight-related comorbid condition, based on a global, pivotal phase 3 study I8F-MC-GPHK (SURMOUNT-1) and five supportive phase 3 studies (SURPASS-1 to -5) in participants with T2DM and BMI ≥ 27 kg/m2. SURMOUNT-1 is a phase 3, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of tirzepatide once weekly in participants without type 2 diabetes who have obesity or are overweight with weight related comorbidities. As a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0033/2023 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0033/2023 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

Not applicable.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	8 March 2023
Start of procedure:	25 March 2023
CHMP Rapporteur Assessment Report	19 May 2023
PRAC Rapporteur Assessment Report	24 May 2023
CHMP Co-Rapporteur Assessment	31 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	15 June 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	29 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur Assessment Report	7 September 2023
Request for supplementary information (2nd RSI)	14 September 2023
CHMP Rapporteur Assessment Report	26 October 2023
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	9 November 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Obesity is defined as abnormal or excessive fat accumulation that impairs health (WHO 2021). It is a chronic progressive disease caused by disruptions in the normal mechanisms that control energy balance.

In 2016, the World Health Organization reported that more than 1.9 billion adults aged 18 years and older (39% of adult population) were living with obesity or overweight based on BMI criteria. Of these, over 650 million adults had obesity (WHO 2021).

Obesity is a risk factor for long-term health consequences, many of which represent the top causes of mortality globally (WHO 2020). More than 200 health complications have been associated with obesity, including cardiometabolic, inflammatory, degenerative, mechano-physical, neoplastic, and psychological conditions (Wilding and Jacob 2021). Obesity significantly impacts patients' daily activities and quality of life (Poon et al. 2022). Obesity is also associated with depression, anxiety, and increased suicidality (Luppino et al. 2010; Dutton et al. 2013; Wagner et al. 2013). Recently, studies indicated that individuals with obesity were more likely to be hospitalized, require mechanical ventilation, and die from COVID-19 than those without obesity (Foo et al. 2021; Gao et al. 2021; Smati et al. 2021).

In 2015, excess body weight accounted for approximately 4 million deaths and 120 million disability-adjusted life years worldwide (GBD 2015 Obesity Collaborators 2017). Secondary to the emergence of multisystem comorbid disease, obesity shortens life expectancy, with Class 3 obesity decreasing life expectancy by up to 20 years (OECD 2019; Müller et al. 2022).

State the claimed the therapeutic indication

Tirzepatide is approved as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. The present application is for the use of tirzepatide for chronic weight management (CWM). The following indication is proposed to be added to section 4.1 of the SmPC:

"Weight management

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

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

Management

Patients with obesity or overweight often do not achieve sustainable weight loss with lifestyle therapies alone. Lifestyle-based treatment achieves a 10% weight reduction at 1 year in only some individuals (Wing and Hill 2001), and among those that do maintain at 1 year, most regain the weight over longer periods of time (Knowler et al. 2009). In addition, weight reduction beyond that achieved with lifestyle alone is often needed for the resolution of obesity-related comorbidities and reduction of CV mortality (Wing et al. 2011). Bariatric surgery is an effective option for substantial and durable weight reduction in select people with obesity. However, the risk of perioperative and postoperative complications, limited access, and apprehension regarding the invasive and permanent nature of the procedure, results in less than 1% of the eligible population (based on BMI) receiving bariatric surgery as a treatment for obesity (ASMBS 2021). Some anti-obesity drugs are available, with the recently approved GLP-1 receptor agonists being the most efficacious. Tirzepatide addresses an unmet medical need as the effect size of weight reduction exceeds the one achieved with GLP-1 receptor agonists.

2.1.2. About the product

Tirzepatide consists of 39 amino acids, and is engineered from the native glucose-dependent insulinotropic polypeptide (GIP) sequence, modified to bind to both GIP and glucagon-like peptide-1 (GLP-1) receptors. The structure of tirzepatide includes a C20 fatty diacid moiety and its molecular weight is 4.8 kDa. Tirzepatide has a mean half-life of approximately 5 days, which enables once-weekly dosing.

Mode of action of tirzepatide: in preclinical studies, tirzepatide showed equal affinity for the GIP receptors compared with native GIP but bound with the GLP-1 receptors with approximately 5-fold weaker affinity than native GLP-1. Based on the known physiology and pharmacology of GIP and GLP-1 as well as the results from preclinical studies, the dual signaling triggered by tirzepatide is expected to result in a greater body weight reduction and improved control of carbohydrate and lipid metabolism, beyond that observed with selective GLP-1 receptor agonists alone.

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

The following studies provide primary evidence for this application:

-SURMOUNT-1 study in participants with overweight or obesity, and without diabetes mellitus, and – subgroup analyses of the SURPASS-1, -2, -3, -4, and -5 studies in participants with overweight or obesity, and with T2DM. SURPASS subgroup analyses supporting this application are in participants with body mass index of 27 kg/m^2 or higher.

Additionally, supportive data from the 36-week open-label tirzepatide lead-in treatment period of the SURMOUNT-4 study are summarized. SURMOUNT-4 is an ongoing global Phase 3 study in participants with overweight or obesity but without T2DM.

No specific SA had been requested for the CWM indication. The development for CWM was generally well in line with the recommendations in Guideline EMA/CHMP/ 311805/2014.

Paediatric development

With the "Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral and a waiver EMA/PDCO/781854/2022, 16th Dec 2022" the PDCO granted a waiver for children from birth to less than 6 years. A PIP for CWM in children from 6 years to 18 years was agreed upon.

2.1.4. General comments on compliance with GCP

GCP compliance had been confirmed by the Applicant. During assessment no issue of GCP non-compliance arose.

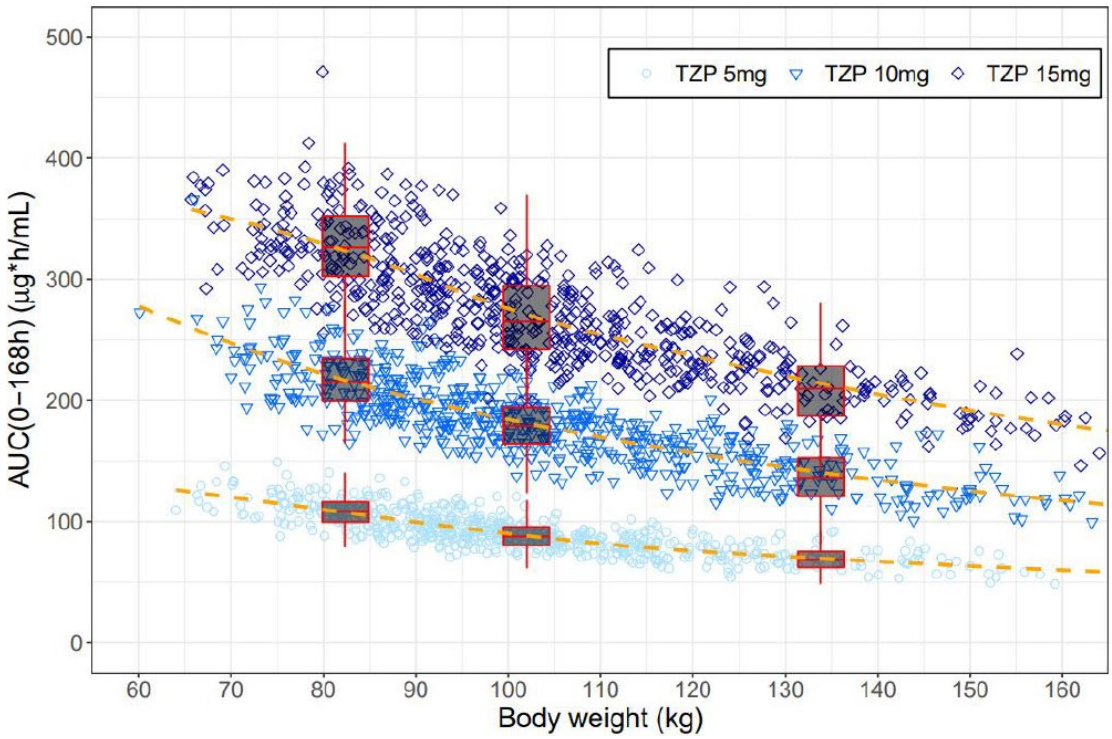
2.2. Non-clinical aspects

2.2.1. Toxicology

The applicant did not perform new toxicology studies in support of this extension of indication but re-calculated the exposure margins for the existing studies (i.e. the studies performed in support of the diabetes indication), which is acceptable. In the newly submitted clinical study in non-diabetic obese

subjects (Study SURMOUNT-1) the exposure was slightly higher than in the diabetes programme (SURPASS studies). In the SURPASS programme, the mean expose, expressed as AUC(0-τ), τ=168h, was 250000 ng•hr/mL (=250 µg•hr/mL). In SURMOUNT-1, it was 266000 ng•hr/mL (=266 µg•hr/mL). The following figure shows the dependency of the exposure from body weight. Exposure was markedly lower (around 170 µg•hr/mL) in subjects with the highest body weight (around 180 kg) than in subjects with low body weight (around 370 µg•hr/mL at 65 kg; values for the 15 mg dose).

Figure 1. 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).

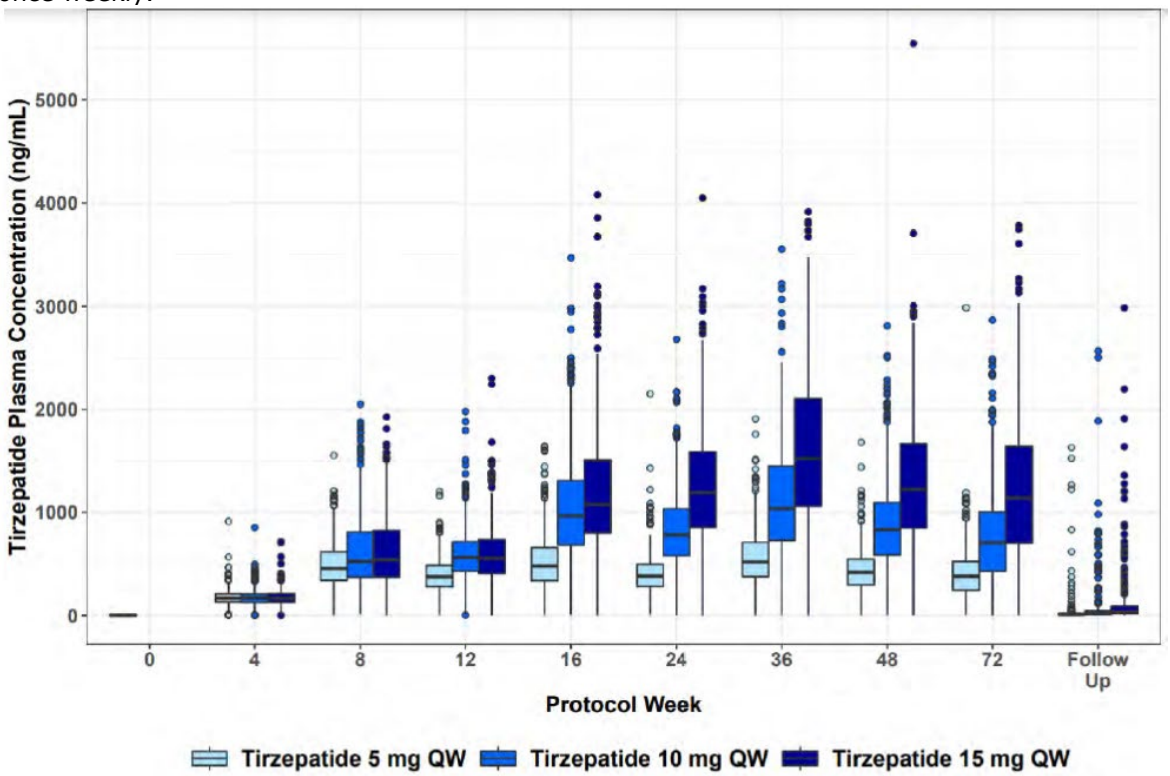
There is some inconsistency in exposure between the SURMOUNT-1 study (non-diabetic obese subjects) and the SURPASS programme (diabetic subjects) as shown in the table below. Within the SURPASS programme, exposure (given as mean steady-state concentration (Css) here) was inversely correlated with baseline body weight at all doses tested, i.e. higher body weight led to lower exposure (**bold** numbers in the table) as expected. In contrast, in SURMOUNT-1 exposure was higher (<u>underlined</u> numbers) than in the diabetic patients of SURPASS despite a markedly higher mean baseline body weight in SURMOUNT-1 (105 kg in SURMOUNT vs. 90 kg in SURPASS [T2DM subjects]).

Table 1. Summary of Tirzepatide Population Pharmacokinetic Post hoc Parameters in Participants with or without T2DM

	Geometric Mean (CV%)			
PK Parameter	**Non-T2DM in T2DM Program[a] (n=307)**	**T2DM in T2DM Program (n=5495)**	**T2DM with BMI ≥27 kg/m² subpopulation in SURPASS[b] (n=1422)**	**Non-T2DM CWM 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/hr)	0.0378 (23.7)	0.0366 (9.51)	0.0374 (10.4)	0.0319 (4.83)
Apparent clearance (CL/F, L/hr)	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 ($t_{1/2}$, 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)

Due to the desired action of tirzepatide, the patients markedly lost weight during the study so that the body weight at study start may not be relevant for the comparison of the steady-state plasma levels across the studies. Due to the weight loss during the studies and due to the fact that tirzepatide exposure decreases with increasing body weight and vice versa, it is expected that the weight loss during the studies leads to an increase in mean tirzepatide plasma levels. However, this was not the case in SURMOUNT-1 as shown in the figure below. The highest exposure was observed at Week 36 (note that the dose was up-titrated up to Week 20, explaining increasing exposure in this period). Thereafter, plasma levels declined again. Dosing was terminated at Week 72.

Figure 2. Tirzepatide plasma concentrations following administration of tirzepatide 5, 10, or 15 mg once weekly.



Dose escalation was allowed in the studies if there were problems with tolerability. Nevertheless, the patient remained in the dose group to which he or she was originally assigned.

Based on the mean exposure of AUC(0-τ) = 266000 ng•hr/mL (266 µg•hr/mL) in obese subjects without diabetes, i.e. the SURMOUNT-1 population, the applicant re-calculated the exposure margins for each dose group of each toxicology study of the diabetes programme of tirzepatide. Since the exposure in non-diabetic subjects was 6.4% higher than in diabetic subjects (266 vs. 250 µg•hr/mL), the exposure multiples decreased accordingly. The results are presented in the table below. For comparison, the exposure multiples originally calculated for the diabetes programme are also provided (in grey).

Table 2. Exposure Multiples for Subcutaneous Administration of Tirzepatide in Pivotal Toxicology Studies

Species **Dose**	**$AUC_{0-\tau}$, steady-state (ng•hr/mL)**	**Exposure Multiple Diabetes**	**Exposure Multiple Obesity**
Human			
15 mg/week	266000a		–
Repeat-Dose Toxicology			
4-Week 001178-WT Mouse (Study 8376621)[b,c]			
1 mg/kg/twice weekly	171500	1.20	1.13
3 mg/kg/twice weekly	493000	3.45	3.24
30 mg/kg/twice weeklyd	5165000	36.16	34.0
1-Month Rat (Study 8325822)[b,e]			
0.15 mg/kg/twice weekly	14050	0.10	0.09
0.5 mg/kg/twice weekly	45450	0.32	0.30
1.5 mg/kg/twice weeklyd	133500	0.93	0.88

6-Month Rat (Study 8337876)[b,f]			
0.5 mg/kg/twice weekly	53950	0.38	0.35
1.5 mg/kg/twice weekly	142000	0.99	0.93
3 mg/kg/twice weeklyd	279500	1.96	1.84
1-Month Monkey (Study 8325823)[g,h]			
0.05 mg/kg/weekly	33300	0.13	0.13
0.15 mg/kg/weekly	114500	0.46	0.43
0.5 mg/kg/weeklyd	424000	1.70	1.59
6-Month Monkey (Study 8336517)[g,i]			
0.05 mg/kg/weekly	34050	0.14	0.13
0.15 mg/kg/weekly	111500	0.45	0.42
0.5 mg/kg/weeklyd	336500	1.35	1.27
Carcinogenicity			
26-Week Transgenic Mouse (Study 8392063)[b,j]			
1 mg/kg/twice weekly	168000	1.18	1.11
3 mg/kg/twice weekly	490000	3.43	3.22
10 mg/kg/twice weeklyk	1520000	10.64	10.0
104-Week Rat (Study 8392734)[b,l,m]			
0.15 mg/kg/twice weekly	17600	0.12	0.12
0.5 mg/kg/twice weekly	51200	0.36	0.34
1.5 mg/kg/twice weekly	145000	1.02	0.95
Reproductive and Developmental Toxicology			
Rat Male Fertility (Study 00353430)[b,n]			
0.5 mg/kg/twice weeklyo	43400	0.30	0.29
1.5 mg/kg/twice weekly	147000	1.03	0.97
3 mg/kg/twice weekly	245000	1.72	1.61
Rat Female Fertility (Study WIL-353356)[b,p,q]			
0.5 mg/kg/twice weekly	41900	0.29	0.28
1.5 mg/kg/twice weekly	129000	0.90	0.85
3 mg/kg/twice weekly	269000	1.88	1.77
Rat Embryo/Fetal Development (Study WIL-353354)[r,s]			
0.02 mg/kg/every 3 days	821	0.03	0.02
0.1 mg/kg/every 3 dayst	4010	0.07	0.06
0.5 mg/kg/every 3 days	35800	0.45	0.42
Rabbit Embryo/Fetal Development (Study WIL-353355)[u]			
0.01 mg/kg/weekly	3560	0.01	0.01
0.03 mg/kg/weekly[t]	14700	0.06	0.06
0.1 mg/kg/weekly	56400	0.23	0.21

Abbreviations: AUC0-τ = area under the plasma concentration-time curve from time zero to tau (dosing interval); EM = exposure multiple; GD = gestation day; LD = lactation day; NOEL = no-observed-effect level; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetic(s).

a Dose shown is the highest clinical dose. Plasma PK parameters shown were based on the PK model developed with data from participants with obesity or overweight in SURMOUNT-1. Mean baseline body weight = 105 kg.
b EM is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 96 hours in mice and rats and 168 hours in humans. Therefore, EM in mouse and rat = (rodent AUC/96)/(human AUC/168). Steady state AUC0-τ values are the average of male and female values when studies include both male and female rodents.
c Plasma AUC determined on Day 26.
d NOAEL for target organ toxicity.
e Plasma AUC determined on Day 29.
f Plasma AUC determined on Day 176.
g EM is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 168 hours in monkeys and humans. Therefore, EM in monkey = (monkey AUC/168)/(human AUC/168). Monkey steady state AUC0-τ values are the average of male and female values.
h Plasma AUC determined on Day 29.
i Plasma AUC determined on Day 176.

j Plasma AUC determined on Day 358.
k NOEL for neoplasia.
l Plasma AUC determined on Day 358.
m A NOEL was not determined for thyroid C-cell neoplasia, but the high dose (1.5 mg/kg/twice weekly) was the NOEL for all other neoplasias.
n Plasma AUC determined on Day 28.
o NOAEL for reproductive toxicity.
p Plasma AUC determined on GD 6.
q NOAEL for reproductive toxicity not determined.
r EM is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 21 (0.02 mg/kg), 40 (0.1 mg/kg), or 54 (0.5 mg/kg) hours in maternal rats and 168 hours in humans.
s Plasma AUC determined on GD 17.
t NOAEL for developmental toxicity.
u EM is calculated as (AUC0-τ/τ in animals)/(AUC0-τ/τ in humans). τ is 168 hours in rabbits and humans. Therefore, EM in rabbits = (rabbit AUC/168)/(human AUC/168). Plasma AUC determined on GD 14.

Other toxicity studies

Study on Impurities

Qualification Study 8485844

The purpose of this study was to qualify impurities (D-Ser32/C-terminal, Gln19, and Gln24 deamidation) in the test article, tirzepatide, when administered twice weekly (5 total doses) by SC injection to rats for at least 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).

Lot A had a purity (in respect to tirzepatide) of 96.3%, and Lot B of 90.2%. Thus, Lot B contained more impurities.

Rats were dosed by SC injection at a volume of 1.5 mL/kg on Days 1, 5, 8, 12, and 15 of the dosing phase.

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

Noteworthy findings are presented below.

Mortality

All rats survived to their scheduled sacrifice.

Body weight and food consumption

Tirzepatide (LY3298176) markedly reduce food consumption and body weight gain as expected from its pharmacodynamic action. Reduction in food consumption and – consecutive – body weight gain was in general slightly more pronounced with Lot B, i.e. the lot that contained a higher amount of impurities, see table below.

Table 3. Mean Body Weights and Food Consumption

Sex	**Male**			**Female**		
Dose (mg LY3298176/kg)	**0**	**3 (Lot A)**	**3 (Lot B)**	**0**	**3 (Lot A)**	**3 (Lot B)**
Mean Body Weight (g or % difference from control)						

Day 1	389	-1	4	229	1	0
Day 5	409	-16*	-14*	235	-14*	-16*
Day 8	420	-18*	-19*	239	-16*	-18*
Day 12	438	-14*	-16*	244	-8*	-12*
Day 15	446	-17*	-19*	248	-13*	-16*
Day 18	457	-16*	-19*	254	-13*	-16*
Mean Food Consumption (g/animal/day or % difference from control)						
Day 1 to 5	29	-68*	-75*	18	-69*	-66*
Day 5 to 8	28	-45*	-59*	17	-45*	-56*
Day 8 to 12	30	-27*	-51*	19	-34*	-41*
Day 12 to 15	28	-49*	-72*	18	-59*	-67*
Day 15 to 18	29	-32*	-50*	18	-43*	-43*

* = p ≤ 0.05

Organ weights

Lot A and Lot B differently affected thyroid (plus parathyroid) weight. This effect was statistically significant when regarding the ratio thyroid/body weight in males. Numerical differences, albeit not statistically significant, were also observed in females and for all parameters (absolute weight, weight relative to body and relative to brain), see table below.

Table 4. LY3298176-Related Effects in Organ Weight Parameters

Sex	**Males**			**Females**		
Dose Level (mg LY3298176/kg)	**0**	**3 (Lot A)**	**3 (Lot B)**	**0**	**3 (Lot A)**	**3 (Lot B)**
Thyroid/Parathyroid						
Absolute Weight (g)	0.0157	128	114	0.0170	102	84
Body Weight Ratio (%)	0.0038	155*	142*	0.0075	122	107
Brain Weight Ratio (%)	0.7147	132	116	0.8845	99	84

* = Statistically significant difference (absolute or relative) compared with respective control mean value.
Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for dosed groups expressed as percentage control mean value.

Microscopic findings

LY3298176-related microscopic findings were limited to minimally decreased zymogen granules in the pancreas, which occurred generally at a low incidence and at a similar severity in rats administered 3 mg/kg LY3298176 (Lot A) or 3 mg/kg LY3298176 (Lot B).

Toxicokinetics

N/A.

2.2.2. Ecotoxicity/environmental risk assessment

The ERA provided is considered complete and acceptable. No ERA studies are required with respect to the chemical nature of the molecule. Tirzepatide is not expected to pose a risk to the environment.

However, the applicant provided a test on ready biodegradability.

Substance (INN/Invented Name): tirzepatide (39 amino acids)			
CAS-number (if available): 2023788-19-2			
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Ready Biodegradability Test	OECD 301 B	readily biodegradable	

The provided test is valid and plausible.

2.2.3. Discussion on non-clinical aspects

This variation includes two independent non-clinical aspects. First, the applicant re-calculated the exposure multiples of the human therapeutic exposure (at the highest recommended dose) vs. the animal exposure in the toxicity studies performed during the diabetes development. This was done because mean therapeutic exposure was higher in non-diabetic subjects (SURMOUNT-1 study) than in diabetic subjects (SURPASS studies). Otherwise, no specific concerns arise from the resulting small decrease in the exposure multiples. The multiples remain rather low due to low tolerability of tirzepatide in the animal repeated-dose studies and consecutively low dose levels. The fact that no new toxicology studies were performed for the obesity programme is acceptable since no higher doses are intended in obese patients compared to diabetes patients.

The second non-clinical aspect was the submission of a new 2-week repeated-dose study in rats to rule out unexpected toxicity of certain impurities (D-Ser32/C-terminal, Gln19, and Gln24 deamidation). The animals either received a tirzepatide batch containing around 10% impurities, a batch with a markedly lower level of impurities or vehicle. Tirzepatide caused the expected pharmacodynamic effects, most pronounced was reduced food intake and consecutive decreased weight gain. Notably, this effect was somewhat stronger in animals treated with the high-impurity batch. The reason is unclear; since toxicokinetic data were not obtained, it cannot be ruled out that this batch had a higher bioavailability and hence caused higher exposure. Nevertheless, it is reassuring that no hitherto unknown toxic effects were observed, and there is therefore no need to pursue this further.

2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of tirzepatide.

Considering the above data, tirzepatide is not expected to pose a risk to the environment.

The application is acceptable from a non-clinical viewpoint.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Overview of clinical studies

Clinical pharmacology study supporting the CWM indication (not included in the original T2DM application) **Study GPHU** was conducted to characterise gastric emptying in participants with obesity.

Tirzepatide clinical development program for the CWM application:

- One pivotal phase 3 study in participants with obesity or overweight, without T2DM (**SURMOUNT-1**);
- Supportive: the 36-week tirzepatide open-label lead-in period data for a phase 3 study in participants with obesity or overweight, without diabetes mellitus (**SURMOUNT-4**, ongoing);

- Supportive: *post-hoc subgroup analyses* of the **SURPASS 1-5** studies in patients with T2DM; these studies were pivotal for the T2DM indication; only subgroup analysis results in patients with BMI above 27kg/m2 are described in this AR.

N.B. In this AR only studies which had been submitted newly for the CWM indication are described and assessed in detail. For studies which were part of the original T2DM application only aspects considered relevant for CWM are reported.

2.3.2. Pharmacokinetics

Population PK model

A population PK analysis was conducted with the data from adults with obesity or overweight. Sparse PK sample collection was implemented in Phase 3 study SURMOUNT-1, such that participants were randomized to sampling PK time windows of 1 – 24 hours, 24 – 96 hours, or 120 – 168 hours post dose at the 3 protocol-specified visits (Weeks 8, 16, and 36) across the duration of the study and PK samples were collected pre-dose at the same time as immunogenicity samples at 6 visits (Weeks 0, 4, 12, 24, 48, and 72) across the duration of the study.

The model structure and parameter estimates from the previously for the T2DM patients data developed model were used to inform the base model for the population PK analysis of data from SURMOUNT-1. The observed tirzepatide concentrations from adult participants with obesity or overweight in SURMOUNT-1 were adequately described by the same model structure as the population PK model previously developed from studies of tirzepatide for treatment of patients with T2DM. The PRIOR subroutine in NONMEM had been implemented to incorporate the parameter estimate information from the population PK model developed from the extensive tirzepatide concentrations collected in the studies of tirzepatide for treatment of patients with T2DM. The bioavailability of tirzepatide was incorporated into the PK model as a fixed value parameter based on the results of Study GPGE.

In the development of the T2DM population PK model, the model estimate for the fraction of fat mass contributing to the allometry of CL and Q was close to 1 and when fixed to 1 did not show a significant change in objective function. Thus, total body weight (TBW) was included in the allometric effect on tirzepatide CL in the population PK model for patients with T2DM. In the analysis of SURMOUNT-1, the estimate for the fraction of fat mass contributing to the allometry of CL and Q was 0.711 and was associated with a significant decrease in objective function compared to a model utilizing TBW. Thus, FFM and 71% of fat mass, a combined body mass less than TBW, was included in the allometric effect on tirzepatide CL and Q in the final population PK model for SURMOUNT-1. FFM and fat mass were calculated as follows:

Eq 1. FFM (male) = 9270 x BW / (6680 + 216 x BMI)

Eq 2. FFM (female) = 9270 x BW / (8780 + 244 x BMI)

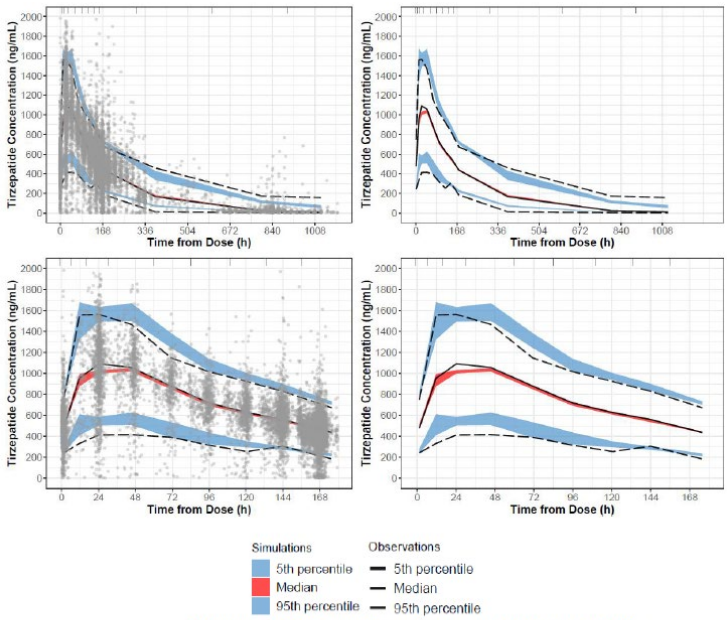
Eq 3. Fat Mass = BW – FFM

The final model was a 2-compartment model with first-order absorption and interindividual variability (IIV) on ka, CL, Vc, and proportional residual error. Body weight as a time-varying factor was included on clearance and volume of distribution parameters. Allometric exponents were included as fixed values on CL, Q, Vc, and Vp parameters in the tirzepatide population PK base and final models (0.8 or 1 for CL and Vd parameters, respectively).

Overall, the population estimates from the SURMOUNT-1 population PK model were similar to the model estimates from the population PK model developed with data from patients with T2DM.

PcVPCs for different time frames are shown in figure 3 below.

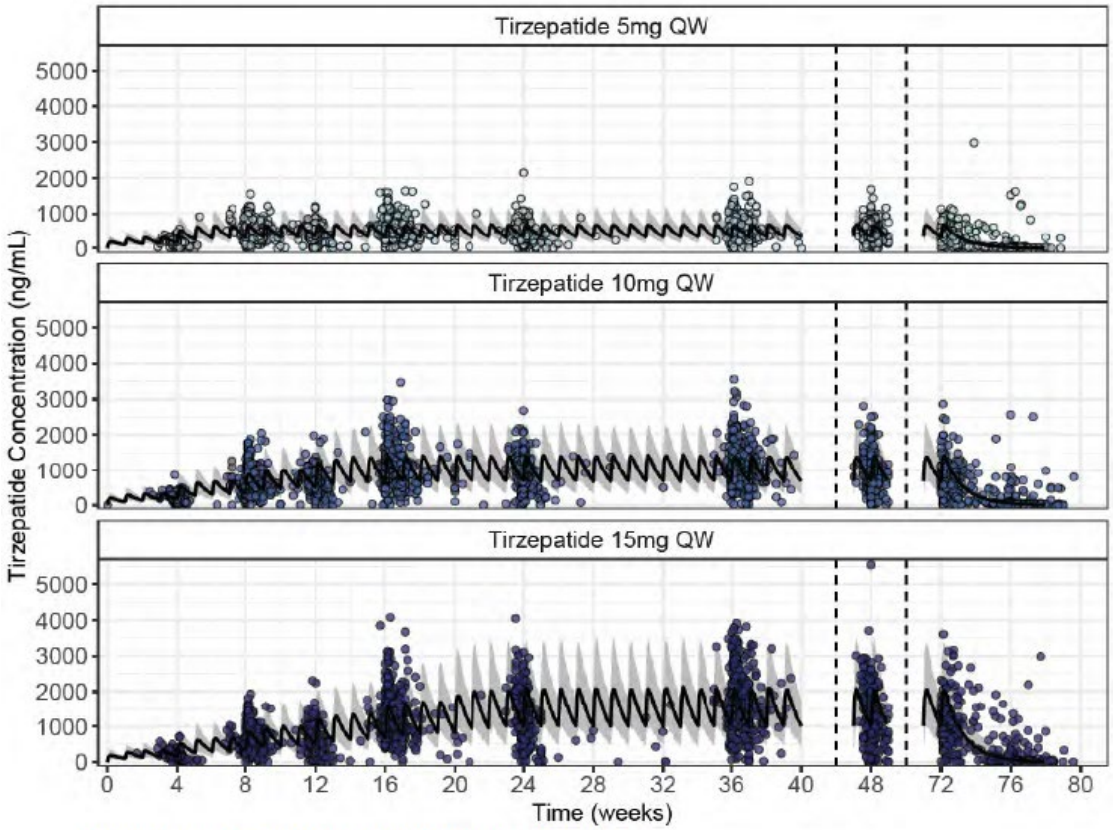
Figure 3. pcVPC of the final population PK model with (left) and without (right) overlaid observed data after tirzepatide dose with x-axis up to 6 weeks (1008 h) (top) and 1 week (168 h) (bottom)



Abbreviations: pcVPC = prediction-corrected visual predictive check; PK = pharmacokinetics.
Note: Solid circles denote individual values, shaded areas denote 95% confidence interval of simulation percentiles, and the dashed lines denote the observation percentiles.

Tirzepatide concentrations over time for the different doses are shown in figure 4.

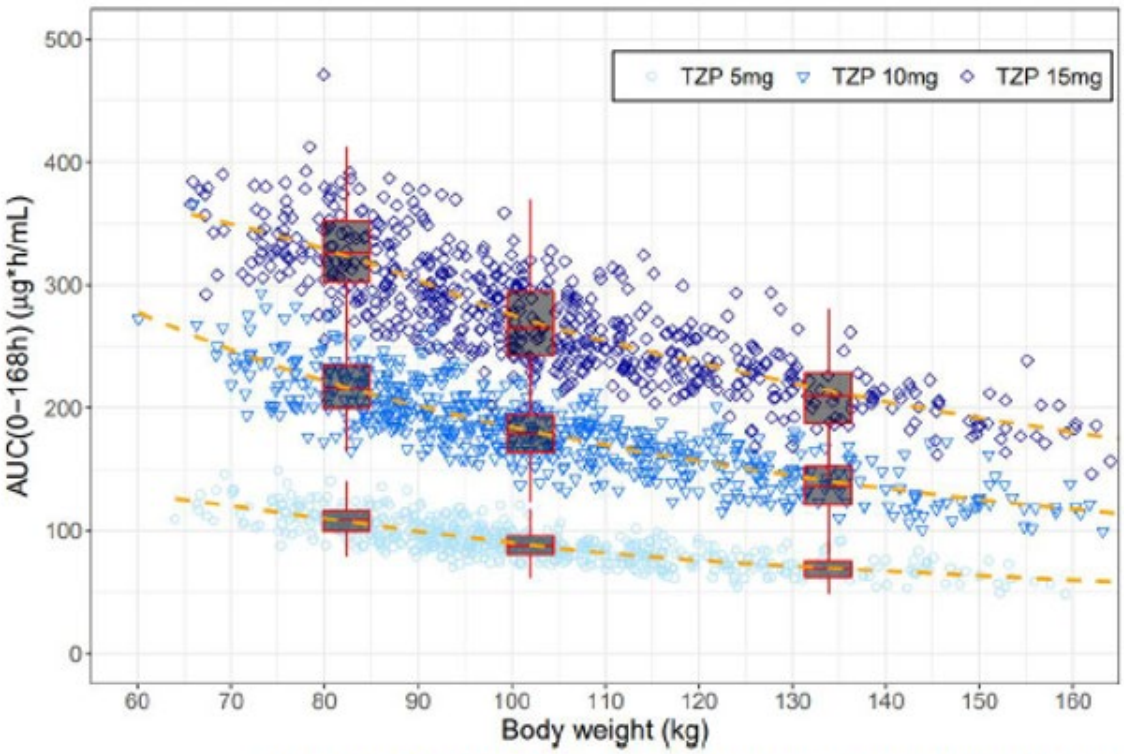
Figure 4. Comparison of observed tirzepatide concentrations and model-predicted tirzepatide concentrations by treatment group



Abbreviations: PK = pharmacokinetic(s); QW = once weekly.
Note: Circles represent observed tirzepatide concentrations. Simulation was performed with the PK model for 1000 replicates. The solid line represents the median of the simulation, and the shaded area is the 90% prediction interval.

Tirzepatide exposure changed by approximately 1.1% per kg over a body weight range of 80 to 130 kg.

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

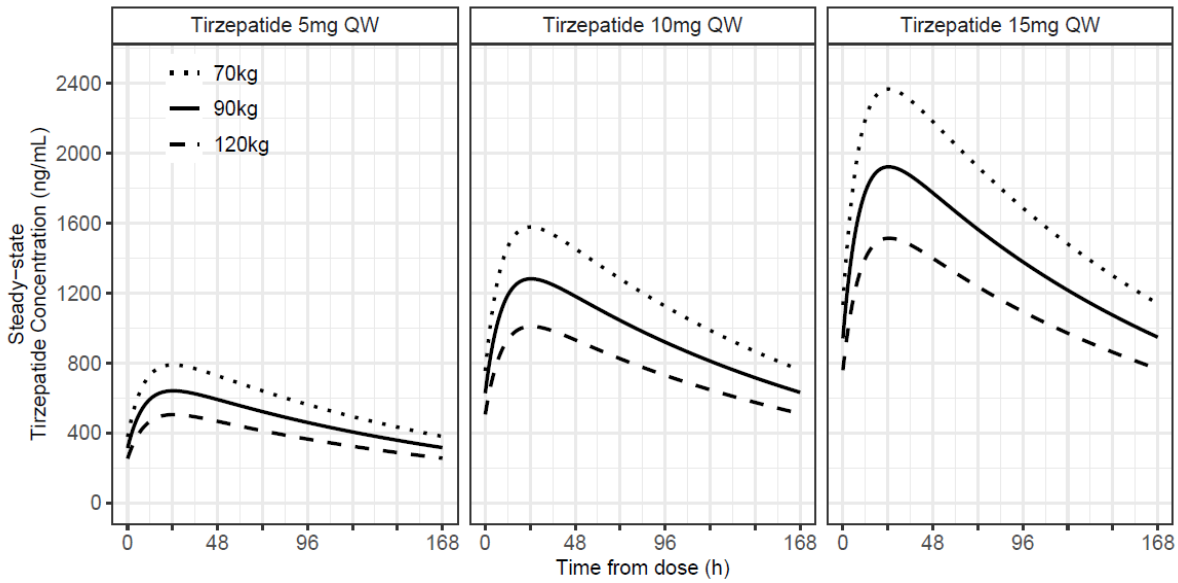


Abbreviation: AUC(0-168h) = area under the concentration versus time curve from time 0 to 168 hour after dose at steady state; TZP = tirzepatide.
Note: Symbols denote individual values. The dashed lines are the loess smoothing fit for each treatment arm. The top and bottom margins of the boxplot represent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

Effect of body weight on tirzepatide PK

Body weight had been identified to have a significant influence on tirzepatide PK (*Population PK analysis, procedure EMA/H/C/5620*). As tirzepatide treatment is associated with significant weight loss 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 ($AUC_{0-\tau}$).

Figure 6. Model-predicted steady-state tirzepatide concentration over time from dose following tirzepatide 5, 10, or 15 mg QW for an individual with body weight of 70, 90, or 120 kg.



As visualised in the figure 6 above, exposure to tirzepatide increases with increasing body weight with the difference between weight groups most pronounced with 15 mg.

Newly submitted exposure data from SURMOUNT-1 do *not* indicate a marked increase in tirzepatide exposure over time (see pop PK in this AR).

Gastric emptying (GE) delay

Study GPHU: was a phase 1, open-label, fixed-sequence study to assess the effect of multiple doses of tirzepatide (5 to 15 mg) on the PK parameters of acetaminophen to determine the impact on gastric emptying, PD, safety, and tolerability of tirzepatide in participants with obesity or overweight with or without T2DM when administered using a prefilled syringe.

A total of 36 participants with obesity or overweight (18 with T2DM and 18 without T2DM) between the ages of 28 and 65 years, inclusive, with a body mass index of 27.12 to 44.87 kg/m^2, inclusive, received at least 1 dose of study treatment, and 30 participants (15 T2DM participants and 15 non-T2DM participants) completed the study. All 36 (100.0%) participants were of Hispanic or Latino ethnicity.

Results: peak plasma concentration of acetaminophen as measured by C_{max} was reduced by approximately 55% and 32% when acetaminophen was administered in the presence of 5 mg (Day 2) or 15 mg (Day 37) tirzepatide, respectively, compared to dosing with acetaminophen alone (Day -1). This is indicative of tirzepatide delaying GE, and the effect diminishes with repeated dosing over time.

Peak plasma concentration of acetaminophen, as measured by C_{max}, was reduced by a similar extent between participants without T2DM (55%) and participants with T2DM (56%) when acetaminophen was administered in the presence of 5 mg tirzepatide on day 2 compared to when administered alone, with geometric LS means ratio (90% CI) of 1.03 (0.796, 1.34). However, the reduction in C_{max} 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, with geometric LS means ratio (90% CI) of 1.40 (1.06, 1.85). Overall exposure to acetaminophen, as measured by $AUC_{(0\text{-}tlast)}$ and $AUC_{(0\text{-}24)}$ was similar when acetaminophen was administered alone (Day -1), in the presence of 5 mg tirzepatide (Day 2), and in the presence of 15

mg tirzepatide (Day 37). Overall exposure of acetaminophen, as measured by $AUC_{(0\text{-tlast})}$, changed similarly for participants without T2DM and participants with T2DM, with geometric LS means ratio (90%) of 1.02 (0.842, 1.23) for 5 mg tirzepatide on day 2 and 1.14 (0.934, 1.40) for 15 mg tirzepatide on day 37. Delays in t_{max} of 1.00 and 0.50 hours were observed when acetaminophen was administered in the presence of 5 and 15 mg tirzepatide, respectively. The extent of delay was similar between participants without T2DM and participants with T2DM. The median tmax was approximately 24 and 18 hours for 5 and 15 mg tirzepatide, respectively. The PK profiles and parameters of tirzepatide were generally similar between participants without T2DM and participants with T2DM.

PD: The magnitude of the decrease in the 6-point PG was much more pronounced in participants with T2DM than in participants without T2DM at all time points.

Safety: the co-administration of tirzepatide and acetaminophen was generally well tolerated in these groups of participants without T2DM and participants with T2DM. There were no clinically relevant changes in clinical laboratory evaluations, vital sign measurements, or electrocardiograms. No hypoglycaemic events or injection site reactions were reported. Overall, the TEAEs reported at the highest frequency were GI (nausea, vomiting, and abdominal distension), which is consistent with the safety profile of tirzepatide and drugs in the GLP-1 receptor agonist class.

2.3.3. Pharmacodynamics

No new pharmacodynamics studies have been submitted, which is acceptable (for pharmacodynamics please refer to the AR for the initial MAA).

2.3.4. PK/PD modelling

Body Weight Model

The model developed from extensive PK and body weight data collected from multiple studies with participants with T2DM was used to guide the model development for analysis of SURMOUNT-1 data. In this study, the primary efficacy measure was body weight and was evaluated at Weeks 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, and 72 across the study. Similar to the previously established PK/PD model for body weight reduction, a sequential PK/PD modeling approach was used to characterize the effect of tirzepatide on reduction in body weight in adult participants with obesity or overweight. Individual post hoc PK parameters from the population PK model were used to predict the time course of tirzepatide concentration, and the time-varying impact of weight reduction on PK was accounted for in the model by updating an individual's PK parameters with each weight observation over time.

An indirect response model was used to account for a delay in the effect of tirzepatide in reducing body weight. To best elucidate the effect of tirzepatide in reducing body weight, the dependent variables used for the modeling were FFM and fat mass. Although the model was developed using the subcomponents only, the sum of the predicted FFM and fat mass gives the model-predicted total body weight, which was compared against the observed body weight. Therefore, model diagnostics included FFM, fat mass, and total body weight.

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 loss of body weight. A maximum effect model best described the concentration-effect relationship. 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. Sex was a significant covariate 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. Females had a higher Imax and IC50 relative to males. Asian race was also a significant covariate in the model, with Asian patients being estimated to have 11% lower and 25% lower FFM and fat mass at baseline, respectively.

Nausea, Vomiting, and Diarrhoea Models

Adverse events of special interest, such as nausea, vomiting, and diarrhoea were reported by participants and entered by study personnel into the electronic case report form at each study visit.

During model building, tolerance was incorporated into the drug effects acting on the probability of transitioning from no AE to mild AE [P(1|0)], and no AE to moderate/severe AE [P(2|0)]. Accumulation and decay of the hypothetical tolerance compartment concentration is driven by the first-order rate constant, KTOL. A 'first event' effect was included to capture the increased probability of transitioning to a mild or moderate/severe state following occurrence of the first event and the presence of nausea impacted the transition probability to vomiting. A separate linear drug effect was applied to P(0|1) and P(0|2). P(1|2) and P(2|1) were not estimable for vomiting due to low number of transitions between mild and moderate/severe states and were fixed to low probability value.

Differences in AEs between sex was 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 men resulting in a higher and more persistent probability of nausea and vomiting. In the NVD model submitted in the original T2DM application, Hispanic ethnicity and Japanese sub-race were included as significant covariates on the KTOL parameter. In these participants with obesity or overweight, Japanese differences were not estimable as there were no moderate/severe AEs and very few reported AE in general. Therefore, the transitions and differences to non-Japanese were fixed to low probability values or no differences. Caucasian patients had an increase in baseline probability of mild nausea relative to non-Caucasians.

According to the Applicant, no patient-specific characteristics or tirzepatide administration conditions were associated with clinically relevant changes in tirzepatide efficacy, tolerability, or safety and hence, thus, no dose adjustments are recommended based on the PKPD models.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Study GPHU was newly submitted for the CWM program. It investigated gastric emptying delay caused by tirzepatide in overweight and obese patients with or without T2DM. Results showed that tirzepatide delayed GE, and the effect diminished with repeated dosing over time. No clinically relevant difference in delay of gastric emptying was shown in patients with or without T2DM. Delay of gastric emptying is one mechanism by which tirzepatide increases satiety and is therefore a desired action.

Gastric emptying delay is adequately described in the SmPC. As study GPHU showed similar results as study GPGA (performed for the T2DM indication), the respective wording likewise applies to the CWM population and does not need to be amended.

In section 5.2 of the SmPC it is stated: "Special populations; Age, gender, race, ethnicity or body weight, do not have a clinically relevant effect on the pharmacokinetics (PK) of tirzepatide."

In SURMOUNT-1 absolute weight loss exceeded 20 kg in a considerable proportion of patients (63% of patients achieved >20% weight reduction corresponding to an absolute weight loss of 28 kg in a person with baseline weight 140 kg). Based on the PK modelling result, every kilogram increase in weight was associated with a 1.1% decrease in tirzepatide exposure (AUC0-τ), and it can be expected that tirzepatide exposures increase over time during weight loss, necessitating dose reduction.

These findings contrast with the exposure data from SURMOUNT-1, which showed no marked increase over time (see Pop PK in this AR).

Although it is recognised that tirzepatide is up-titrated individually based on efficacy and tolerability, there may be inertia to reduce the dose; this may cause side effects in individual patients. The Applicant was asked to justify the sentence above in section 5.2 of the SmPC; the Applicant`s response indicated a dependency of tirzepatide PK on body weight. The population PK model, describing tirzepatide exposure between populations grouped by intrinsic factors, *accounted for body weight*. The Pop PK model showed exposure decreases with increasing body weight. According to the response, this did neither lead to insufficient exposure in patients with high body weight nor to excess exposure (and more frequent gastrointestinal AEs) in patients with low body weight.

To adequately reflect the finding of a dependency of PK on body weight, the MAH was asked to change the sentence in section 5.2 to:

"Special populations; Age, gender, race, ethnicity or body weight, do not have a clinically relevant effect on the pharmacokinetics (PK) of tirzepatide. Based on a population PK analysis, the exposure of tirzepatide increases with decreasing body weight; however, the effect of body weight on the PK of tirzepatide does not appear to be clinically relevant."

Overall, the issue of (moderately) increasing exposure during tirzepatide treatment is considered to be manageable in clinical practice where individual up-titration will be performed according to individual treatment goals and the dose may be adapted based on the physician`s judgement.

Pop PK: in principle the model development is agreed and pcVPCs show adequate predictions.

Pharmacodynamics

No new studies have been submitted, which is acceptable.

2.3.6. Conclusions on clinical pharmacology

Study GPHU showed, that tirzepatide delayed gastric emptying, and that the effect diminishes with repeated dosing over time. No clinically relevant difference in delay of gastric emptying was shown in patients with or without T2DM. Delay of gastric emptying is one mechanism by which tirzepatide increases satiety and is therefore a desired action. Gastric emptying delay is adequately described in the SmPC. As study GPHU showed similar results as study GPGA (performed for the T2DM indication), this wording likewise applies to the CWM population and does not need to be amended.

Effect of body weight (loss) on PK was further elucidated and accordingly reflected in section 5.2 of the SmPC.

2.4. Clinical efficacy

2.4.1. Main studies

The following table summarises the studies contributing to the tirzepatide CWM application:

Table 5. Global Phase 3 Clinical Studies Contributing to the Tirzepatide CWM Application

Design Elements	I8F-MC-GPHK SURMOUNT-1	I8F-MC-GPHN SURMOUNT-4	I8F-MC-GPGK SURPASS-1	I8F-MC-GPGL SURPASS-2	I8F-MC-GPGH SURPASS-3	I8F-MC-GPGM SURPASS-4	I8F-MC-GPGI SURPASS-5
	Conducted under the tirzepatide CWM development program		Conducted under the tirzepatide T2DM development program				
Participant Population	Participants without diabetes, with obesity, or overweight with at least 1 weight-related comorbid condition	Participants without diabetes, with obesity, or overweight with at least 1 weight-related comorbid condition	Participants with T2DM with inadequate glycaemic control with diet and exercise alone, naive to diabetes injectable therapies, and have not been treated with any OAM	Participants with T2DM with inadequate glycaemic control on metformin alone	Participants with T2DM with inadequate glycaemic control on metformin with or without SGLT-2i and naive to insulin treatment	Participants with T2DM and increased CV risk with inadequate glycaemic control on at least 1 and no more than 3 OAMs, which may include metformin, SGLT-2i, and/or SU	Participants with T2DM with inadequate glycaemic control on insulin glargine (U100) QD with or without metformin
Comparator	Placebo	None[b]	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo
Randomisation (TZP 5 mg: TZP 10 mg: TZP 15 mg: comparator)	1:1:1:1	N/A[b]	1:1:1:1	1:1:1:1	1:1:1:1	1:1:1:3	1:1:1:1
Treatment Duration	72 weeks[a]	36 weeks[b]	40 weeks	40 weeks	52 weeks	Up to 104 weeks[c]	40 weeks
Primary Endpoint	• Mean percent change in body weight • Proportion of participants who achieved ≥5% body weight reduction	Mean percent change in body weight[b]	Mean change in HbA1c[d]				
Blinding	Double blind	Open label[b]	Double blind	Open label	Open label	Open label	Double blind
Trial Size (N)	2539[a]	782[b]	478	1878	1437	1995	475

Number of Participants with Obesity or Overweight, n (%)	2539 (100)	782 (100)	371 (77.6)	1670 (88.9)	1255 (87.3)	1689 (84.7)	407 (85.7)
Number Of Participants with Obesity or Overweight from EU/UK, n (%)	-	-	-	69 (4.1)	677 (53.9)	490(29.0)	322(79.1)
Countries that Enrolled Participants	Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and United States	Argentina, Brazil, Taiwan, and United States	India, Japan, Mexico, and United States	Argentina, Australia, Brazil, Canada, Israel, Mexico, United Kingdom, and United States	Argentina, Austria, Greece, Hungary, Italy, Poland, Romania, South Korea, Spain, Taiwan, Ukraine, and United States	Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania, Russian Federation, Slovakia, Spain, Taiwan, and United States	Czech Republic, Germany, Japan, Poland, Slovakia, Spain, and United States

Abbreviations: BMI = body mass index; CV = cardiovascular; CWM = chronic weight management; HbA1c = haemoglobin A1c; n = number of participants with BMI ≥27 kg/m^2 at baseline; N = number of participants in category; N/A = not applicable; OAM = oral antihyperglycaemic medication; QD = once daily; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

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

b Information in this table for SURMOUNT-4 is for the completed 36-week tirzepatide open-label lead-in period, except for primary endpoint, which will be assessed at Week 88.

c For SURPASS-4, the primary endpoint is 52 weeks with a variable treatment duration of up to 104 weeks.

d Mean change from baseline in body weight was a key secondary endpoint controlled for type 1 error.

Note: EU/UK includes Austria, Czech Republic, Germany, Greece, Hungary, Italy, Poland, Romania, Slovakia, Spain, and United Kingdom.

2.4.2. Phase 3 studies

SURMOUNT-1- study-patients without T2DM

Study Number 18-F-MC-GPHK

Title of study

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

Objectives and Endpoints

Table 6. Objectives and endpoints

Objectives	Endpoints
Primary, at 72 weeks, by dose analysis	
To demonstrate that tirzepatide 10 mg QW is superior to placebo for • percent change in body weight, and • percentage of participants with ≥5% body weight reduction AND/OR To demonstrate that tirzepatide 15 mg QW is superior to placebo for • percent change in body weight, and • percentage of participants with ≥5% body weight reduction	• Mean percent change in body weight from randomization • Percentage of study participants who achieve ≥5% body weight reduction from randomization
Key Secondary (controlled for type 1 error) at 20 weeks, pooled dose analysis	
To demonstrate superiority to placebo for body weight for pooled tirzepatide 10- and 15-mg QW doses	Mean change in body weight (kg) from randomization
Key Secondary (controlled for type 1 error) at 72 weeks, by dose analysis	
To demonstrate that tirzepatide 5 mg QW is superior to placebo for • percent change in body weight, and • percentage of participants with ≥5% body weight reduction	• Mean percent change in body weight from randomization • Percentage of study participants who achieve ≥5% body weight reduction from randomization
For tirzepatide 10- and/or 15-mg QW doses, to demonstrate superiority to placebo for • body weight • waist circumference	• Percentage of participants who achieve o ≥10% body weight reduction from randomization o ≥15% body weight reduction from randomization o ≥20% body weight reduction from randomization • Mean change in waist circumference (cm) from randomization
Key Secondary (controlled for type 1 error) at 72 weeks, pooled dose analysis	
To demonstrate that pooled tirzepatide 10 and 15 mg QW is superior to placebo for patient-reported outcomes (SF-36v2 acute form Physical Functioning domain score)	Mean change in SF-36v2 acute form Physical Functioning domain score from randomization
Key Secondary (controlled for type 1 error) at 72 weeks, pooled dose analysis	

Objectives	Endpoints
For tirzepatide QW (all doses combined), to demonstrate superiority to placebo for • lipid parameters	• Mean change from randomization in o triglycerides (mg/dL) o non-HDL cholesterol (mg/dL) o HDL cholesterol (mg/dL)
• SBP	• Mean change in SBP (mmHg) from randomization
• fasting insulin	• Mean change in fasting insulin (pmol/L) from randomization
Additional secondary at 72 weeks, by dose analysis	
For tirzepatide 5-mg QW dose, to demonstrate superiority to placebo for • body weight	• Percentage of participants who achieve o ≥10% body weight reduction from randomization o ≥15% body weight reduction from randomization
• waist circumference	• Mean change in waist circumference (cm) from randomization
• patient-reported outcomes (SF-36v2 Physical Functioning)	• Mean change in SF-36v2 acute form Physical Functioning domain score from randomization
For tirzepatide 5-, 10-, and/or 15-mg QW doses, to demonstrate superiority to placebo for • body weight	• Mean change in body weight (kg) from randomization • Mean change in BMI (kg/m^2) from randomization
• glycemic control	• Mean change in HbA1c (%, mmol/mol) from randomization • Mean change in fasting glucose (mg/dL) from randomization
• Patient-reported outcomes	• Mean change in IWQOL-Lite-CT Physical Function composite score from randomization
Additional secondary at 72 weeks, pooled dose analysis	
For tirzepatide QW (all doses combined), to demonstrate superiority to placebo for • DBP	• Mean change in DBP (mmHg) from randomization
• lipid parameters	• Mean change from randomization in o LDL-cholesterol (mg/dL) o total cholesterol (mg/dL) o VLDL-cholesterol (mg/dL) o Free Fatty acids (mg/dL)

Objectives	Endpoints
Additional Secondary	
Pharmacokinetics/Pharmacodynamics To characterize the population PK of tirzepatide and explore the relationships between the tirzepatide concentration and efficacy, safety, and tolerability measures	Population PK and PD parameters

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical Trials Version; LDL = low-density lipoprotein; PD = pharmacodynamics; PK = pharmacokinetics; QW = once weekly; SBP = systolic blood pressure; SF-36v2 = Short-Form-36 Health Survey, Version 2, VLDL = very low-density lipoprotein.

Patient-reported outcomes (additional secondary endpoints)

SF-36v2 acute form

The SF-36v2 acute, 1-week recall version is a 36-item, generic, participant-administered measure. The measure assesses eight domains, including

- Physical Functioning
- Role-Physical
- Bodily Pain
- General Health
- Vitality
- Social Functioning
- Role-Emotional, and
- Mental Health.

The Physical Functioning domain assesses health functioning at the time of assessment, whereas the other seven domains assess health functioning from the past week.

Scoring of domains

Each item is scored individually on Likert scales of varying lengths:

- 3-point scale
- 5-point scale, or
- 6-point scale.

The 8 domain scores are then further aggregated into 2 component summary scores:

- Physical Component Summary, and
- Mental Component Summary.

Higher domain and summary scores indicate (Maruish 2011)

- better levels of function

- better health, or
- better health and function.

IWQOL-Lite-CT

The IWQOL-Lite-CT is a 20-item, obesity-specific patient-reported outcome instrument developed for use in obesity clinical trials. It assesses two primary domains of obesity-related health-related quality of life:

- Physical composite, which includes 7 items, and
- Psychosocial composite, which includes 13 items.

The IWQOL-Lite-CT total score is calculated by using all 20 items.

This table describes what each composite score evaluates.

Table 7. Composite score description

Composite Score	**Description of Composite**
Physical Composite Score	Describes the physical impact experienced by participants due to their weight
Physical Function Composite Score	Describes the physical impacts related to daily activities
Psychosocial Composite score	Describes the emotional and social impact experienced by participants due to their weight
IWQOL-Lite Total Score	Describes the overall health-related quality of life and functioning associated with weight

Participant rating of IWQOL-Lite-CT items and scoring

All items are rated on a 5-point

- frequency scale where 1 equals "never" and 5 equals "always," or
- truth scale where 1 equals "not true at all" and 5 equals "completely true."

Raw scores are then transformed to a range from 0 to 100. A lower IWQOL-Lite-CT raw score and a higher transformed score correspond to better health-related quality of life and functioning.

EQ-5D-5L

The EQ-5D-5L (EuroQoL Group 2019) is a standardized measure of health status. The EQ-5D-5L consists of 2 components including a

- descriptive system of the respondent's health, and
- rating of their current health state using a 0 to 100 mm VAS.

Overview of descriptive system of respondent's health

The descriptive system is made up of 5 dimensions:

- mobility
- self-care

- usual activities
- pain or discomfort, and
- anxiety or depression.

In 2005, the 5L version was introduced. The 5L version scores each dimension at 5 levels:

- no problems
- slight problems
- moderate problems
- severe problems, and
- unable to perform or extreme problems.

A formula that attaches weights to each of these 5 levels can then be used to derive a single health state index for each participant. The single health state index values range between (Dolan 1997)

- <0, indicating values as worse than death
- 0, indicating health equivalent to death, and
- 1, indicating perfect health.

Overview of current health state rating

The EQ-VAS records the participant's self-rated health status on a vertical VAS. The vertical VAS endpoints are labelled as

- 100 or best imaginable health state, and
- 0 or worst imaginable health state.

Estimands

For objectives controlled for type 1 error at 72 weeks, there were two estimands of interest when evaluating the primary and key secondary efficacy objectives:

1. The treatment-regimen estimand (also referred to in the dossier as "hybrid estimand"), defined as 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.*
2. The efficacy estimand, defined as 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 weeks treatment duration.*

Design

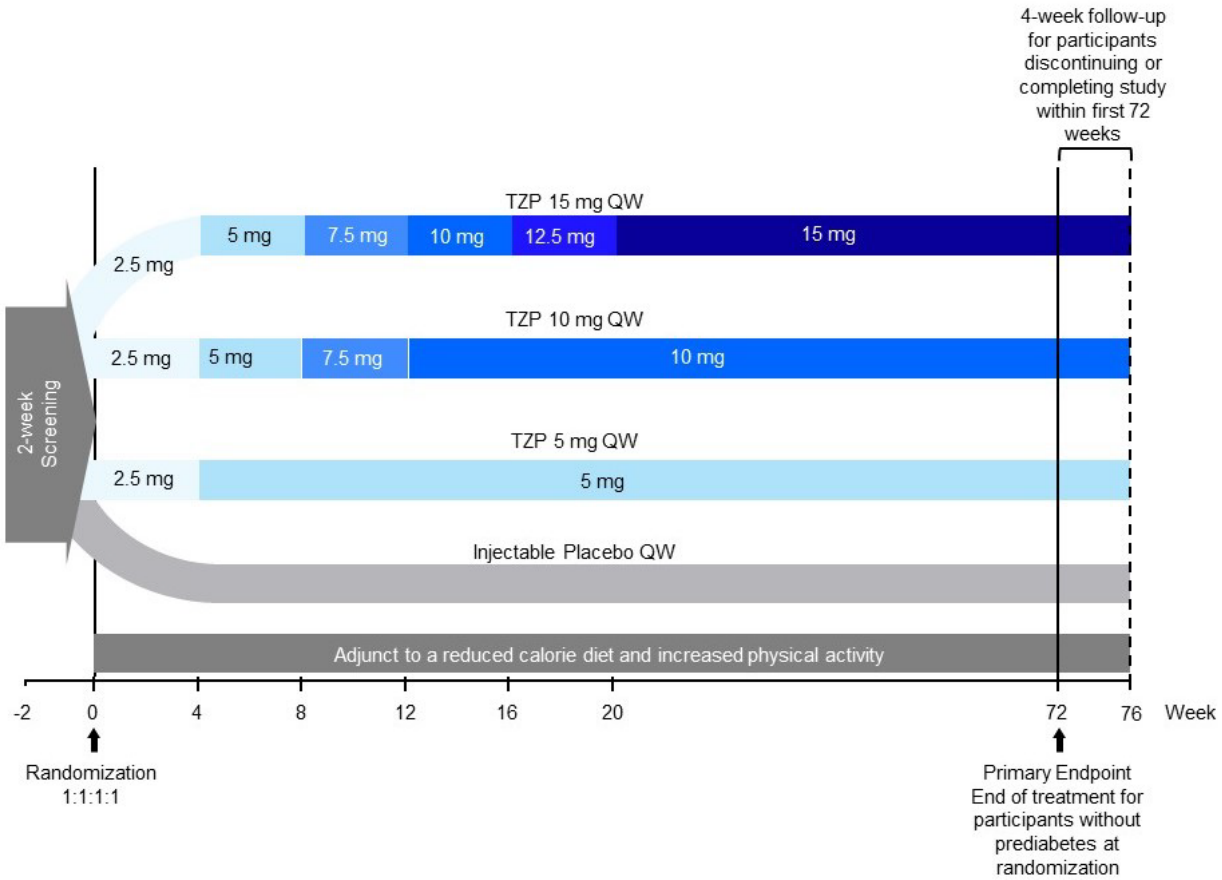
SURMOUNT-1 was a Phase 3, multicenter, double-blind study that randomly assigned participants to receive once-weekly, injectable placebo or tirzepatide 5, 10, or 15 mg. The study investigated the efficacy and safety of once-weekly doses of tirzepatide 5, 10, and 15 mg compared with placebo on weight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

The 72-week primary study period in SURMOUNT-1 included a

- 2-week screening period
- 72-week primary treatment period for all participants, and
- 4-week safety follow-up period for all participants except for those with prediabetes at randomization continuing into the additional 2-year treatment period.

Only data from the 72-week treatment period (the primary study period) in all study participants have been reported. The design is depicted in the following figure 7.

Figure 7. Study schema



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 (this 2 year treatment period for patients with pre-diabetes is *ongoing*). Randomisation was stratified by prediabetes status, country and sex

Study drug, dose, and mode of administration

Tirzepatide 5mg, 10mg, 15mg, or matched placebo was administered subcutaneously once weekly via single-dose pen.

Dose-escalation scheme

Study drug dose escalation was double-blinded. The escalation period lasted up to 20 weeks. For participants randomly assigned to tirzepatide, the starting dose was tirzepatide 2.5 mg. Participants injected tirzepatide 2.5 mg QW for 4 weeks then increased the dose by 2.5 mg every 4 weeks until reaching the appropriate maintenance dose of

- tirzepatide 5 mg
- tirzepatide 10 mg, or
- tirzepatide 15 mg.

The study drug-escalation period lasted 20 weeks. Participants in the placebo group received matching once-weekly placebo.

Study drug dose modification was not permitted during the primary study period except for management of intolerable GI symptoms.

Background therapy

For all participants, lifestyle modification was advised. This consisted of

- a hypocaloric diet with a 500-calorie deficit that was individually calculated, and
- an increase in physical activity by 150 minutes per week.

Lifestyle counseling was administered throughout the entire study.

Number of patients

Number of Participants (planned and analyzed):

- Number planned: 2400;
- Number randomized: 2539;
- Number completed primary study period on study drug: 2080;
- Number completed primary study period: 2184.

Main inclusion criteria

Participants were enrolled if they

- were 18 years or older,
- had a history of 1 self-reported unsuccessful dietary effort to lose weight, and
- had a body mass index (BMI) ≥30 kg/m2, or a BMI ≥27 kg/m2 and at least 1 weight-related comorbidity.

Acceptable weight-related comorbidities for participants with BMI ≥27 kg/m2 and <30 kg/m2 included obstructive sleep apnoea, hypertension, dyslipidaemia, or cardiovascular disease.

Main exclusion criteria

Participants were not eligible for this study if they had

- type 1 diabetes mellitus or type 2 diabetes mellitus
- received treatment with medications or remedies that may cause weight gain or weight loss within 3 months prior to randomization
- 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
- a history of chronic or acute pancreatitis
- a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- a history of significant active or unstable major depressive disorder or other severe psychiatric disorders within the last 2 years, or
- any lifetime history of a suicide attempt

Statistical methods

Analysis population and datasets:

- Modified intent-to-treat (mITT) population: All randomly assigned participants who took at least 1 dose of study drug. In the event of a treatment error, participants were analyzed according to the treatment to which they were randomly assigned.
- Efficacy analysis set (EAS): Data obtained during treatment period from mITT population, excluding data after early, permanent discontinuation of study drug (last dose date +7 days).
- Full analysis set (FAS): All available data obtained during treatment period from mITT population, regardless of adherence to study drug.
- Safety analysis set (SS): Data obtained during treatment period plus safety follow-up period from mITT, regardless of adherence to study drug.

There were 2 estimands of interest in evaluating primary and key secondary efficacy objectives controlled for type 1 error:

- The treatment-regimen estimand (also referred to as the hybrid estimand in the study protocol and SAP), defined as 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.
- The efficacy estimand, defined as 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 weeks treatment duration.

(Note: For a single key secondary objective, the prespecified time point is 20 weeks.)

Analyses related to the treatment-regimen estimand were conducted using the FAS. Analyses of continuous variables used an analysis of covariance (ANCOVA) model with multiple imputation of missing data. Analyses of percentage of participants achieving target thresholds used a logistic regression, with missing continuous values imputed first and then dichotomized. Both models were adjusted for baseline value and stratification factors. Multiple imputation of missing data was conducted using hybrid imputation:

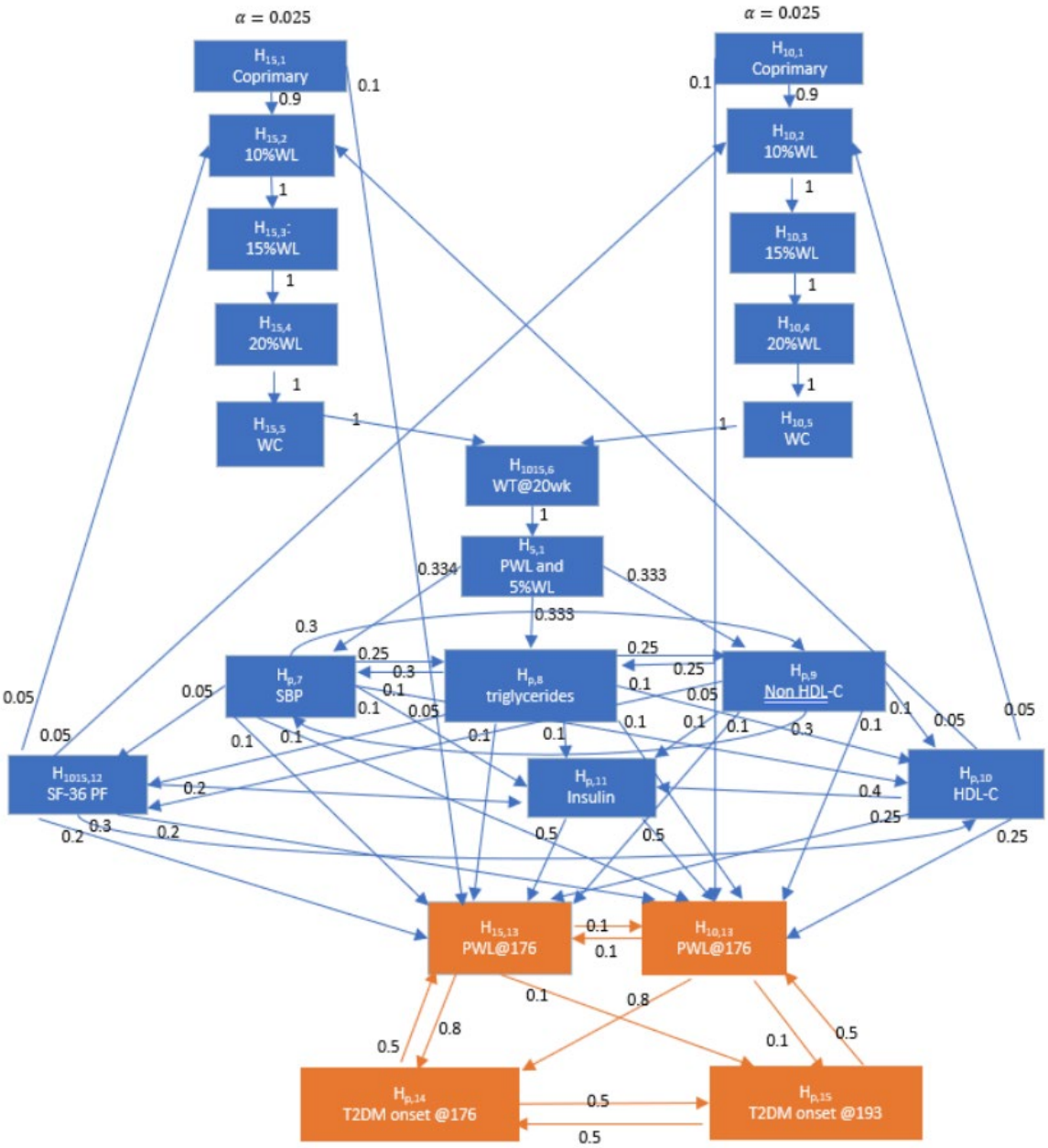
- For missing data solely due to exceptional circumstances, such as pandemic or natural disasters (after other reasons for missing data were ruled out), missing data were imputed using all non-missing data of the outcome measurement from the same treatment group.
- For missing data due to all other intercurrent events, missing data were imputed based on retrieved dropouts defined as observed outcome measurements from participants in the same treatment group who had their outcome measurement collected after early discontinuation of study drug.

An additional sensitivity analysis for the co-primary endpoints was conducted using the FAS and guided by the treatment-regimen estimand where all missing data at the primary endpoint time point of 72 weeks were imputed from retrieved dropouts only, regardless of the 2 missing data categories.

Analyses related to the efficacy estimand were conducted using the EAS. Analyses of longitudinal continuous variables used a mixed model for repeated measures (MMRM) including treatment group, visit, treatment-by-visit interaction, stratification factors as fixed effects, and baseline value as a covariate. Restricted maximum likelihood (REML) was used to obtain model parameter estimates and the Kenward-Roger option was used to estimate the denominator degrees of freedom. An unstructured covariance structure was used to model relationship of within-patient errors. If this model failed to converge, the following variance covariance structures were tested in order until convergence was achieved: heterogeneous Toeplitz, heterogeneous first order autoregressive, heterogeneous compound symmetry, Toeplitz, first order autoregressive, and compound symmetry. Analyses of percentage of participants achieving target thresholds used a logistic regression, with missing continuous values imputed using the predicted values from the MMRM analysis and then dichotomized. For continuous health outcomes collected only once postbaseline per schedule of activities, the last observation carried forward (LOCF) approach was applied to impute the missing endpoint, unless specified otherwise.

No type 1 error rate adjustments were made for conducting analyses relative to the efficacy and treatment-regimen estimands, as these 2 estimands were intended for different purposes. Within each estimand, the type 1 error was controlled at 5% two-sided for evaluating the primary and key secondary efficacy objectives as illustrated by the following figure.

Figure 8. Type 1 error control strategy for primary and key secondary efficacy endpoints.



Abbreviations: HDL-C = high-density lipoprotein cholesterol; SBP = systolic blood pressure; SF-36v2 PF = Short-Form-36 Health Survey, Version 2 physical functioning; T2DM = type 2 diabetes mellitus; p = tirzepatide all doses combined; PWL = percent weight loss; WC = waist circumference; wk = week; WL = weight loss; WT = weight loss in kilograms.
Notes: The orange arrows and text boxes refer to the end of the 3-year study treatment which includes the Week 176 and Week 193 time points. Data from the 176-week and 193-week periods will be presented in a separate clinical study report upon study completion.

$H_{15,1}$: Superiority test of tirzepatide 15 mg versus placebo for percent change in body weight from randomization and percentage of participants with ≥5% body weight reduction at 72 weeks.
$H_{10,1}$: Superiority test of tirzepatide 10 mg versus placebo for percent change in body weight from randomization and percentage of participants with ≥5% body weight reduction at 72 weeks.
$H_{15,2}$: Superiority test of tirzepatide 15 mg versus placebo for percentage of participants achieving ≥10% body weight reduction from randomization at 72 weeks.
$H_{10,2}$: Superiority test of tirzepatide 10 mg versus placebo for percentage of participants achieving ≥10% body weight reduction from randomization at 72 weeks.
$H_{15,3}$: Superiority test of tirzepatide 15 mg versus placebo for percentage of participants achieving ≥15% body weight reduction from randomization at 72 weeks.

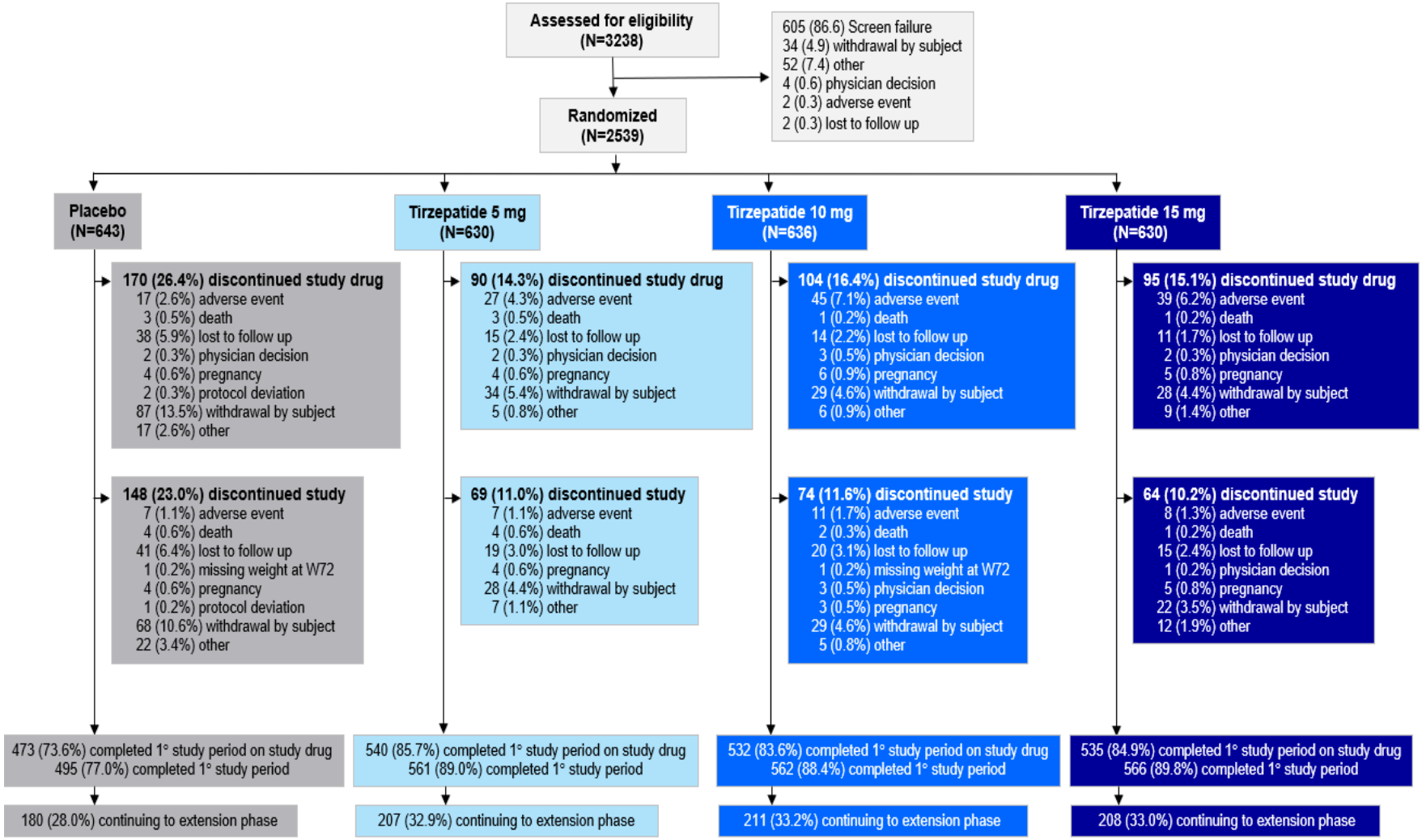
$H_{10,3}$: Superiority test of tirzepatide 10 mg versus placebo for percentage of participants achieving ≥15% body weight reduction from randomization at 72 weeks.
$H_{15,4}$: Superiority test of tirzepatide 15 mg versus placebo for percentage of participants achieving ≥20% body weight reduction from randomization at 72 weeks.
$H_{10,4}$: Superiority test of tirzepatide 10 mg versus placebo for percentage of participants achieving ≥20% body weight reduction from randomization at 72 weeks.
$H_{15,5}$: Superiority test of tirzepatide 15 mg versus placebo for change from randomization in waist circumference at 72 weeks.
$H_{10,5}$: Superiority test of tirzepatide 10 mg versus placebo for change from randomization in waist circumference at 72 weeks.
$H_{1015,6}$: Superiority test of pooled tirzepatide 10 and 15 mg versus placebo for change in body weight from randomization at 20 weeks.
$H_{1015,12}$: Superiority test of pooled tirzepatide 10 and 15 mg versus placebo for change in SF-36v2 acute form Physical Functioning domain score from randomization at 72 weeks.
$H_{5,1}$: Superiority test of tirzepatide 5 mg versus placebo for percent change in body weight from randomization and percentage of participants achieving ≥5% body weight reduction at 72 weeks.
$H_{p,7}$: Superiority test of pooled tirzepatide 5, 10, and 15 mg versus placebo for change in SBP from randomization at 72 weeks.
$H_{p,8}$: Superiority test of pooled tirzepatide 5, 10, and 15 mg versus placebo for change in triglycerides from randomization at 72 weeks.
$H_{p,9}$: Superiority test of pooled tirzepatide 5, 10, and 15 mg versus placebo for change in non-HDL-C from randomization at 72 weeks.
$H_{p,10}$: Superiority test of pooled tirzepatide 5, 10, and 15 mg versus placebo for change in HDL-C from randomization at 72 weeks.
$H_{p,11}$: Superiority test of pooled tirzepatide 5, 10, and 15 mg versus placebo for mean change in fasting insulin from randomization at 72 weeks.

Results

Disposition of participants

The figure below presents participant disposition for the study from screening to safety follow-up. A total of 2539 participants were randomized. All participants randomly assigned to treatment received at least one dose of study drug.

Figure 9. Study participant disposition figure from screening to safety follow-up



Abbreviations: N = number of participants who were randomly assigned and received at least 1 dose of study drug; W72 = Week 72. Note: The 2 participants with missing weight at Week 72, 1 in the placebo group and 1 in the tirzepatide 10-mg group, were classified as being discontinued from the study based on the study completion definition provided earlier in this section.

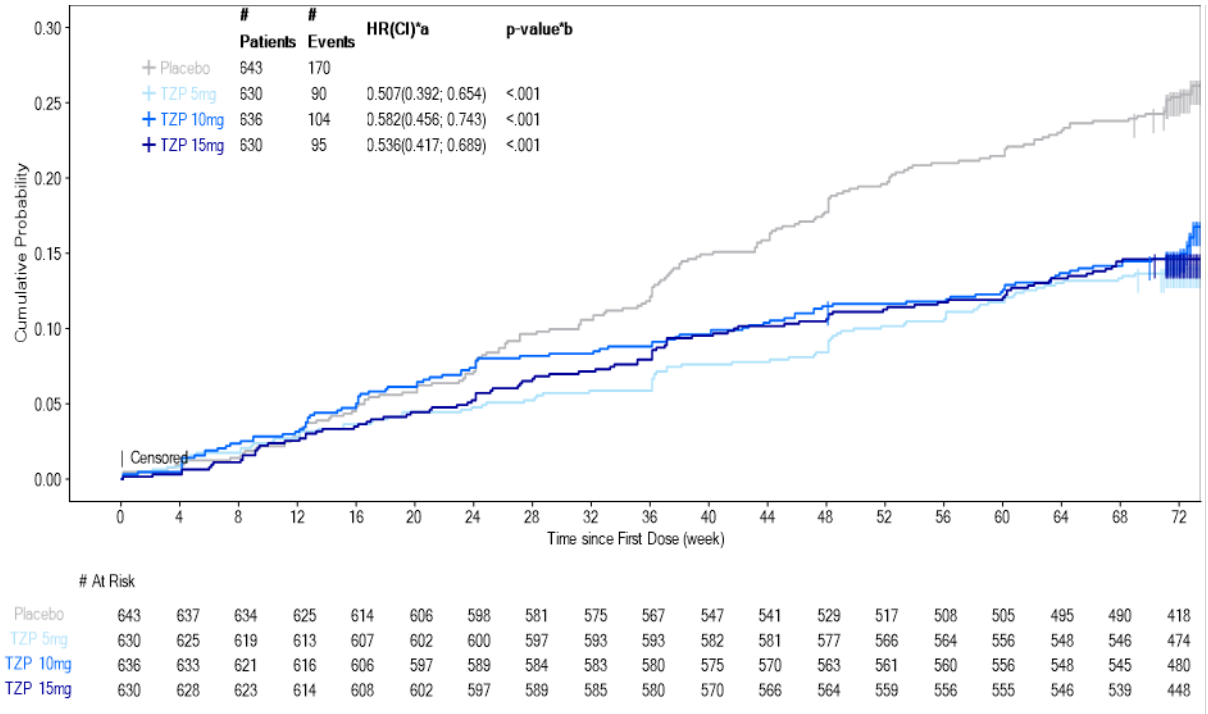
Reason for premature discontinuation from study and study drug

The most common reason for study discontinuation and study drug discontinuation was withdrawal by subject (5.8% and 7.0%, respectively).

Kaplan-Meier plot of time to premature discontinuation

Permanent premature discontinuations from study drug occurred throughout the duration of the study for participants in all treatment groups. There was a higher probability of treatment discontinuation for participants in the placebo group compared with participants in the tirzepatide groups.

Figure 10. Kaplan-Meier plot of time to premature discontinuation from baseline to Week 72



Abbreviations: CI = confidence interval; HR = hazard ratio; TZP = tirzepatide; *a HR - unstratified hazard ratio from Cox proportional hazard model and 95% CI; *b WALD unstratified p-value(2-sided) for comparison of treatment versus Placebo from Cox proportional-hazards model.

Protocol deviations

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.

Investigational Product Category

Incorrect stratification

There were 151 participants identified with important protocol deviations related to the investigational product category with the deviation term of Incorrect stratification category. Of these participants, 84 were incorrectly stratified as having prediabetes at randomization and 39 as having normoglycaemia at randomization. For participants who were incorrectly stratified in IWRS, the Applicant corrected this error by changing the glycaemic status. This allowed participants with prediabetes to continue onto the

additional 2-year treatment period for participants with prediabetes at randomization. The corrected glycaemic statuses were used for all data analyses.

There were also 26 participants incorrectly stratified for the ABPM addendum as using or not using HR-controlling medications at random. Participants who were incorrectly stratified in the ABPM addendum were not corrected in IWRS as there were no implications to the study. Data analyses used the corrected medication based on protocol deviations.

One participant was misclassified under the Incorrect stratification category. This participant should have been classified as an inadvertent enrollment for the ABPM addendum.

Table 8. Summary of Incorrect Stratification by Category and Subcategory

Category **Subcategory**	**n, number of participants**			
	Placebo (N = 643)	**TZP 5 mg (N = 630)**	**TZP 10 mg (N = 636)**	**TZP 15 mg (N = 630)**
Glycaemic Status				
Normoglycaemia corrected to Prediabetes	24	16	20	24
Prediabetes corrected to Normoglycaemia	6	12	7	14
ABPM Addendum				
HR controlling user to not HR controlling user	9	3	4	6
Not HR controlling user to HR controlling user	1	0	2	1
Other				
Incorrect IWRS Gender	1	0	0	0

Abbreviations: ABPM = ambulatory blood pressure monitoring; IWRS = interactive web-response system; HR = heart rate; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in specified category; TZP = tirzepatide.

Potential overdose

Overdose was defined as taking more than 15 mg of tirzepatide in less than 72 hours. During double-blind trial conduct, potential tirzepatide overdoses were defined as two or more study drug injections within 72 hours. Potential overdoses were reported for 38 participants. Upon further review after unblinding of treatment assignment, eight of the 38 participants met the definition of tirzepatide overdose. Six participants were from the tirzepatide 10mg group and two were from the tirzepatide 15mg group.

Eligibility

There were 84 (3.3%) participants with important protocol deviations related to the protocol deviation category of Eligibility.

Inadvertent enrollment in main study

Of the 84 participants with important protocol deviations related to Eligibility, there were 28 (1.1%) participants with important protocol deviations related to the main study.

Inadvertent enrollment in ABPM addendum

Of the 84 participants with important protocol deviations related to Eligibility, there were 56 (2.2%) participants with important protocol deviations with the deviation term of Inadvertent enrollment in ABPM addendum. Inadvertent enrollment in the ABPM addendum was due to a discrepancy between the inclusion and exclusion criteria between the main study and the addendum. For the main study, participants were excluded from the study if they had uncontrolled hypertension defined as SBP ≥160 mmHg and/or DBP ≥100 mmHg (Exclusion Criterion 20). To be eligible for the ABPM addendum, participants should have had well-controlled BP (<140/90 mmHg), regardless of antihypertensive treatment. The 56 participants inadvertently enrolled in the ABPM addendum had SBP ≥140 mmHg and/or DBP ≥90 mmHg. This had no impact on the integrity of the addendum or on the safety of the participants.

Pregnant and/or breastfeeding category

Overall, 23 participants were identified with important protocol deviations related to the eligibility and safety categories with the deviation term of Pregnant and/or breastfeeding. Six participants were indicated as having important protocol deviations related to eligibility with the deviation term of Pregnant and/or breastfeeding. However, none of these participants were pregnant or breastfeeding during the study. These participants were of childbearing potential and were not on the required contraception prior to randomization (see inclusion criterion). All six participants completed the primary study period on study drug.

Safety deviation category

There were 16 female participants and 1 participant's wife who became pregnant during the study that were reported as important protocol deviations. These pregnancies were reported as important protocol deviations under the safety protocol deviation category. Per protocol, all 16 female participants who became pregnant permanently discontinued study drug.

Overall, 3 participants were identified in the Applicant`s internal safety database as being pregnant during the study. All three female participants who became pregnant discontinued study drug.

Prohibited Concomitant Therapies

Use of metformin during the study was only permitted for participants diagnosed with T2DM. Important protocol deviations were captured for six participants who were not diagnosed with T2DM but received metformin. One participant did not have an important protocol deviation reported because they initiated metformin at the safety follow-up.

During the study, the use of weight gain- and weight loss-promoting medications was discouraged, although not strictly prohibited. There were 14 participants, across all treatment groups, who used weight gain-promoting medications. FDA-approved weight loss medications were used by 4 participants, 3 in the placebo group and 1 in the tirzepatide 10-mg group, with the intention to treat obesity and overweight.

One additional participant was reported under the deviation term Received weight loss medication for receiving a GLP-1 receptor agonist during the study. GLP-1 receptor agonists were not permitted under any circumstances during the study. Six participants in total received either semaglutide or liraglutide during the study and are captured as important protocol deviations.

Informed Consent Not Obtained

One participant randomly assigned to the tirzepatide 15-mg group had an important protocol deviation with the deviation term Informed consent not obtained. The study site failed to obtain the

reimbursement ICF. Following this event, the study site monitor re-educated the site on the importance of ensuring all Informed Consent are obtained prior to study activities.

Missing Body Weight at Week 72

Following database lock, two important protocol deviations with the deviation term Missing weight at Week 72 were identified.

Demographics and baseline disease characteristics

The following table summarizes baseline demographics and clinical characteristics.

Table 9. Summary of Selected Baseline Demographic Characteristics; All Randomized 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, 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, 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)
Country/Region, n (%)					
Argentina	93 (14.5)	90 (14.3)	90 (14.2)	91 (14.4)	364 (14.3)
Brazil	59 (9.2)	59 (9.4)	61 (9.6)	60 (9.5)	239 (9.4)
China	7 (1.1)	9 (1.4)	7 (1.1)	7 (1.1)	30 (1.2)
India	8 (1.2)	9 (1.4)	9 (1.4)	6 (1.0)	32 (1.3)
Japan	33 (5.1)	30 (4.8)	30 (4.7)	31 (4.9)	124 (4.9)
Mexico	108 (16.8)	110 (17.5)	107 (16.8)	108 (17.1)	433 (17.1)
Russian Federation	32 (5.0)	29 (4.6)	30 (4.7)	27 (4.3)	118 (4.6)
Taiwan	15 (2.3)	12 (1.9)	15 (2.4)	16 (2.5)	58 (2.3)
The United States	288 (44.8)	282 (44.8)	287 (45.1)	284 (45.1)	1141 (44.9)
Race, n (%)					
American Indian or Alaska Native	58 (9.0)	56 (8.9)	58 (9.1)	59 (9.4)	231 (9.1)
Asian	71 (11.0)	68 (10.8)	71 (11.2)	66 (10.5)	276 (10.9)
Black or African American	55 (8.6)	48 (7.6)	47 (7.4)	51 (8.1)	201 (7.9)
Multiple	7 (1.1)	9 (1.4)	6 (0.9)	8 (1.3)	30 (1.2)
Native Hawaiian or Other Pacific Islander	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.5)	9 (0.4)
White	450 (70.0)	447 (71.0)	452 (71.1)	443 (70.3)	1792 (70.6)
Ethnicity, n (%)					

Attribute	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)	Total (N = 2539)
Hispanic or Latino	310 (48.2)	308 (48.9)	297 (46.7)	299 (47.5)	1214 (47.8)
Not Hispanic or Latino	281 (43.7)	276 (43.8)	286 (45.0)	280 (44.4)	1123 (44.2)
Missing	52 (8.1)	46 (7.3)	53 (8.3)	51 (8.1)	202 (8.0)
Education (year), mean ± SD	14.1 ± 4.2	14.0 ± 3.7	14.1 ± 3.8	13.9 ± 4.0	14.0 ± 3.9

Abbreviations: N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the specified category; SD = standard deviation; TZP = tirzepatide.

Baseline disease-related characteristics

The following table summarizes the baseline disease-related characteristics and CV risk factors.

Table 10. Summary of Selected Baseline Clinical Characteristics; All Randomized Population

Attribute	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)	Total (N = 2539)
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/m2), mean ± SD	38.2 ± 6.9	37.4 ± 6.6	38.2 ± 7.0	38.1 ± 6.7	38.0 ± 6.8
BMI Categories, 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 (%)					
No	373 (58.0)	383 (60.8)	374 (58.8)	377 (59.8)	1507 (59.4)
Yes	270 (42.0)	247 (39.2)	262 (41.2)	253 (40.2)	1032 (40.6)
Duration of obesity (year), 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
Fasting insulin (mIU/L), mean ± SD	14.3 ± 9.9	13.6 ± 10.0	14.1 ± 12.2	14.4 ± 9.3	14.1 ± 10.4
Lipid levels (mg/dL), geometric mean (% CV)					
Total cholesterol	187.5	187.1	190.6	187.5	188.2

Attribute	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)	Total (N = 2539)
	(20.5)	(21.0)	(19.9)	(19.9)	(20.4)
HDL cholesterol	46.6 (27.0)	47.6 (26.3)	47.6 (26.1)	47.6 (25.8)	47.3 (26.3)
LDL cholesterol	109.4 (30.7)	108.7 (30.1)	112.3 (30.3)	109.3 (29.8)	109.9 (30.2)
Triglycerides	130.8 (49.2)	128.7 (51.7)	125.7 (51.1)	128.1 (47.3)	128.3 (49.8)
eGFR (CKD-EPI), (mL/min/1.73 m2), mean ± SD	98.1 ± 18.3	97.6 ± 17.9	98.3 ± 18.3	98.2 ± 17.7	98.1 ± 18.0
eGFR Categories, n (%)					
≥30 to <45	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)	5 (0.2)
≥45 to <60	6 (0.9)	7 (1.1)	10 (1.6)	16 (2.5)	39 (1.5)
≥60 to <90	194 (30.2)	224 (35.6)	184 (28.9)	171 (27.1)	773 (30.4)
≥90	442 (68.7)	398 (63.2)	441 (69.3)	441 (70.0)	1722 (67.8)

Abbreviations: BMI = body mass index; CKD-EPI = Chronic Kidney Disease-Epidemiology; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the specified category; SD = standard deviation; TZP = tirzepatide.

Baseline-related comorbidities

The table below summarizes the comorbidities reported at baseline.

Table 11. Baseline-Related Comorbidities; Randomized Population

Comorbidities	n (%)				
	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)	Total (N = 2539)
Hypertension	199 (30.9)	205 (32.5)	208 (32.7)	207 (32.9)	819 (32.3)
Dyslipidemia	186 (28.9)	201 (31.9)	188 (29.6)	182 (28.9)	757 (29.8)
ASCVD	21 (3.3)	16 (2.5)	20 (3.1)	21 (3.3)	78 (3.1)
PCOS	13 (2.0)	7 (1.1)	13 (2.0)	6 (1.0)	39 (1.5)
Obstructive sleep apnea	59 (9.2)	41 (6.5)	51 (8.0)	46 (7.3)	197 (7.8)
Osteoarthritis	76 (11.8)	87 (13.8)	86 (13.5)	77 (12.2)	326 (12.8)
Anxiety/Depression	108 (16.8)	119 (18.9)	101 (15.9)	94 (14.9)	422 (16.6)
NAFLD	46 (7.2)	42 (6.7)	44 (6.9)	48 (7.6)	180 (7.1)
Asthma or COPD	78 (12.1)	72 (11.4)	64 (10.1)	53 (8.4)	267 (10.5)
Gout	35 (5.4)	35 (5.6)	34 (5.3)	32 (5.1)	136 (5.4)

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; COPD = chronic obstructive pulmonary disease; NAFLD = nonalcoholic fatty liver disease; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the specified category; PCOS = polycystic ovary

syndrome; TZP = tirzepatide.

a Comorbidities were assessed through review of medical history.

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Please note: The above mentioned co-morbidities do not entirely match with the co-morbidity inclusion criterion; acceptable weight-related comorbidities for participants with BMI ⩾27 kg/m2 and <30 kg/m2 included obstructive sleep apnea, hypertension, dyslipidemia, or cardiovascular disease.

Concomitant therapy

Per protocol, participants were permitted to use concomitant medications that they required during the study.

Exceptions

During the study

- GLP-1 receptor agonists and DPP-4 inhibitors were not permitted under any circumstances
- metformin was only permitted for participants diagnosed with T2DM, and
- weight gain- and weight loss-promoting medications were discouraged, although not strictly prohibited.

Concomitant medications used during study

A total of 2289 (90.2%) participants used at least 1 concomitant medication during the study. The percentage of participants using concomitant medications was similar across treatment groups.

Antihypertensive concomitant medication

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
At baseline, the most frequently used antihypertensive therapy classes were angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and thiazides.

The table below summarizes the change in status of antihypertensive therapy from baseline through SFU.

Table 12. Summary of Status Change in Antihypertensive Therapy from Baseline through Safety Follow-Up mITT Population – Safety Analysis Set

Change Status	n (%)			
	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
No use at both baseline and postbaseline period	441 (68.6)	429 (68.1)	437 (68.7)	430 (68.3)
Increased	15 (2.3)	14 (2.2)	7 (1.1)	10 (1.6)
Not changed	74 (11.5)	69 (11.0)	61 (9.6)	71 (11.3)
Decreased	13 (2.0)	18 (2.9)	33 (5.2)	31 (4.9)
Cannot be determined	100 (15.6)	100 (15.9)	98 (15.4)	88 (14.0)

Abbreviations: mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in prespecified category; TZP = tirzepatide.

Lipid-Lowering Medications

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 table below summarizes the change in status of lipid-lowering therapy from baseline through SFU.

Table 13. Summary of Status Change in Lipid-Lowering Therapy from Baseline through Safety Follow-Up mITT Population – Safety Analysis Set

Change Status	n (%)			
	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
No use at both baseline and postbaseline period	503 (78.2)	500 (79.4)	529 (83.2)	522 (82.9)
Increased	10 (1.6)	8 (1.3)	8 (1.3)	5 (0.8)
Not changed	58 (9.0)	46 (7.3)	27 (4.2)	34 (5.4)
Decreased	7 (1.1)	9 (1.4)	10 (1.6)	8 (1.3)
Cannot be determined	65 (10.1)	67 (10.6)	62 (9.7)	61 (9.7)

Abbreviations: mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in prespecified category; TZP = tirzepatide.

Antidiarrhoeal and Antiemetic Medications

Investigators were allowed to prescribe medications such as antiemetic or antidiarrhoeal medications to mitigate GI symptoms and manage intolerable GI AEs after participants started study drug.

Generally, more participants treated with tirzepatide than with placebo took antidiarrhoeal or antiemetic medications during the postbaseline period (subjects with more than one antidiarrhoeal medication: placebo 1.2%, tirzepatide 5 mg 5.4%, tirzepatide 10 mg 6.6%, tirzepatide 15 mg 6.3%; subjects with more than one anti-emetic medication: placebo 6.4%, tirzepatide 5 mg 14.1%, tirzepatide 10 mg 16.0%, tirzepatide 15 mg 18.1%). The most common antidiarrhoeal and antiemetic medications used were loperamide and ondansetron, respectively.

Antihyperglycaemic Medications

Use of antihyperglycaemic medications during the study

If participants developed diabetes during the study, initiation of antihyperglycaemic therapies was allowed at the discretion of the participant's usual care provider. DPP-4 inhibitors and GLP-1 receptor agonists were prohibited from use in the study. Participants that developed diabetes during the study were allowed to continue in the study and continue on study treatment. However, if a participant that developed diabetes was started and remained on a DPP-4 inhibitor or GLP-1 receptor agonist, then study treatment was discontinued.

There were 20 (0.8%) participants who initiated use of antihyperglycaemic medications after randomization. Antihyperglycaemic medications were predominately used in the placebo group compared with the tirzepatide groups, irrespective of a reason to initiate the therapy.

Participants diagnosed with T2DM who received antihyperglycaemic medications

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 randomization. Four of the participants were in the placebo group, and 1 participant was in tirzepatide 10 mg group.

Participants without a T2DM diagnosis who received antihyperglycaemic medications

The remaining 15 participants were not diagnosed with T2DM but received antihyperglycaemic medications. Of these,

- 9 received metformin (n=7) or dapagliflozin (n=2) to treat

-prediabetes

-glucose intolerance

-insulin resistance, or

-polycystic ovary syndrome

- 1 received insulin lispro to treat postoperative hyperglycaemia, and
- 5 received semaglutide (n=2) or liraglutide (n=3) to treat obesity or overweight, after having discontinued study drug.

Important protocol deviations were determined in 12 of these patients (for details see section "protocol deviations" of this AR).

Compliance with study drug

Treatment compliance was defined as taking at least 75% of the required doses of study drug. Overall, study drug compliance during the entire treatment period was high (2473 participants, 97.4%) and did not differ across the treatment groups.

Efficacy results

Results of Multiplicity-Adjusted Testing Scheme for Primary and Key Secondary Endpoints

The statistical analysis plan specified a graphical multiple-testing procedure for the primary and key secondary objectives for the efficacy estimand and treatment-regimen estimand. This procedure controlled the family-wise type 1 error rate at a 2-side alpha level of 0.05 for individual estimands.

For both the treatment-regimen and the efficacy estimands,

- tirzepatide 10 and 15 mg achieved superiority to placebo on the co-primary objectives of

-percent change in body weight at Week 72, and

-percentage of participants with ≥5% body weight reduction at Week 72

- pooled tirzepatide 10 and 15 mg achieved superiority to placebo on the key secondary objective of mean change in body weight at Week 20
- tirzepatide 5 mg achieved superiority to placebo on the key secondary objectives of

-percent change in body weight at Week 72, and

-percentage of participants with ≥5% body weight reduction at Week 72

- tirzepatide 10 and 15 mg achieved superiority to placebo on the key secondary objectives of

-percentage of participants with ≥10% body weight reduction at Week 72

-percentage of participants with ≥15% body weight reduction at Week 72

-percentage of participants with ≥20% body weight reduction at Week 72, and

-mean change in waist circumference at Week 72

- pooled tirzepatide 5, 10, and 15 mg achieved superiority to placebo on the key secondary objectives of mean percent change in

-triglycerides at Week 72

-non-HDL cholesterol at Week 72

-HDL cholesterol at Week 72

-SBP at Week 72, and

-fasting insulin at Week 72, and

- pooled tirzepatide 10 and 15 mg achieved superiority to placebo on the key secondary objective of mean change in SF-36v2 acute form Physical Functioning domain score at Week 72.

The full alpha = 0.05 will be passed along to the remaining endpoints at the end of the additional 2-year follow-up period and final study completion.

Results for the co-primary endpoint

The **co- primary endpoints** for the 10 mg and 15 mg tirzepatide doses consist of

- mean percent change from baseline in body weight at 72 weeks, and
- percentage of participants achieving at least 5% body weight reduction at 72 weeks.

The same objectives had been pre-defined for the 5 mg dose as key secondary endpoints.

Please note: results for the tirzepatide 5 mg are given in this section (albeit pre-defined as key secondary).

Percent change in body weight at Week 72 (first component of the co-primary endpoint)

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. 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 discusses the results for the tirzepatide 5-mg group.

b ANCOVA with hybrid imputations for missing body weight at 72 weeks.

c MMRM analysis.

Note: Shown are least squares means.

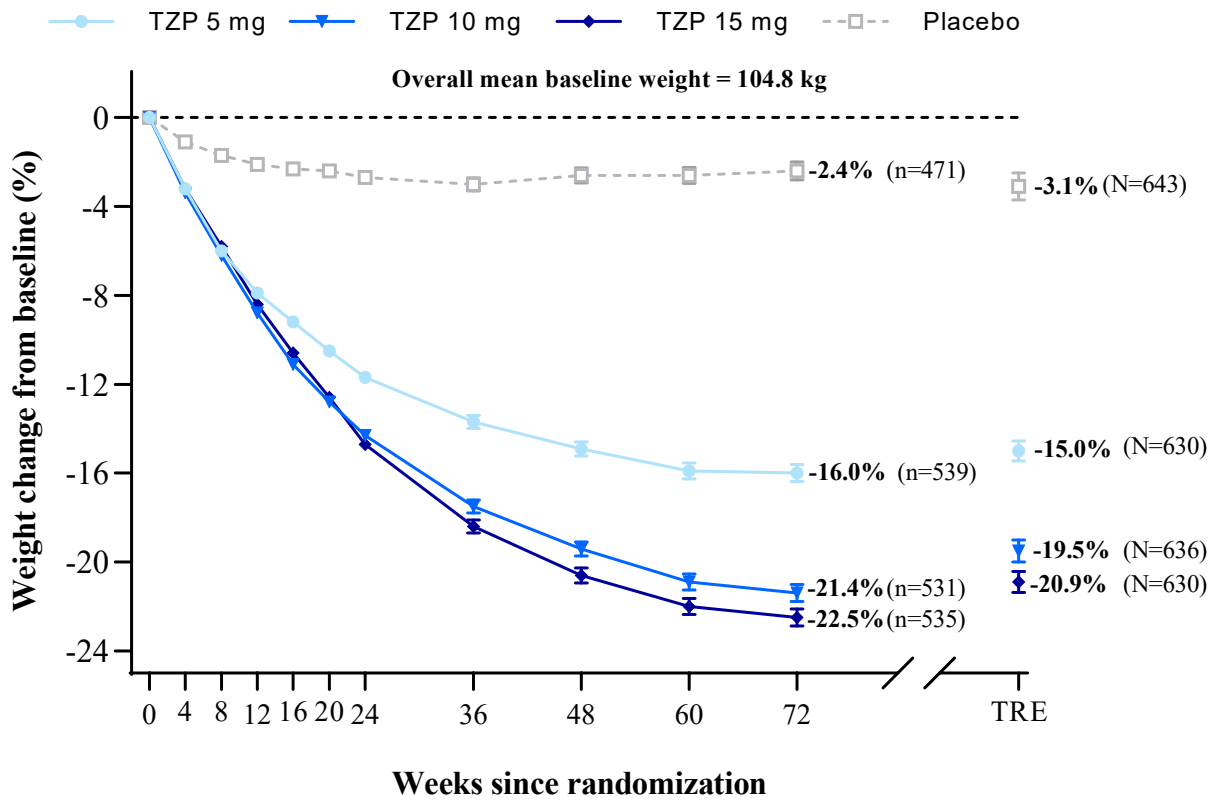
***p-Value <0.001 versus placebo for superiority.

†††p-Value <0.001 versus baseline.

Percent change in body weight over time

The following figure presents the percent change in body weight over time. Patients treated with tirzepatide 5, 10, and 15 mg had significant reductions in body weight from baseline compared with placebo starting at Week 4 –the first time-point assessed- until Week 72.

Figure 11. Body weight percent change over time (sustainability of action)



Sensitivity analysis for percent change in body weight (all missing data imputed by retrieved drop-outs)

A sensitivity analysis for percent change in body weight was conducted using the FAS and guided by the treatment-regimen estimand where all missing data at 72 weeks are imputed from retrieved dropouts only, regardless of the 2 missing data categories (in the analyses above a hybrid imputation approach was applied which handled missing data due to exceptional circumstances by using non-missing data of the primary outcome measure from the same treatment arm=missing at random). This sensitivity analysis results showed consistency with the results given for the hybrid estimand. *For brevity, results of this sensitivity analysis are not further detailed in this AR.*

Body weight change at 20 weeks

Pooled tirzepatide 10 and 15 mg achieved superiority compared with placebo on the key secondary endpoint of mean change from baseline (reduction) in body weight at 20 weeks, using both the treatment-regimen estimand (-10.1 kg, placebo adjusted) and efficacy estimand (10.7 kg, placebo-adjusted).

Table 15. 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 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.

Percent patients with a weight reduction of ≥5% body weight (second component of the co-primary primary endpoint)

The co-primary objective for tirzepatide 10 and 15 mg and the key secondary objective for tirzepatide 5 mg were achieved, with each dose demonstrating superiority to placebo for the percentage of participants achieving ≥5% weight reduction from baseline to 72 weeks.

Table 16.

	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.

Sensitivity Analysis for Percentage of Participants with ≥5% Body Weight Reduction

A sensitivity analysis for the percentage of participants with ≥5% body weight reduction was conducted using the FAS and guided by the treatment-regimen estimand where all missing data at 72 weeks are imputed from retrieved dropouts only, regardless of the 2 missing data categories. The sensitivity analysis results showed consistency with the evaluation per hybrid estimand based on the percentage of participants achieving ≥5% body weight reduction. *For brevity, results of this sensitivity analysis are not further detailed in the AR.*

Subgroup analyses

Subgroup analyses for the first component of the primary endpoint: Percent change in body weight

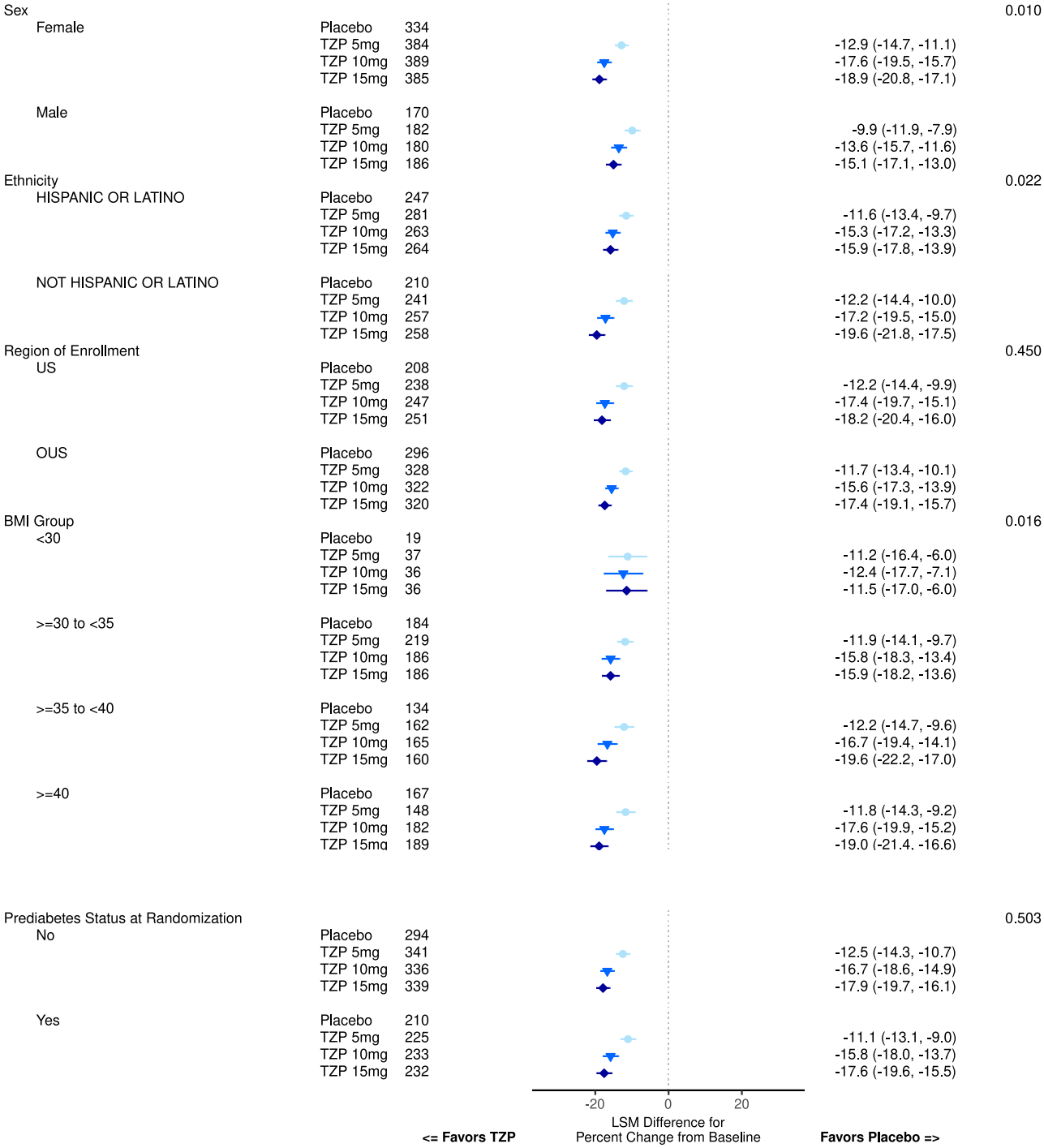
Treatment-regimen estimand

The figure below presents the results of the subgroup analyses for the percent change in body weight for the treatment-regimen estimand.

Figure 12. Summary and analysis of percent change in body weight (%) by subgroup: mITT population, full analysis set

Summary and Analysis of Percent Change in Body Weight (%) by Subgroup
ANCOVA with Multiple Imputation by Treatment for Missing Data at 72 Weeks
Modified Intent-to-Treat - Full Analysis Set
I8F-MC-GPHK Primary Study Period
Variable Analyzed: Percent Change from Baseline of Body Weight (kg) and Percent Change
[At Week 72 (Visit 21)]

Subgroup Category	Treatment	No. of Participants	LSM Difference (95% CI)	Interaction p-value
Age Group				0.365
<65	Placebo	478		
	TZP 5mg	519	-12.1 (-13.6, -10.6)	
	TZP 10mg	540	-16.6 (-18.1, -15.0)	
	TZP 15mg	537	-17.9 (-19.4, -16.3)	
>=65	Placebo	26		
	TZP 5mg	47	-9.3 (-13.8, -4.9)	
	TZP 10mg	29	-13.2 (-18.1, -8.3)	
	TZP 15mg	34	-15.5 (-20.3, -10.8)	
Race				0.569
AMERICAN INDIAN OR ALASKA NATIVE	Placebo	51		
	TZP 5mg	53	-11.1 (-14.7, -7.4)	
	TZP 10mg	52	-12.7 (-16.4, -9.0)	
	TZP 15mg	55	-14.7 (-18.4, -10.9)	
ASIAN	Placebo	64		
	TZP 5mg	64	-10.3 (-13.6, -7.0)	
	TZP 10mg	63	-14.6 (-18.1, -11.2)	
	TZP 15mg	63	-16.3 (-19.5, -13.1)	
BLACK OR AFRICAN AMERICAN	Placebo	38		
	TZP 5mg	39	-10.4 (-14.8, -6.0)	
	TZP 10mg	39	-16.5 (-21.1, -11.9)	
	TZP 15mg	43	-17.8 (-22.3, -13.2)	
WHITE	Placebo	343		
	TZP 5mg	402	-12.4 (-14.2, -10.6)	
	TZP 10mg	407	-17.0 (-18.7, -15.2)	
	TZP 15mg	400	-18.4 (-20.1, -16.6)	
MULTIPLE	Placebo	7		
	TZP 5mg	7	-17.2 (-30.1, -4.2)	
	TZP 10mg	6	-22.4 (-37.2, -7.4)	
	TZP 15mg	7	-22.1 (-36.1, -8.1)	



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).
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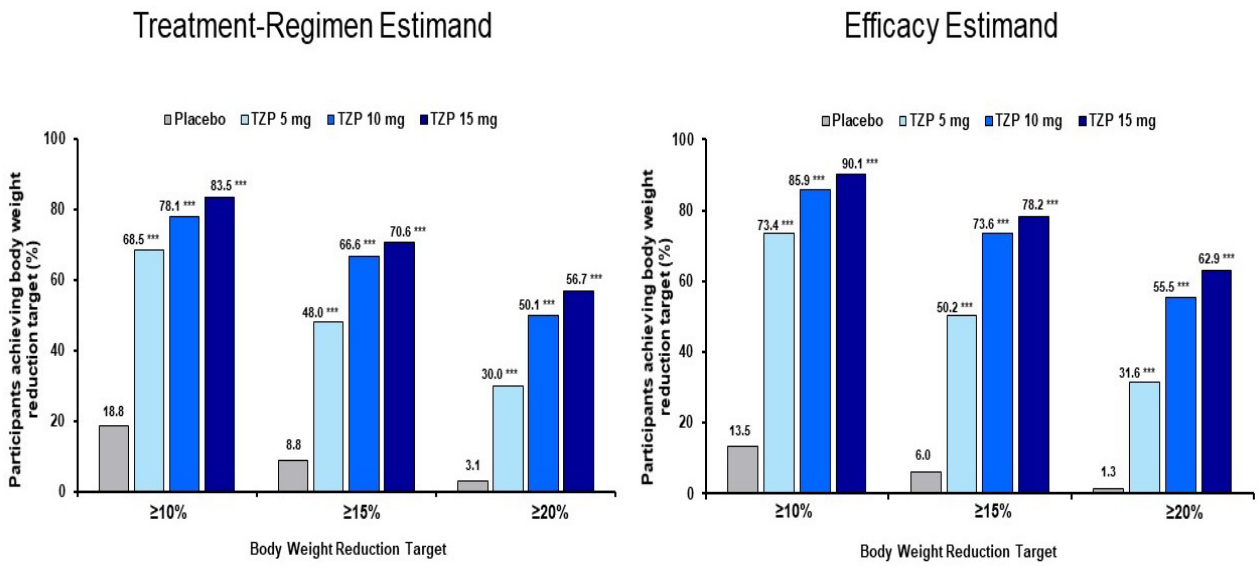
Results for key secondary endpoints

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. 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 (pre-defined as additional secondary endpoint).

Figure 13. Percentage of participants from randomization 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.
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.
***p-Value <0.001 versus placebo for superiority.

Body weight change at 20 weeks

Body weight change at 20 weeks was assessed as a measure of *early* efficacy of tirzepatide on body weight reduction. Pooled tirzepatide 10 and 15 mg achieved superiority compared with placebo on the key secondary endpoint of mean change from baseline (reduction) in body weight at 20 weeks, using both the treatment-regimen estimand (-10.1 kg, placebo adjusted) and efficacy estimand (10.7 kg, placebo-adjusted).

Percent change from baseline in total body fat mass (primary endpoint in the dual-energy-X-ray absorptiometry=DXA sub-study of SURMOUNT-1)

The aim of this sub-study was to demonstrate that once-weekly pooled TZP 5 mg, 10 mg, and 15 mg is superior to placebo for percent change from baseline in total body fat mass.

Investigative sites performed the body composition DXA scans on either Hologic™ or Lunar™ DXA scanners at baseline and week 72 (or early termination); 255 participants enrolled in the DXA addendum.

The table summarizes 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 17. 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.

Change in waist circumference

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

Change in waist circumference was a key secondary endpoint controlled for type 1 error for tirzepatide 10 and 15 mg and was an additional secondary endpoint not controlled for type 1 error for tirzepatide 5 mg.

Table 18. Mean Change from Baseline in Waist Circumference at Week 72 in SURMOUNT-1; mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameter (cm)	**Placebo (N=643)**	**TZP 5 mg (N=630)**	**TZP 10 mg (N=636)**	**TZP 15 mg (N=630)**
Treatment-regimen Estimand[a]				
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[b]				
Baseline	114.0	113.2	114.9	114.4
Change from baseline at 72 weeks	-3.4†††	-14.6†††	-19.4†††	-19.9†††

Parameter (cm)	Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
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 ANCOVA with hybrid imputations for values at 72 weeks.

b MMRM analysis.

Note: Shown are least squares means.

***p-Value <0.001 versus placebo for objectives controlled for type 1 error.

###p-Value <0.001 versus placebo for objectives not controlled for type 1 error.

†††p-Value <0.001 versus baseline within each treatment group.

Mean Change from Baseline in BMI at Week 72

At Week 72, tirzepatide 5, 10, and 15 mg each resulted in statistically significant mean reductions in BMI from baseline compared with placebo.

Table 19. Mean Change in BMI from Baseline to 72 Weeks; mITT Population – Efficacy Analysis Set

Parameters (kg/m2)	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Baseline	38.2	37.4	38.3	38.1
Change from baseline at 72 weeks	-0.9†††	-5.9†††	-8.1†††	-8.6†††
Change difference from placebo at 72 weeks (95% CI)	N/A	-5.1*** (-5.5, -4.6)	-7.2*** (-7.7, -6.8)	-7.7*** (-8.2, -7.3)

Abbreviations: BMI = body mass index; 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.

Note 1: MMRM analysis for postbaseline measures.

Note 2: Shown are least-squares means.

*** p-Value <0.001 versus placebo.

†††p-Value <0.001 versus baseline.

Change in lipid parameters

Pooled tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo in mean change in triglycerides (reduction), mean change in non-HDL-C (reduction), and mean change in HDL-C (increase) at 72 weeks, using both the treatment-regimen and efficacy estimands.

Table 20. Change from Baseline in Lipid Parameters at 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		
Triglycerides		
Baseline (mg/dL)	130.8	127.5

Parameters	Placebo (N = 643)	Pooled TZP 5/10/15 mg (N = 1896)
Change from baseline at 72 weeks (mg/dL)	-7.2	-31.8
Percent change from baseline at 72 weeks (%)	-5.6†	-24.8†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-20.3*** (-24.3, -16.1)
HDL-C		
Baseline (mg/dL)	46.6	47.6
Change from baseline at 72 weeks (mg/dL)	-0.3	3.8
Percent change from baseline at 72 weeks (%)	-0.7	8.0†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	8.8*** (6.1, 11.5)
Non-HDL-C		
Baseline (mg/dL)	138.3	138.3
Change from baseline at 72 weeks (mg/dL)	-3.2	-13.4
Percent change from baseline at 72 weeks (%)	-2.3	-9.7†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-7.5*** (-10.1, -4.9)
Efficacy Estimand		
Triglycerides		
Baseline (mg/dL)	130.5	127.8
Change difference from baseline at 72 weeks (mg/dL)	-8.1	-35.5
Percent change from baseline at 72 weeks (%)	-6.3†††	-27.6†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-22.7*** (-25.6, -19.8)
HDL-C		
Baseline (mg/dL)	46.5	47.5
Change from baseline at 72 weeks (mg/dL)	0.1	3.7
Percent change from baseline at 72 weeks (%)	0.3	7.9†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	7.7*** (5.9, 9.5)
Non-HDL-C		
Baseline (mg/dL)	137.2	138.2
Change difference from baseline at 72 weeks (mg/dL)	-2.5	-15.6
Percent change from baseline at 72 weeks (%)	-1.8	-11.3†††
Percent change difference from placebo at 72 weeks (%) (95% CI)	N/A	-9.7*** (-11.7, -7.7)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; 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 lipid parameter values at 72 weeks.

b MMRM analysis

Note 1: Shown are estimated means.

Note 2: 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.

Systolic blood pressure

Pooled tirzepatide 5, 10, and 15 mg achieved superiority in mean change in SBP (reduction) compared with placebo at 72 weeks, using both the treatment-regimen and efficacy estimands.

Table 21. Mean Changes in Systolic Blood Pressure at 72 Weeks in SURMOUNT-1; 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 (95% CI)	N/A	-6.2*** (-7.7, -4.8)
Efficacy Estimand[b]		
Baseline	122.8	123.4
Change from baseline	-1.3††	-8.1†††
Change difference from placebo (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; TZP = tirzepatide.

a ANCOVA with hybrid imputations for missing systolic blood pressure at 72 weeks.

b MMRM analysis.

Note: Shown are least squares means.

***p-Value <0.001 versus placebo for objectives controlled for type 1 error.

††p-Value <0.01, †††p-value <0.001 versus baseline within each treatment group.

Diastolic blood pressure

Pooled tirzepatide 5, 10, and 15 mg significantly reduced DBP from baseline compared with placebo at 72 weeks, using both the treatment-regimen and efficacy estimands.

Table 22. Mean Change in Diastolic Blood Pressure from Baseline to Week 72 in SURMOUNT-1; mITT Population – Full Analysis Set and Efficacy Analysis Set

Parameter (mmHg)	**Placebo (N=643)**	**TZP 5/10/15 mg (N=1896)**
Treatment-Regimen Estimand[a]		
Baseline	79.6	79.5
Change from baseline	-0.8	-4.8†††
Change difference from placebo (95% CI)	N/A	-4.0### (-4.9, -3.1)
Efficacy Estimand[b]		
Baseline	79.5	79.5
Change from baseline	-1.0††	-5.3†††
Change difference from placebo (95% CI)	N/A	-4.2### (-5.0, -3.5)

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 ANCOVA with hybrid imputations for missing diastolic blood pressure at 72 weeks.

b MMRM analysis.

Note: Shown are least squares means.

###p-Value <0.001 versus placebo for objectives not controlled for type 1 error.

††p-Value <0.01, †††p-value <0.001 versus baseline within each treatment group.

Ambulatory blood pressure monitoring (ABPM) addendum

Table 23. Primary objective, endpoint, and statistical method

Primary objective, 36 weeks	**Endpoint**	**Statistical Method**
To evaluate the impact of TZP 5 mg, 10 mg, and 15 mg compared to placebo on HR and BP at Week36	Mean change in 24-hour mean HR and BP from baseline	**Safety Analysis Set**: ANCOVA at Week 36

Abbreviations: ANCOVA = analysis of covariance; BP = blood pressure; HR = heart rate; TZP = tirzepatide.

Methodology

At Visit 2 (Week -1), participants received education and training about ABPM. Prior to Visit 3 (Week 0) and following Visit 12 (Week 36), study sites collected ambulatory monitoring of heart rate (HR) and blood pressure (BP).

Diagnosis and main criteria for inclusion and exclusion

A subset of participants eligible for SURMOUNT-1 was asked to participate in the ABPM addendum. Eligible participants for this addendum

- had well-controlled BP that was less than 140 mmHg over 90 mmHg, regardless of antihypertensive treatment, and
- if they were receiving treatment for hypertension, were on a stable regimen for at least 3 months prior to screening.

Participant disposition and characteristics

A total of 2539 participants were randomized in SURMOUNT-1. Of these, 600 participants enrolled in the ABPM addendum.

Results

At Week 36, participants randomly assigned to tirzepatide 5, 10, or 15 mg compared with placebo had

- significantly reduced 24-hour mean SBP (-7.4, -10.6, and -8.0 mmHg, respectively)
- reduced 24-hour mean diastolic BP (-2.0, -2.9, and -0.5 mmHg, respectively), and
- significantly increased 24-hour mean HR (2.1, 2.3, and 5.4 bpm, respectively).

Changes in glycaemic control measures

Fasting insulin, pooled-dose analysis

Pooled tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo on the mean change (reduction) in fasting insulin at 72 weeks, using both the treatment-regimen and the efficacy estimands.

Table 24. Mean Changes in Fasting Insulin from Baseline to Week 72 in SURMOUNT-1; 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
	pmol/L	83.2	81.4
Change from baseline	mIU/L	-0.8	-5.1
	pmol/L	-5.4	-35.1
Percent change from baseline (%)	N/A	-6.6	-42.9†††
Percent change difference from placebo (%) (95% CI)	N/A	N/A	-38.9*** (-44.8, -32.4)
Efficacy Estimand[b]			
Baseline	mIU/L	12.0	11.7
	pmol/L	83.2	81.1
Change from baseline	mIU/L	-1.1	-5.5
	pmol/L	-7.9	-38.3
Percent change from baseline (%)	N/A	-9.7†††	-46.9†††
Percent change difference from placebo (%) (95% CI)	N/A	N/A	-41.2*** (-44.9, -37.3)

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

a ANCOVA with hybrid imputation for missing fasting insulin at 72 weeks.

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 objectives controlled for type 1 error.

†††p-Value <0.001 versus baseline within each treatment group.

HbA1c

Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline compared with placebo at 72 weeks using both the treatment-regimen and efficacy estimand. This analysis was not controlled for type 1 error.

Table 25. Mean change in HbA1c from Baseline to Week 72 in SURMOUNT-1; mITT Population – Full Analysis Set; Efficacy Analysis Set

Parameters		**Placebo (N=643)**	**TZP 5 mg (N=630)**	**TZP 10 mg (N=636)**	**TZP 15 mg (N=630)**
Treatment-Regimen Estimand[a]					
Baseline	%	5.6	5.6	5.6	5.6
	mmol/mol	37.4	37.3	37.1	37.2
Change from baseline	%	-0.1†††	-0.4†††	-0.4†††	-0.4†††
	mmol/mol	-1.0†††	-4.0†††	-4.8†††	-4.9†††

Parameters		Placebo (N=643)	TZP 5 mg (N=630)	TZP 10 mg (N=636)	TZP 15 mg (N=630)
Change difference from placebo (95% CI)	%	N/A	-0.3### (-0.3, -0.2)	-0.4### (-0.4, -0.3)	-0.4### (-0.4, -0.3)
	mmol/mol		-3.0### (-3.5, -2.5)	-3.9### (-4.4, -3.3)	-3.9### (-4.4, -3.4)
Efficacy Estimand[b]					
Baseline	%	5.6	5.6	5.6	5.6
	mmol/mol	37.4	37.2	37.1	37.1
Change from baseline	%	-0.1†††	-0.4†††	-0.5†††	-0.5†††
	mmol/mol	-0.8†††	-4.4†††	-5.3†††	-5.6†††
Change difference from placebo (95% CI)	%	N/A	-0.3### (-0.4, -0.3)	-0.4### (-0.5, -0.4)	-0.4### (-0.5, -0.4)
	mmol/mol		-3.6### (-4.0, -3.2)	-4.6### (-4.9, -4.2)	-4.8### (-5.2, -4.5)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; HbA1c = glycosylated hemoglobin A1c; 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 HbA1c at 72 weeks.

b MMRM analysis.

Note: Shown are least squares means.

###p-Value <0.001 versus placebo for objectives not controlled for type 1 error.

†††p-Value <0.001 versus baseline within each treatment group.

Patient-reported Outcomes

SF-36v2 acute form

All doses of tirzepatide showed significant improvements compared with placebo for all eight domains of the SF-36v2 (including Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) and for both Mental and Physical Component Summary scores.

Table 26. Change from Baseline in SF-36v2 Component Scores (Norm-Based) at Week 72 mITT Population – Efficacy Analysis Set

Parameters	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
Mental Component Score				
n	481	543	539	538
Baseline	53.5	53.3	53.8	53.4
Change from baseline at 72 weeks	-0.5	0.7†	0.4	0.7†
Change difference from placebo at 72 weeks (95% CI)	N/A	1.2** (0.4, 2.0)	0.9* (0.1, 1.7)	1.2** (0.4, 2.0)
Physical Component Score				
n	481	542	539	538
Baseline	50.9	51.0	50.6	50.7
Change from baseline at 72 weeks	1.6†††	3.5†††	3.6†††	4.2†††
Change difference from placebo at 72	N/A	1.8***	2.0***	2.6***

Parameters	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
weeks (95% CI)		(1.2, 2.5)	(1.3, 2.7)	(1.9, 3.2)
Role-Physical				
n	482	544	539	538
Baseline	51.5	51.1	51.7	51.3
Change from baseline at 72 weeks	1.4†††	2.5†††	2.1†††	2.8†††
Change difference from placebo at 72 weeks (95% CI)	N/A	1.1** (0.4, 1.8)	0.7* (0.0, 1.4)	1.3*** (0.6, 2.1)
Bodily Pain				
n	481	544	539	537
Baseline	51.8	52.5	52.1	52.0
Change from baseline at 72 weeks	0.4	1.7†††	2.1†††	2.8†††
Change difference from placebo at 72 weeks (95% CI)	N/A	1.2** (0.3, 2.1)	1.6*** (0.7, 2.5)	2.4*** (1.5, 3.3)
General Health				
n	482	544	541	539
Baseline	52.7	53.0	52.1	52.0
Change from baseline at 72 weeks	1.0†††	3.3†††	3.9†††	4.2†††
Change difference from placebo at 72 weeks (95% CI)	N/A	2.3*** (1.5, 3.1)	2.9*** (2.1, 3.7)	3.2*** (2.4, 4.0)
Vitality				
n	482	543	539	538
Baseline	54.9	54.4	54.9	54.5
Change from baseline at 72 weeks	0.2	2.8†††	2.3†††	3.2†††
Change difference from placebo at 72 weeks (95% CI)	N/A	2.6*** (1.7, 3.4)	2.1*** (1.3, 3.0)	3.0*** (2.1, 3.9)
Social Functioning				
n	482	544	539	538
Baseline	52.4	52.6	52.4	52.6
Change from baseline at 72 weeks	0.3	1.3†††	1.2†††	1.1†††
Change difference from placebo at 72 weeks (95% CI)	N/A	1.0** (0.3, 1.7)	0.9* (0.1, 1.6)	0.9* (0.1, 1.6)
Role-Emotional				
n	481	544	539	538
Baseline	50.8	50.7	51.0	50.5
Change from baseline at 72 weeks	0.3	1.7†††	1.3†††	1.8†††
Change difference from placebo at 72 weeks (95% CI)	N/A	1.4** (0.5, 2.2)	1.0* (0.2, 1.9)	1.5*** (0.6, 2.3)
Mental Health				
n	482	543	539	538
Baseline	53.4	53.4	54.0	53.4
Change from baseline at 72 weeks	-0.2	0.8††	0.8††	1.1†††
Change difference from placebo at 72 weeks (95% CI)	N/A	1.1* (0.2, 1.9)	1.1* (0.2, 1.9)	1.3** (0.4, 2.1)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried

forward; mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the mITT efficacy analysis set with baseline and postbaseline values; N/A = not applicable; SF-36 = Short-Form-36 Health Survey, Version 2; TZP = tirzepatide.
Note 1: ANCOVA, LOCF. Only the non-missing postbaseline observation prior to study discontinuation was carried forward.
Note 2: Shown are least-squares means.
*p-Value <0.05, **p-value <0.01, ***p-value <0.001 versus placebo.
†p-Value <0.05, ††p-value <0.01, †††p-value <0.001 versus baseline

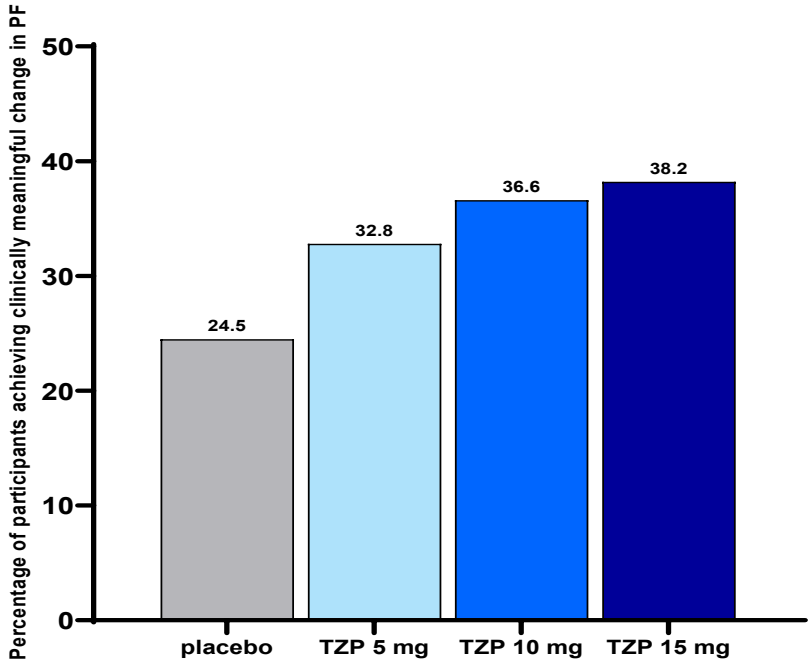
The Physical Functioning domain assesses how a participant's health limits them in activities completed during a typical day. The SF-36v2 Physical Functioning domain score was a key secondary endpoint controlled for type 1 error. Pooled tirzepatide 10/15 mg achieved superiority on the change from baseline (increase) in mean SF-36v2 Physical Functioning domain score compared with placebo.

Tirzepatide 5 mg also achieved a significantly greater improvement in SF-36v2 acute form Physical Functioning domain at Week 72 compared with placebo (additional secondary efficacy endpoint).

Greater improvements in physical functioning were seen for the subgroup of participants with limitations in physical functioning at baseline (assessed by the PGIS-Physical Function item).

A meaningful within-patient change threshold was 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 norm-based score (with an associated range from 3.84 to 9.60). When applied to individual patient change scores from baseline to Week 72 for the Physical Functioning norm-based score, 32.8%, 36.6%, and 38.2% of participants receiving tirzepatide 5, 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 24.5% in the placebo group.

Figure 14. Proportions of participants in SURMOUNT-1 who achieved clinically meaningful improvements in physical functioning, defined as ≥5.76 change from baseline in SF-36v2 Physical Functioning domain score.



Abbreviations: PF = physical functioning; SF-36v2 = Short-Form 36; Version 2; TZP = tirzepatide.

IWQOL-Lite-CT

The IWQOL-Lite-CT is an obesity-specific PRO instrument developed for use in obesity clinical trials. Compared with placebo all doses of tirzepatide had significantly greater improvements in scores measuring

- overall HRQoL and functioning, and
- physical function.

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.

Table 27. Summary of Results for IWQOL-Lite-CT at Baseline and Week 72, mITT Population – Efficacy Analysis Set

Score	**Placebo (N = 643)**	**TZP 5 mg (N = 630)**	**TZP 10 mg (N = 636)**	**TZP 15 mg (N = 630)**
Physical Composite Score				
n	477	545	539	535
Baseline	63.3	64.0	61.5	62.7
Change from baseline at 72 weeks	9.7†††	16.8†††	19.5†††	20.8†††
Change difference from placebo at 72 weeks (95% CI)	N/A	7.2*** (5.2, 9.2)	9.9*** (7.9, 11.9)	11.1*** (9.1, 13.1)
Physical Function Composite Score				

Score	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
n	477	545	539	535
Baseline	64.0	64.4	61.9	63.3
Change from baseline at 72 weeks	10.1†††	17.8†††	20.7†††	21.8†††
Change difference from placebo at 72 weeks (95% CI)	N/A	7.7*** (5.6, 9.8)	10.7*** (8.6, 12.8)	11.7*** (9.6, 13.8)
Psychosocial Composite Score				
n	477	545	539	535
Baseline	63.2	64.3	62.1	63.2
Change from baseline at 72 weeks	11.0†††	19.6†††	22.1†††	23.6†††
Change difference from placebo at 72 weeks (95% CI)	N/A	8.7*** (6.7, 10.6)	11.2*** (9.3, 13.1)	12.7*** (10.7, 14.6)
Total Score of IWQOL-Lite-CT				
n	477	545	539	535
Baseline	63.2	64.2	61.9	63.0
Change from baseline at 72 weeks	10.5†††	18.6†††	21.2†††	22.6†††
Change difference from placebo at 72 weeks (95% CI)	N/A	8.1*** (6.3, 9.9)	10.7*** (8.9, 12.5)	12.1*** (10.3, 13.9)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the mITT analysis set with a baseline value and at least 1 postbaseline value; N/A = not applicable; TZP = tirzepatide.

Note 1: ANCOVA, LOCF. Only the nonmissing postbaseline observation prior to study discontinuation was carried forward.

Note 2: Shown are least-squares means.

***p-Value <0.001 versus placebo.

†††p-Value <0.001 versus baseline.

EQ-5D-5L

The table below summarizes the baseline and change from baseline at 72 weeks (LOCF) for EQ VAS and the Health State Index scores. EQ VAS and Health State Index scores for all 4 treatment groups significantly improved from baseline to 72 weeks, indicating better overall health status. Compared with placebo, all three tirzepatide groups had improved EQ VAS and Health State index scores.

Table 28. Summary of Results for EQ-5D-5L Health Index Score (UK Algorithm) and EQ VAS Score at Baseline and 72 Weeks; mITT Population – Efficacy Analysis Set

Parameters	Placebo (N = 643)	TZP 5 mg (N = 630)	TZP 10 mg (N = 636)	TZP 15 mg (N = 630)
EQ-5D-5L VAS Score				
n	475	537	536	532
Baseline	79.3	78.9	78.5	77.7
Change from baseline at 72	2.4†††	6.8†††	8.2†††	8.6†††

weeks				
Change difference from placebo (95% CI) at 72 weeks	N/A	4.4*** (3.0, 5.8)	5.8*** (4.4, 7.3)	6.2*** (4.8, 7.6)
EQ-5D-5L Health State Index (UK)				
n	473	537	532	532
Baseline	0.85	0.85	0.84	0.85
Change from baseline at 72 weeks	0.02††	0.04†††	0.05†††	0.07†††
Change difference from placebo at 72 weeks (95% CI)	N/A	0.03** (0.01, 0.04)	0.03** (0.01, 0.05)	0.05*** (0.03, 0.06)

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = number of participants who were randomly assigned and received at least 1 dose of study drug; n = number of participants in the mITT efficacy analysis set with a baseline value and at least 1 postbaseline value; N/A = not applicable; TZP = tirzepatide; VAS = visual analog scale.

Note 1: ANCOVA, LOCF. Only the non-missing postbaseline observation prior to study drug discontinuation was carried forward.

Note 2: Shown are least-squares means.

**p-Value <0.01, ***p-value <0.001 versus placebo.

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

Percentage of Participants with BMI Shifts (exploratory endpoint)

Percentage of participants achieving a postbaseline BMI <25 kg/m2

There were 390 participants that achieved a postbaseline BMI <25kg/m2:

- placebo: 4 (0.6%) participants
- tirzepatide 5 mg: 93 (14.8%) participants
- tirzepatide 10 mg: 145 (22.8%) participants, and
- tirzepatide 15 mg: 148 (23.5%) participants.

Percentage of participants with Class 3 obesity (baseline BMI ≥40 kg/m2) achieving a postbaseline BMI <25 kg/m2

At baseline, 807 participants had BMI ≥40 kg/m2. Of the 390 participants with postbaseline BMI <25 kg/m2, 13 participants shifted from baseline BMI ≥40 kg/m2:

- placebo: 0 (0 of 213) participants
- tirzepatide 5 mg: 2 (1.1% of 177) participants
- tirzepatide 10 mg: 6 (2.9% of 205) participants, and
- tirzepatide 15 mg: 5 (2.4% of 212) participants.

Percentage of participants with Class 2 obesity (baseline BMI ≥35 and <40 kg/m2) achieving a postbaseline BMI <25 kg/m2

At baseline, 730 participants had BMI ≥35 and <40 kg/m2. Of the 390 participants with postbaseline BMI <25 kg/m2, 68 participants shifted from baseline BMI ≥35 and <40kg/m2:

- placebo: 0 (0 of 182) participants
- tirzepatide 5 mg: 8 (4.5% of 176) participants

- tirzepatide 10 mg: 27 (14.4% of 187) participants, and
- tirzepatide 15 mg: 33 (17.8% of 185) participants.

Percentage of participants with Class 1 obesity (baseline BMI ≥30 and <35 kg/m2) achieving a postbaseline BMI <25 kg/m2

At baseline, 866 participants had BMI ≥30 and <35 kg/m2. Of the 390 participants with postbaseline BMI <25 kg/m2, 233 participants shifted from baseline BMI ≥30 and <35 kg/m2:

- placebo: 2 (0.9% of 224) participants
- tirzepatide 5 mg: 60 (24.9% of 241) participants
- tirzepatide 10 mg: 89 (43.0% of 207) participants, and
- tirzepatide 15 mg: 82 (42.3% of 194) participants.

Percentage of participants with overweight (baseline BMI ≥25 and <30 kg/m2) achieving a postbaseline BMI <25 kg/m2

At baseline, 136 participants had BMI ≥25 and <30 kg/m2. Of the 390 participants with post-baseline BMI <25 kg/m2, 76 participants shifted from baseline BMI ≥25 and <30 kg/m2:

- placebo: 2 (8.3% of 24) participants
- tirzepatide 5 mg: 23 (63.9% of 36) participants
- tirzepatide 10 mg: 23 (62.2% of 37) participants, and
- tirzepatide 15 mg: 28 (71.8% of 39) participants.

SURMOUNT-4 study-patients without T2DM (ongoing; supportive study)

Study Design

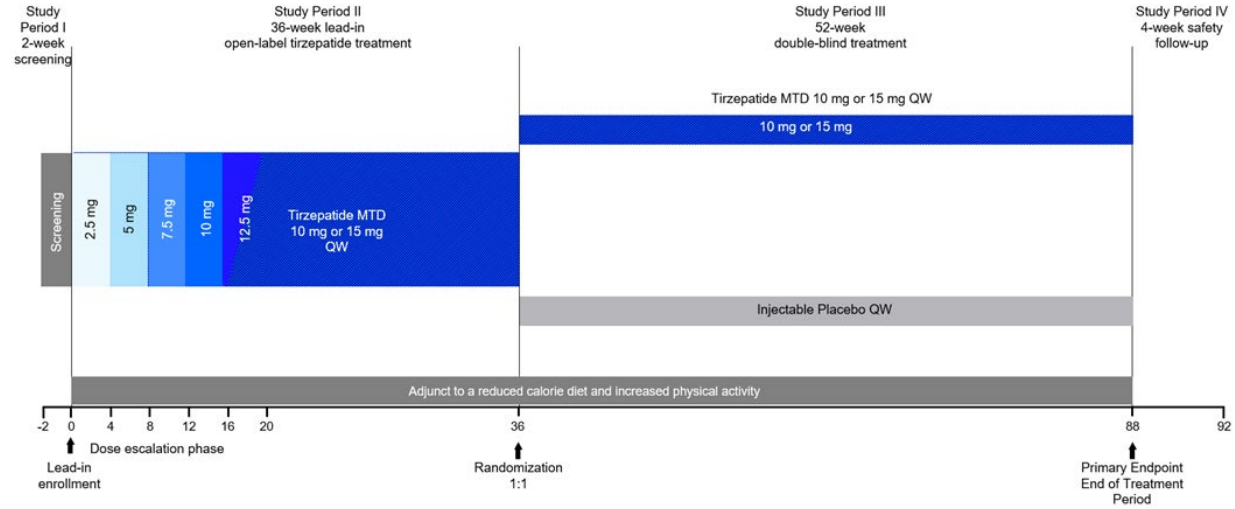
SURMOUNT-4 is an ongoing phase 3, multicenter, double-blind, placebo-controlled study that was designed to assess the efficacy and safety of once-weekly tirzepatide maximal tolerated dose (MTD; 10 or 15 mg) compared with once-weekly placebo for maintenance of weight reduction. During an initial 36-week, 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. The open-label tirzepatide lead-in period and protocol-specified interim database lock at 36 weeks are complete with results described below. The post-randomization double-blind phase of the study is ongoing.

The design of SURMOUNT-4 includes

- a 2-week screening period
- a 36-week open-label tirzepatide lead-in treatment period (results included in this summary)
- a 52-week placebo-controlled double-blind treatment period (ongoing), and
- a 4-week safety follow-up period (ongoing).

The following figure illustrates the study design, including the dose-escalation scheme.

Figure 15. Study design



Abbreviations: MTD = maximum tolerated dose; QW = once weekly.

SURMOUNT-4 study design

Baseline Demographics and Clinical Characteristics

The baseline demographic and clinical characteristics of participants in the 36-week open-label tirzepatide treatment period are given in the following table.

Table 29. Summary of Baseline Demographics and Clinical Characteristics in SURMOUNT-4; 36-Week Open-Label Treatment Period

Attribute	**36-Week Open-Label Treatment Period (N=783)**
Age (years), mean ± SD	47.62 ± 12.9
Age Category 1 (years), n (%)	
<65	701 (89.5)
≥65	82 (10.5)
Age Category 2 (years), n (%)	
<75	773 (98.7)
≥75	10 (1.3)
Female, n (%)	546 (69.7)
Male, n (%)	237 (30.3)
Weight (kg), mean ± SD	107.0 ± 22.5
Height (cm), mean ± SD	166.8 ± 9.7
BMI (kg/m2), mean ± SD	38.3 ± 6.6

Attribute	36-Week Open-Label Treatment Period (N=783)
BMI categories (kg/m2), n (%)	
<30	23 (2.9)
≥30 to <35	254 (32.4)
≥35 to <40	250 (31.9)
≥40	256 (32.7)
Waist circumference (cm), mean ± SD	115.1 ± 14.6
Duration of obesity (years), mean ± SD	15.3 ± 11.8
Systolic blood pressure (mmHg), mean ± SD	126.1 ± 13.0
Diastolic blood pressure (mmHg), mean ± SD	80.9 ± 8.3
Pulse rate (bpm), mean ± SD	72.6 ± 9.6
Lipid parameters	
Total cholesterol (mg/dL)	191.9 ± 39.2
HDL-C (mg/dL)	51.1 ± 13.1
LDL-C (mg/dL)	113.8 ± 32.9
Triglycerides (mg/dL)	135.7 ± 78.6
Non-HDL-C (mg/dL)	140.7 ± 37.2
VLDL-C (mg/dL)	60.4 ± 27.9
Free fatty acids (mEq/L)	0.53 ± 0.22
eGFR (CKD-EPI), (mL/min/1.73 m2), mean ± SD	97.6 ± 17.5

Abbreviations: BMI = body mass index, CKD-EPI= chronic kidney disease-epidemiology; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein-cholesterol; ISE = integrated summary of efficacy; LDL-C = low-density lipoprotein-cholesterol; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; VLDL-C = very low-density lipoprotein-cholesterol.

a Lipids presented in conventional units in the table.

Weight-Related Comorbidities

The percentages of participants with weight-related comorbidities were similar with those observed in SURMOUNT-1. At baseline, two thirds of participants in SURMOUNT-4 had 1 or more weight-related comorbidity, including

- 35.0% had hypertension
- 31.9% had dyslipidaemia
- 7.0% had obstructive sleep apnoea, and

- 4.9% had atherosclerotic CV disease.

Disposition

A total of 782 of the 783 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. Participants who were not able to tolerate the 10- or 15-mg dose of tirzepatide as their MTD by the end of the 36-week lead-in period were discontinued from the study. The final doses of tirzepatide administered during the 36-week open-label tirzepatide treatment period were distributed as follows:

Final dose of tirzepatide	**n (%)**
2.5 mg	12 (1.5)
5 mg	16 (2.0)
7.5 mg	13 (1.7)
10 mg	23 (2.9)
12.5 mg	32 (4.1)
15 mg	686 (87.7)

Overall, 87.0% of the enrolled participants completed the 36-week lead-in period and 85.6% of the enrolled participants completed the lead-in period on tirzepatide. The highest percentages of participants in the open-label tirzepatide lead-in period discontinued from the study or study drug due to an AE (5.5% and 6.8%, respectively) or withdrawal by subject (3.8% and 4.1%, respectively).

Results Summary

Please note: these results are evaluated descriptively based on the observed data during the open-label period in SURMOUNT-4 without imputation of missing data.

Change in Body Weight Measures

At the completion of the 36-week open-label tirzepatide lead-in period of SURMOUNT-4, participants treated with tirzepatide reduced body weight from baseline by on average 20.9%.

In addition, the percentages of participants achieving body weight reduction targets 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.

Additional Measures

Improvements from baseline were also observed for cardiometabolic and PRO-related measures by the end of the 36-week open-label tirzepatide lead-in period of SURMOUNT-4.

SURPASS 1-5- studies in patients with T2DM (supportive studies)

*Please note: results from the SURPASS studies presented here are derived from **post hoc analyses on the subpopulations of participants with obesity or overweight (BMI ≥27 kg/m2)**, which include 86% of participants from the overall SURPASS populations. The placebo-controlled studies*

SURPASS-1 and -5 are presented first, followed by the T2DM active comparator-controlled studies, SURPASS-2, -3, and -4.

The assessment of the SURPASS program`s contribution to the CWM indication is done in a common box below the description of SURPASS-4. For a detailed assessment of the individual studies it is referred to the AR for the initial MAA.

SURPASS-1

Study Design

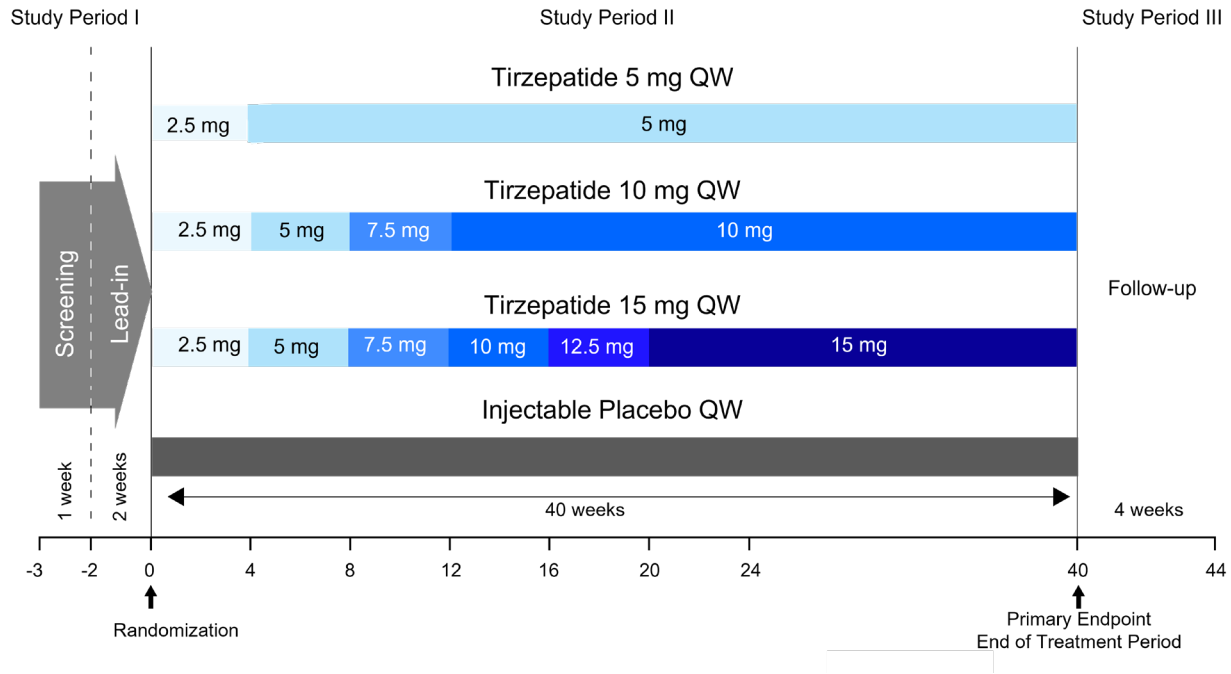
SURPASS-1 was a 40-week, placebo-controlled study, designed to examine the efficacy and safety of tirzepatide versus placebo in participants who had inadequate glycaemic control with diet and exercise alone and were naive to diabetes injectable therapy and had not been treated with any oral OAMs during the 3 months preceding the start of the study.

The design of SURPASS-1 included:

- an approximately 3-week screening and lead-in period (Study Period I)
- a 40-week treatment period (Study Period II), and
- a 4-week safety follow-up period (Study Period III).

The following figure illustrates the study design, including the dose-escalation scheme.

Figure 16. Study design



Abbreviation: QW = once weekly.

SURPASS-1 study design

Baseline Demographics and Clinical Characteristics

Table 30. Key Participant Demographics and Clinical Characteristics at Baseline in SURPASS-1; participants with Obesity or Overweight

Attribute	**Placebo (N=85)**	**TZP 5 mg (N=97)**	**TZP 10 mg (N=94)**	**TZP 15 mg (N=95)**	**Total (N=371)**
Age (years), mean ± SD	53.0 ± 13.2	52.5 ± 11.5	55.6 ± 10.9	51.1 ± 12.0	53.0 ± 12.0
Age Category 1 (years), n (%)					
<65	65 (76.5)	78 (80.4)	70 (74.5)	83 (87.4)	296 (79.8)
≥65	20 (23.5)	19 (19.6)	24 (25.5)	12 (12.6)	75 (20.2)
Age Category 2 (years), n (%)					
<75	82 (96.5)	97 (100.0)	92 (97.9)	94 (98.9)	365 (98.4)
≥75	3 (3.5)	0	2 (2.1)	1 (1.1)	6 (1.6)
Female, n (%)	50 (58.8)	57 (58.8)	41 (43.6)	46 (48.4)	194 (52.3)
Male, n (%)	35 (41.2)	40 (41.2)	53 (56.4)	49 (51.6)	177 (47.7)
Weight (kg), mean ± SD	91.2 ± 19.0	91.8 ± 20.6	91.4 (18.8)	90.9 ± 16.7	91.3 ± 18.7
Height (cm), mean ± SD	163.1 ± 10.1	164.1 ± 9.9	163.8 ± 10.5	165.0 ± 10.6	164.0 ± 10.2
BMI (kg/m2), mean ± SD	34.1 ± 5.3	34.0 ± 6.6	34.2 ± 7.5	33.3 ± 4.7	33.9 ± 6.1
BMI category (kg/m2), n (%)					
<30	22 (25.9)	34 (35.1)	35 (37.2)	26 (27.4)	117 (31.5)
≥30 to <35	29 (34.1)	30 (30.9)	24 (25.5)	40 (42.1)	123 (33.2)
≥35 to <40	21 (24.7)	20 (20.6)	23 (24.5)	21 (22.1)	85 (22.9)
≥40	13 (15.3)	13 (13.4)	12 (12.8)	8 (8.4)	46 (12.4)
Duration of T2DM (years), mean ± SD	4.2 ± 5.6	4.1 ± 5.1	4.9 ± 5.8	4.2 ± 4.7	4.4 ± 5.3
Dyslipidaemia[a], n (%)	22 (19.1)	35 (28.9)	35 (28.9)	29 (24.0)	121 (25.3)
Hypertension[a], n (%)	65 (56.5)	64 (52.9)	65 (53.7)	60 (49.6)	254 (53.1)
Systolic blood pressure (mmHg), mean ± SD	127.3 ± 14.4	127.7 ± 16.2	128.6 ± 12.9	126.2 ± 14.3	127.5 ± 14.5
Diastolic blood pressure (mmHg), mean ± SD	79.0 ± 8.3	80.6 ± 8.8	79.4 ± 8.0	79.3 ± 8.8	79.6 ± 8.5
Pulse rate (bpm), mean ± SD	74.2 ± 10.4	73.0 ± 8.8	73.3 ± 9.7	74.8 ± 8.6	73.8 ± 9.3
eGFR (CKD-EPI), (mL/min/1.73 m2), mean ± SD	95.1 ± 20.0	97.9 ± 19.7	92.7 ± 18.0	98.4 ± 18.8	96.1 ± 19.2

Abbreviations: BMI = body mass index; CKD-EPI = chronic kidney disease-epidemiology; eGFR = estimated glomerular filtration rate; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; T2DM = type 2 diabetes mellitus; TZP = tirzepatide; a This parameter includes all study participants, not only those with obesity or overweight.

Disposition

The 371 participants with obesity or overweight randomly assigned to treatment in SURPASS-1 received at least one dose of study drug and were included in the mITT population.

In the tirzepatide 5-, 10-, and 15-mg groups,

- 85.3% to 93.8% of participants completed the study, and
- 81.1% to 92.8% of participants completed study drug.

In the placebo group, 84.7% and 84.7% of participants completed the study and study drug, respectively. Overall, the highest percentage of participants across the treatment groups discontinued from the study due to

- withdrawal by subject

-tirzepatide: 1.0% to 9.5%, and

-placebo: 5.9%, and

- lost to follow-up

-tirzepatide: 2.2% to 3.2%, and

-placebo: 4.7%.

Results Summary

Three participants from the mITT population (1 randomly assigned to tirzepatide 15 mg, 2 randomly assigned to placebo) discontinued study drug due to inadvertent enrollment and were not included in the efficacy analysis set or the full analysis set.

Change in Body Weight

Tirzepatide 5, 10, and 15 mg significantly reduced body weight from baseline at 40 weeks compared with placebo, using the treatment-regimen and efficacy estimands. Significantly higher percentages of participants randomly assigned to each dose of tirzepatide compared with placebo achieved body weight reductions of ≥5%, ≥10%, or ≥15%, using the treatment-regimen and efficacy estimands. Participants receiving tirzepatide 15 mg also achieved significant body weight reductions of ≥20%, using both estimands.

Table 31. Summary of Body Weight Measures in SURPASS-1; mITT Population; participants with Obesity or Overweight; Full Analysis Set; Efficacy Analysis Set

Parameter	**Placebo (N=83)**	**TZP 5 mg (N=97)**	**TZP 10 mg (N=94)**	**TZP 15 mg (N=94)**
Body Weight at baseline (kg)				

Parameter	Placebo (N=83)	TZP 5 mg (N=97)	TZP 10 mg (N=94)	TZP 15 mg (N=94)
Treatment-Regimen Estimand [a]	91.0	91.8	91.4	91.1
Efficacy Estimand [b]	90.9	91.8	90.8	91.4
Body Weight Change at Week 40 (%)				
Treatment-Regimen Estimand [a]				
Percent change from baseline	-1.3	-7.3†††	-8.6†††	-9.3†††
Difference in percent change from placebo (95% CI)	N/A	-6.0### (-7.9, -4.1)	-7.3### (-9.2, -5.4)	-8.0### (-10.0, -6.1)
Efficacy Estimand [b]				
Percent change from baseline	-0.9	-7.9†††	-9.4†††	-11.1†††
Difference in percent change from placebo (95% CI)	N/A	-7.0### (-9.0, -5.0)	-8.6### (-10.6, -6.6)	-10.2### (-12.3, -8.2)
Percentage of participants with Weight Reduction ≥5% at Week 40 (%)				
Treatment-Regimen Estimand [c]	13.96	62.60###	70.34###	61.24###
Efficacy Estimand [d]	13.41	67.01###	76.92###	73.63###
Percentage of participants with Weight Reduction ≥10% at Week 40 (%)				
Treatment-Regimen Estimand [c]	0.13	27.85##	35.19##	38.36##
Efficacy Estimand [d]	1.22	29.90###	39.56###	47.25###
Percentage of participants with Weight Reduction ≥15% at Week 40 (%)				
Treatment-Regimen Estimand [c]	0	11.34e###	17.02e###	23.40e###
Efficacy Estimand [d]	0	12.37#	18.68##	25.27##
Percentage of participants with Weight Reduction ≥20% at Week 40 (%)				
Treatment-Regimen Estimand [c]	0	2.06e	6.38e#	15.96e###
Efficacy Estimand [d]	0	3.09	6.59	18.68##

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

a ANCOVA with placebo imputation for missing body weight at 40 weeks.

b MMRM analysis.

c Logistic regression with missing body weight imputed using placebo imputation at 40 weeks.

d Logistic regression with missing body weight imputed using MMRM analysis at 40 weeks.

e Fisher's exact test with placebo multiple imputation.

Note: Shown are least squares means.

#p-Value <0.05, ##p-value <0.01, ###p-value <0.001 versus placebo for objectives not controlled for type 1 error.

†††p-Value <0.001 versus baseline within each treatment group.

Change in Waist Circumference

Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with placebo at 40 weeks, using the treatment-regimen estimand (-3.3, -4.9, and -4.4 cm, respectively; p<0.001). Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with placebo at 40 weeks, using the efficacy estimand (-3.5, -5.2, and -4.9 cm, respectively; p<0.001).

Change in Lipid Parameters

Tirzepatide 5, 10, and 15 mg significantly reduced triglycerides and VLDL-C from baseline at 40 weeks compared with placebo, using the treatment-regimen estimand. Additional improvements in total cholesterol, HDL-C, non-HDL-C, and LDL-C with the tirzepatide 15 mg dose compared with placebo were observed using the treatment-regimen estimand.

Tirzepatide 5, 10, and 15 mg significantly reduced triglycerides, non-HDL-C, VLDL-C, LDL-C, and total cholesterol from baseline at 40 weeks compared with placebo, using the efficacy estimand. Tirzepatide 5 and 15 mg significantly increased HDL-C compared with placebo, using the efficacy estimand.

Systolic blood pressure

Tirzepatide 10 mg was the only dose group that significantly reduced SBP from baseline at 40 weeks compared with placebo in the subpopulation of participants in SURPASS-1 with obesity or overweight, using the treatment-regimen and efficacy estimands (-3.7 and -4.2 mmHg, respectively; p<0.05).

Diastolic blood pressure

Tirzepatide 10 mg was the only dose group that significantly reduced DBP from baseline at 40 weeks compared with placebo in the subpopulation of participants in SURPASS-1 with obesity or overweight, using the treatment-regimen estimand only (-2.4 mmHg; p<0.05).

Percent change from baseline in fasting insulin

Tirzepatide 15 mg significantly reduced fasting insulin from baseline at 40 weeks compared with placebo, using the treatment-regimen estimand (-22.7%; p<0.01). Tirzepatide 5, 10, and 15 mg significantly decreased fasting insulin from baseline at 40 weeks compared with placebo, using the efficacy estimand (-20.1, -20.0, and -27.3%; TZP 5 and 10mg: p<0.05, TZP 15mg: p<0.01).

Change from baseline in HbA1c (%)

Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 40 weeks compared with placebo, using the treatment-regimen (-1.54, -1.54, and -1.63%, respectively; p<0.001) and efficacy (-1.88, -1.87, and -2.15%, respectively; p<0.001) estimands.

Change from baseline in fasting serum glucose

Tirzepatide 5, 10, and 15 mg significantly reduced FSG from baseline at 40 weeks compared with placebo, using the treatment-regimen (-2.2, -2.4, -2.5 mmol/L, respectively; p<0.001) and efficacy (-3.0, -3.3, -3.5 mmol/L, respectively; p<0.001) estimands.

SURPASS-5

Study Design

SURPASS-5 was a 40-week, double-blind, phase 3 study designed to examine the efficacy and safety of tirzepatide versus placebo in participants with T2DM with inadequate glycaemic control on insulin glargine, with or without metformin.

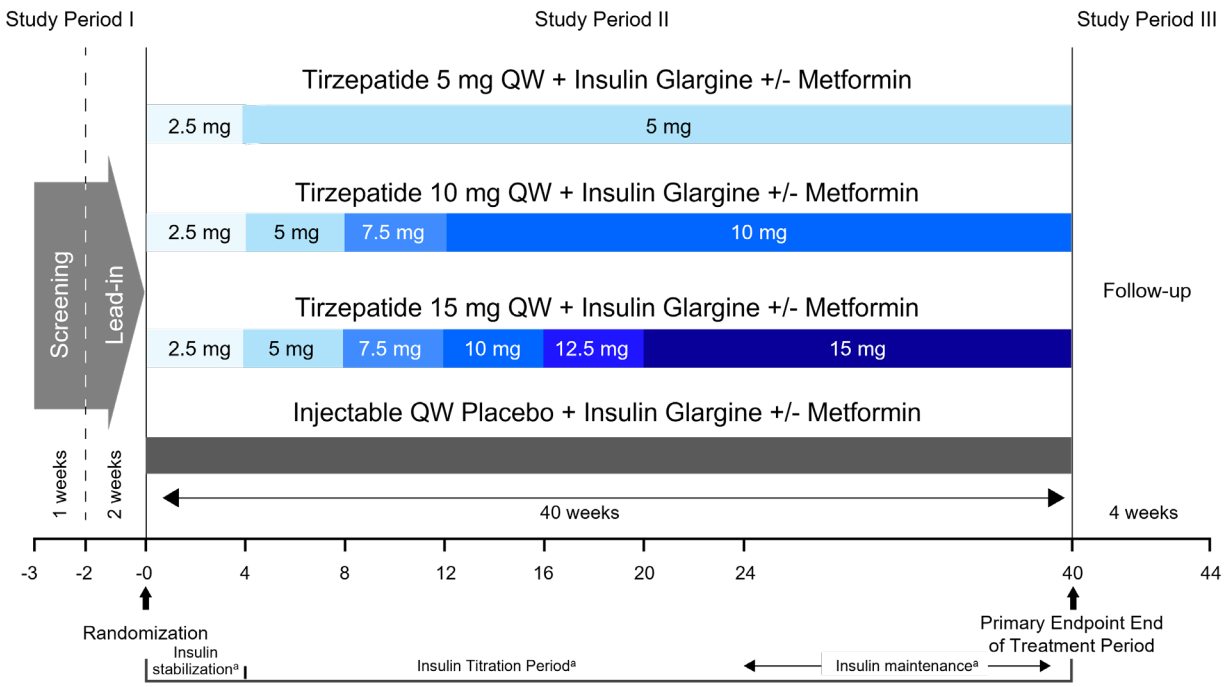
The design of SURPASS-5 included

- an approximately 3-week screening and lead-in period (Study Period I)
- a 40-week treatment period (Study Period II), and
- a 4-week safety follow-up period (Study Period III).

Participants of SURPASS-5 were required to be on stable doses of once-daily insulin glargine (>0.25 U/kg/day or >20U/day) and metformin ≥1500 mg/day (if taken) during the 3-month period prior to Visit 1. To ensure a valid comparison of the randomized study treatments, participants were required to titrate the background insulin glargine using a TTT algorithm (Riddle et al. 2003). Participants were instructed to adjust insulin glargine doses to a target FBG of <100mg/dL (5.5 mmol/L).

The following figure illustrates the study design, including dose-escalation scheme.

Figure 17. Study design



Abbreviation: QW = once weekly.

a "Insulin stabilization" refers to the first 4 weeks after randomization, with restricted insulin dose adjustments. The "Insulin Titration Period" refers to Weeks 4 to 40 (end of treatment/end of study), with

unrestricted insulin dose adjustments. "Insulin maintenance" refers to Weeks 24 to 40 (end of treatment/end of study), within the Insulin Titration Period, when insulin glargine dose is expected to be stable.

SURPASS-5 study design

Baseline Demographics and Clinical Characteristics

Table 32. Key Participant Demographics and Clinical Characteristics at Baseline in SURPASS-5 participants with Obesity or Overweight; all Randomized Population

Attribute	**Placebo (N=99)**	**TZP 5 mg (N=105)**	**TZP 10 mg (N=100)**	**TZP 15 mg (N=103)**	**Total (N=407)**
Age (years), mean ± SD	59.5 ± 9.6	61.5 ± 10.0	60.1 ± 10.5	60.5 ± 10.3	60.4 ± 10.1
Age Category 1 (years), n (%)					
<65	69 (69.7)	56 (53.3)	59 (59.0)	61 (59.2)	245 (60.2)
≥65	30 (30.3)	49 (46.7)	41 (41.0)	42 (40.8)	162 (39.8)
Age Category 2 (years), n (%)					
<75	95 (96.0)	97 (92.4)	92 (92.0)	101 (98.1)	385 (94.6)
≥75	4 (4.0)	8 (7.6)	8 (8.0)	2 (1.9)	22 (5.4)
Female, n (%)	48 (48.5)	52 (49.5)	40 (40.0)	48 (46.6)	188 (46.2)
Male, n (%)	51 (51.5)	53 (50.5)	60 (60.0)	55 (53.4)	219 (53.8)
Weight (kg), mean ± SD	99.4 ± 20.1	98.4 ± 18.9	99.5 ± 20.3	101.0 ± 20.8	99.5 ± 20.0
Height (cm), mean ± SD	168.3 ± 9.9	168.7 ± 9.1	168.3 ± 10.1	169.9 ± 10.7	168.8 ± 10.0
BMI (kg/m2), mean ± SD	35.0 ± 5.5	34.5 ± 5.6	34.9 ± 5.5	34.8 ± 5.1	34.8 ± 5.4
BMI category (kg/m2), (n%)					
<30	21 (21.2)	25 (23.8)	19 (19.0)	19 (18.4)	84 (20.6)
≥30 to <35	32 (32.3)	38 (36.2)	35 (35.0)	38 (36.9)	143 (35.1)
≥35 to <40	30 (30.3)	28 (26.7)	29 (29.0)	28 (27.2)	115 (28.3)
≥40	16 (16.2)	14 (13.3)	17 (17.0)	18 (17.5)	65 (16.0)
Duration of T2DM (years), mean ± SD	12.5 ± 7.4	14.0 ± 8.2	12.1 ± 5.9	13.1 ± 7.6	12.9 ± 7.3
Dyslipidaemiaa, n (%)	41 (34.2)	47 (40.5)	50 (42.0)	55 (45.8)	193 (40.6)
Hypertensiona, n (%)	96 (80.0)	96 (82.8)	92 (77.3)	89 (74.2)	373 (78.5)

Attribute	Placebo (N=99)	TZP 5 mg (N=105)	TZP 10 mg (N=100)	TZP 15 mg (N=103)	Total (N=407)
Systolic blood pressure (mmHg), mean ± SD	139.6 ± 15.2	137.6 ± 16.5	139.2 ± 14.9	137.7 ± 17.2	138.5 ± 15.9
Diastolic blood pressure (mmHg), mean ± SD	82.3 ± 10.5	79.7 ± 11.8	81.7 ± 10.1	80.0 ± 11.2	80.9 ± 10.9
Pulse rate (bpm), mean ± SD	75.6 ± 10.6	75.6 ± 12.4	74.4 ± 10.7	75.5 ± 11.8	75.3 ± 11.4
eGFR (CKD-EPI), (mL/min/1.73 m2), mean ± SD	85.9 ± 18.3	85.8 ± 18.6	87.7 ± 18.9	85.0 ± 17.5	86.1 ± 18.3

Abbreviations: BMI = body mass index; CKD-EPI = chronic kidney disease-epidemiology; eGFR = estimated glomerular filtration rate; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

a This parameter includes all study participants, not only those with obesity or overweight.

Disposition

The 407 participants with obesity or overweight randomly assigned to treatment in SURPASS-5 received at least one dose of study drug and were included in the mITT population. In the tirzepatide 5-, 10-, and 15-mg groups,

- 92.2% to 98.0% of participants completed the study, and
- 82.5% to 92.0% of participants completed study drug.

In the placebo group, 98.0% and 97.0% of participants completed the study and study drug, respectively. Overall, the highest percentage of participants across the treatment groups discontinued from the study due to withdrawal by subject (tirzepatide, 1.0% to 3.9%; placebo, 2.0%). The highest percentages of participants across the treatment groups discontinued from the study drug due to an AE (tirzepatide, 5.7% to 9.7%; placebo, 3.0%) and withdrawal by subject (tirzepatide, 1.0 to 3.9%; placebo, 0%).

Results Summary

Three participants from the mITT population (1 randomly assigned to tirzepatide 10 mg and 2 randomly assigned to tirzepatide 15 mg) discontinued the study drug due to inadvertent enrollment and were not included in the efficacy analysis set or full analysis set.

Change in Body Weight

Tirzepatide 5, 10, and 15 mg significantly reduced body weight from baseline at 40 weeks compared with placebo, using the treatment-regimen and efficacy estimands. Participants randomly assigned to placebo significantly *increased* mean body weight from baseline to 40 weeks, using both estimands.

Compared with placebo, significantly higher percentages of participants randomly assigned to all three doses of tirzepatide achieved body weight reduction of ≥5% and ≥10%, using both estimands. Significantly higher percentages of participants randomly assigned to tirzepatide 10 and 15 mg achieved body weight reduction of ≥15% compared with placebo, using both estimands. Significantly

higher percentages of participants randomly assigned to tirzepatide 15 mg achieved body weight reduction of ≥20% compared with placebo, using both estimands.

Table 33. Summary of Body Weight Measures at Week 40 in SURPASS-5; participants with Obesity or Overweight mITT Population; Full Analysis Set; Efficacy Analysis Set

Parameter	**Placebo (N=99)**	**TZP 5 mg (N=105)**	**TZP 10 mg (N=99)**	**TZP 15 mg (N=101)**
Body Weight at baseline (kg)				
Treatment-Regimen Estimand a	99.4	98.3	99.6	100.7
Efficacy Estimand b	99.3	98.0	100.4	100.9
Body Weight Change at Week 40 (%)				
Treatment-Regimen Estimand a				
Percent change from baseline	1.6†	-5.8†††	-8.1†††	-9.4†††
Difference in percent change from placebo (95% CI)	N/A	-7.3### (-9.1, -5.5)	-9.6### (-11.5, -7.8)	-11.0### (-12.8, -9.2)
Efficacy Estimand b				
Percent change from baseline	1.6†	-6.5†††	-8.5†††	-11.4†††
Difference in percent change from placebo (95% CI)	N/A	-8.1### (-9.9, -6.3)	-10.1### (-11.9, -8.3)	-13.0### (-14.8, -11.2)
Percentage of participants with Weight Reduction ≥5% at Week 40 (%)				
Treatment-Regimen Estimand c	6.1	48.0###	58.6###	70.6###
Efficacy Estimand d	6.1	52.9###	62.1###	84.0###
Percentage of participants with Weight Reduction ≥10% at Week 40 (%)				
Treatment-Regimen Estimand c	0	19.1##	42.4###	40.6###
Efficacy Estimand d	0	21.2##	44.2###	50.0###
Percentage of participants with Weight Reduction ≥15% at Week 40 (%)				
Treatment-Regimen Estimand c	0	6.7e#	22.2e###	23.8e###
Efficacy Estimand d	0	6.7	23.2##	30.0###
Percentage of participants with Weight Reduction ≥20% at Week 40 (%)				
Treatment-Regimen Estimand c	0	3.8e	3.0e	9.9e##
Efficacy Estimand d	0	3.9	3.2	13.0##

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ISE = integrated summary of efficacy; 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, excluding participants who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide.

a ANCOVA with placebo imputation for missing body weight at 40 weeks.

b MMRM analysis.

c Logistic regression with missing body weight imputed using placebo imputation at 40 weeks

d Logistic regression with missing body weight imputed using MMRM analysis at 40 weeks.

e Fisher's exact test with placebo multiple imputation.

Note: Shown are least squares means.

#p-Value <0.05, ##p-value <0.01, ###p-value <0.001 versus placebo for objectives not controlled for type 1 error.

†††p-Value <0.001 versus baseline.

Change in Waist Circumference

Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline at 40 weeks compared with placebo, using the treatment-regimen estimand (-4.2, -8.4, and -8.8 cm, respectively; p<0.001). Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline at 40 weeks compared with placebo, using the efficacy estimand (-4.5, -8.3, and -10.0 cm, respectively; p<0.001).

Change in Lipid Parameters

Tirzepatide 5, 10, and 15 mg significantly reduced triglycerides, total cholesterol, non-HDL-C, LDL-C, and VLDL-C from baseline at 40 weeks compared with placebo, using the treatment-regimen and efficacy estimands. No significant differences were seen for HDL-C for any of the tirzepatide groups compared with placebo.

Systolic blood pressure

Tirzepatide 5, 10, and 15 mg significantly reduced SBP from baseline at 40 weeks compared with placebo, using the treatment-regimen (-4.3, -6.2, and -10.8 mmHg, respectively; TZP 5 mg: p<0.05, TZP 10 and 15 mg: p<0.001) and efficacy estimands (-4.4, -7.0, and -12.3 mmHg, respectively; TZP 5 mg: p<0.05, TZP 10 and 15 mg: p<0.001).

Diastolic blood pressure

Tirzepatide 15 mg significantly reduced DBP from baseline at 40 weeks compared with placebo, using the treatment-regimen and efficacy estimands (-2.2 and -2.6 mmHg, respectively; p<0.05).

Percent change from baseline in fasting insulin

Fasting insulin was not analyzed in this study because all participants received a background of insulin glargine which could confound the assessment of endogenous insulin.

Change from baseline in HbA1c (%)

Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 40 weeks compared with placebo, using the treatment-regimen (-1.26, -1.64, and -1.53%, respectively; p<0.001) and efficacy (-1.33, -1.69, and -1.68%, respectively; p<0.001) estimands.

Change from baseline in fasting serum glucose

Tirzepatide 5, 10, and 15 mg significantly reduced FSG from baseline at 40 weeks compared with placebo, using the treatment-regimen (-1.12, -1.48, -1.32 mmol/L, respectively; p<0.001) and efficacy (-1.28, -1.68, -1.63 mmol/L, respectively; p<0.001) estimands.

SURPASS-2

Study Design

SURPASS-2 was a 40-week Phase 3 study designed to examine the efficacy and safety of tirzepatide versus semaglutide 1 mg once weekly in participants with T2DM who had inadequate glycaemic control with metformin alone. Semaglutide 1 mg once weekly was the highest dose of semaglutide available at the time that SURPASS-2 was designed and initiated.

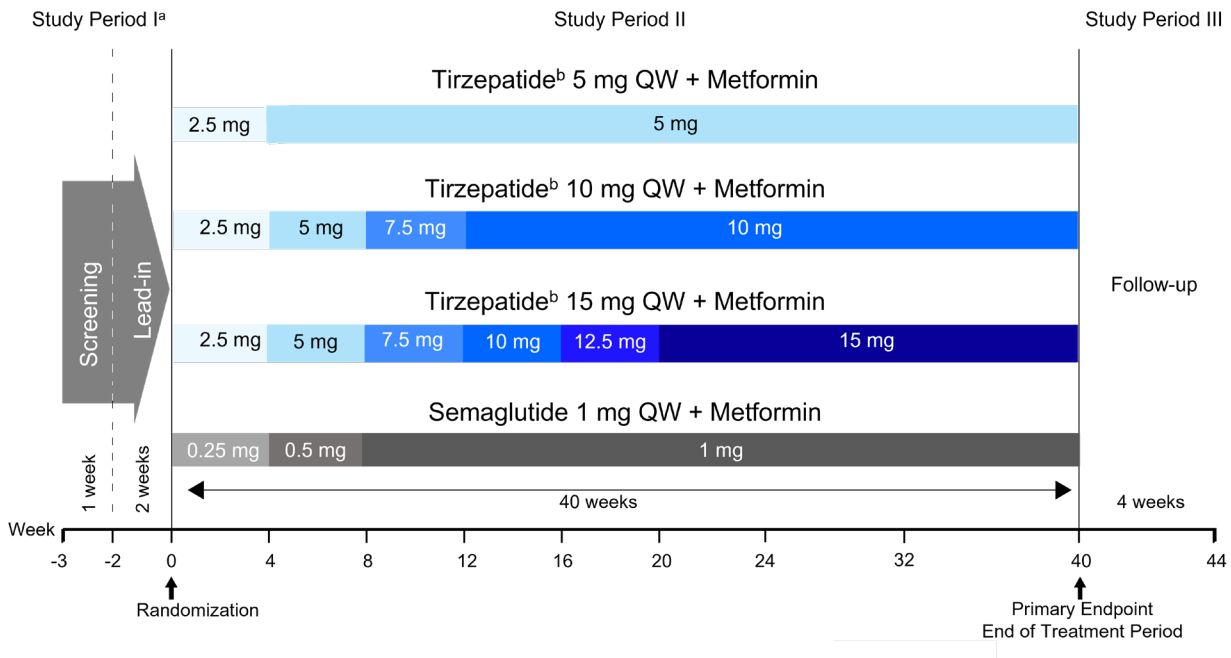
The design of SURPASS-2 included

- an approximately 3-week screening and lead-in period (Study Period I)
- a 40-week treatment period (Study Period II), and
- a 4-week safety follow-up period (Study Period III).

Participants enrolled in SURPASS-2 were required to be on stable doses of metformin ≥1500 mg/day for at least three months prior to screening, during the screening and lead-in period, and throughout the treatment period.

The figure below illustrates the study design, including dose-escalation scheme. The open-label design was used for this study because of the differences in devices and dose-escalation schemes used for tirzepatide and semaglutide 1 mg.

Figure 18. Study design



Abbreviation: QW = once weekly.

a Stable doses of metformin ≥1500 mg/day for at least 3 months prior to Visit 1 and during the screening and lead-in periods. b All tirzepatide doses were double-blinded.

SURPASS-2 study design

Baseline Demographics and Clinical Characteristics

Table 34. Key Participant Demographics and Clinical Characteristics at Baseline in SURPASS-2 Participants with Obesity or Overweight; all Randomized Population

Attribute	**Sema 1 mg (N=422)**	**TZP 5 mg (N=415)**	**TZP 10 mg (N=417)**	**TZP 15 mg (N=416)**	**Total (N=1670)**
Age (years), mean ± SD	56.5 ± 10.7	56.0 ± 10.1	56.9 ± 10.4	55.5 ± 10.4	56.2 ± 10.4
Age Category 1 (years), n (%)					
<65	317 (75.1)	321 (77.3)	313 (75.1)	333 (80.0)	1284 (76.9)
≥65	105 (24.9)	94 (22.7)	104 (24.9)	83 (20.0)	386 (23.1)
Age Category 2 (years), n (%)					
<75	412 (97.6)	407 (98.1)	408 (97.8)	409 (98.3)	1636 (98.0)
≥75	10 (2.4)	8 (1.9)	9 (2.2)	7 (1.7)	34 (2.0)
Female, n (%)	221 (52.4)	229 (55.2)	209 (50.1)	231 (55.5)	890 (53.3)
Male, n (%)	201 (47.6)	186 (44.8)	208 (49.9)	185 (44.5)	780 (46.7)
Weight (kg), mean ± SD	96.2 ± 20.6	95.5 ± 21.2	97.8 ± 22.0	96.8 ± 21.2	96.6 ± 21.2
Height (cm), mean ± SD	165.7 ± 11.7	165.2 ± 10.3	166.0 ± 10.2	164.7 ± 10.3	165.4 ± 10.6
BMI (kg/m2), mean ± SD	35.1 ± 7.0	34.9 ± 6.6	35.3 ± 6.2	35.6 ± 6.8	35.2 ± 6.7
BMI category (kg/m2), n (%)					
<30	97 (23.0)	85 (20.5)	81 (19.4)	81 (19.5)	344 (20.6)
≥30 to <35	157 (37.2)	168 (40.5)	155 (37.2)	156 (37.5)	636 (38.1)
≥35 to <40	98 (23.2)	93 (22.4)	97 (23.3)	95 (22.8)	383 (22.9)
≥40	70 (16.6)	69 (16.6)	84 (20.1)	84 (20.2)	307 (18.4)
Duration of T2DM (years), mean ± SD	7.9 ± 5.6	8.8 ± 6.8	8.3 ± 5.9	8.4 ± 6.8	8.4 ± 6.3
Dyslipidaemia[a], n (%)	181 (38.6)	171 (36.4)	180 (38.4)	163 (34.7)	695 (37.0)

Attribute	Sema 1 mg (N=422)	TZP 5 mg (N=415)	TZP 10 mg (N=417)	TZP 15 mg (N=416)	Total (N=1670)
Hypertension[a], n (%)	296 (63.1)	302 (64.3)	295 (62.9)	303 (64.5)	1196 (63.7)
Systolic blood pressure (mmHg), mean ± SD	130.2 ± 13.1	130.8 ± 14.4	132.0 ± 13.5	131.0 ± 14.6	131.0 ± 13.9
Diastolic blood pressure (mmHg), mean ± SD	79.7 ± 8.6	79.1 ± 9.0	80.7 ± 9.5	79.4 ± 9.1	79.7 ± 9.1
Pulse rate (bpm), mean ± SD	75.1 ± 10.2	75.2 ± 9.4	74.9 ± 10.7	74.3 ± 10.0	74.9 ± 10.1
eGFR (CKD-EPI), (mL/min/1.73 m2), mean ± SD	95.6 ± 17.7	96.8 ± 17.4	95.6 ± 16.6	96.4 ± 17.0	96.1 ± 17.2

Abbreviations: BMI = body mass index; CKD-EPI = chronic kidney disease-epidemiology; eGFR = estimated glomerular filtration rate; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; Sema = semaglutide 1 mg; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

a This parameter includes all study participants, not only those with obesity or overweight.

Disposition

The 1670 participants with obesity or overweight randomly assigned to treatment in SURPASS-2 received at least 1 dose of study drug and were included in the mITT population.

In the tirzepatide 5-, 10-, and 15-mg groups,

- 94.2% to 95.7% of participants completed the study, and
- 88.0% to 91.8% of participants completed study drug.

In the semaglutide 1-mg group, 94.8% and 91.5% of participants completed the study and study drug, respectively.

Overall, the highest percentages of participants across the treatment groups discontinued from the study due to

- lost to follow-up
    - tirzepatide: 1.2% to 1.6%, and
    - semaglutide: 2.6%, and
- withdrawal by subject
    - tirzepatide: 1.4% to 1.7%, and
    - semaglutide: 0.9%.

The highest percentages of participants across the treatment groups discontinued from study drug due to an AE (tirzepatide, 4.6% to 7.0%; semaglutide, 3.6%) and withdrawal by subject (tirzepatide, 1.4%; semaglutide, 1.7%).

Results Summary

One participant from the mITT population (randomly assigned to semaglutide 1 mg) discontinued study drug due to inadvertent enrollment and was not included in the efficacy analysis set or the full analysis set.

Change in Body Weight

Tirzepatide 5, 10, and 15 mg significantly reduced body weight from baseline at 40 weeks compared with semaglutide 1 mg, using the treatment-regimen and efficacy estimands. Significantly higher percentages of participants randomly assigned to each dose of tirzepatide compared with semaglutide 1 mg achieved body weight reductions of ≥5%, ≥10%, ≥15%, or ≥20%, using both estimands.

Table 35. Summary of Body Weight Measures at Week 40 in SURPASS-2; participants with Obesity or Overweight; mITT Population; Full Analysis Set; Efficacy Analysis Set

Parameter	**Sema 1 mg (N=421)**	**TZP 5 mg (N=415)**	**TZP 10 mg (N=417)**	**TZP 15 mg (N=416)**
Body Weight at baseline (kg)				
Treatment-Regimen Estimand[a]	96.2	95.5	97.8	96.8
Efficacy Estimand[b]	96.3	95.5	97.9	96.9
Body Weight Change (%)				
Treatment-Regimen Estimand[a]				
Percent change from baseline	-6.1†††	-8.2†††	-10.2†††	-12.0†††
Percent change difference from Sema 1 mg (95% CI)	N/A	-2.0### (-3.0, -1.0)	-4.0### (-5.0, -3.0)	-5.9### (-6.9, -4.9)
Efficacy Estimand[b]				
Percent change from baseline	-6.6†††	-8.5†††	-11.0†††	-13.2†††
Percent change difference from Sema 1 mg (95% CI)	N/A	-1.9### (-2.9, -0.9)	-4.4### (-5.4, -3.4)	-6.5### (-7.5, -5.5)
Percentage of participants with Weight Reduction ≥5% at Week 40 (%)				
Treatment-Regimen Estimand[c]	53.4	64.3##	75.7###	79.5###
Efficacy Estimand[d]	58.0	67.9##	81.6###	85.9###
Percentage of participants with Weight Reduction ≥10% at Week 40 (%)				
Treatment-Regimen Estimand[c]	22.7	34.1###	47.2###	58.0###
Efficacy Estimand[d]	24.0	35.3###	52.7###	65.0###
Percentage of participants with Weight Reduction ≥15% at Week 40 (%)				
Treatment-Regimen Estimand[c]	7.2	14.7###	24.8###	37.5###
Efficacy Estimand[d]	7.4	15.0###	27.9###	40.4###

Parameter	Sema 1 mg (N=421)	TZP 5 mg (N=415)	TZP 10 mg (N=417)	TZP 15 mg (N=416)
Percentage of participants with Weight Reduction ≥20% at Week 40 (%)				
Treatment-Regimen Estimand[c]	1.5	6.8###	8.7###	16.8###
Efficacy Estimand[d]	1.4	6.9###	10.1###	18.3###

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ISE = integrated summary of efficacy; 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, excluding participants who discontinued study drug due to inadvertent enrollment; N/A = not applicable; Sema = semaglutide 1 mg; TZP = tirzepatide.

a ANCOVA with retrieved dropout imputation for missing body weight at 40 weeks.

b MMRM analysis.

c Logistic regression with missing body weight imputed using retrieved dropout imputation at 40 weeks.

d Logistic regression with missing body weight imputed using an MMRM analysis at 40 weeks.

Note: Shown are least squares means.

##p-Value <0.01, ###p-value <0.001 versus Sema 1 mg for objectives not controlled for type 1 error.

†††p-Value <0.001 versus baseline.

Change in Waist Circumference

Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with semaglutide 1 mg at 40 weeks, using the treatment-regimen estimand (-1.6, -3.5, and -3.8 cm, respectively; TZP 5 mg: $p<0.05$, TZP 10 and 15 mg: $p<0.001$).

Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with semaglutide 1 mg at 40 weeks, using the efficacy estimand (-1.5, -4.2, and -4.3 cm, respectively; TZP 5 mg: $p<0.05$, TZP 10 and 15mg: $p<0.001$).

Change in Lipid Parameters

Tirzepatide 5, 10, and 15 mg significantly reduced triglycerides and VLDL-C from baseline at 40 weeks compared with semaglutide 1 mg, using the treatment-regimen estimand. Tirzepatide 10 and 15 mg significantly increased HDL-C compared with semaglutide 1 mg, using the treatment-regimen estimand. No significant differences were observed between any of the tirzepatide groups and the semaglutide 1-mg group for non-HDL-C, LDL-C, or total cholesterol, using the treatment-regimen estimand.

Tirzepatide 5, 10, and 15 mg significantly reduced triglycerides and VLDL-C and increased HDL-C from baseline at 40 weeks compared with semaglutide 1 mg, using the efficacy estimand. No significant differences were observed between any of the tirzepatide groups and the semaglutide 1-mg group for non-HDL-C, LDL-C, or total cholesterol, using the efficacy estimand.

Systolic blood pressure

Tirzepatide 15 mg significantly reduced SBP from baseline at 40 weeks compared with semaglutide 1 mg in the subpopulation of participants in SURPASS-2 with obesity or overweight, using the treatment-regimen estimand (-2.7 mmHg; p<0.01).

Tirzepatide 10 and 15 mg significantly reduced SBP from baseline at 40 weeks compared with semaglutide 1 mg in the subpopulation of participants in SURPASS-2 with obesity or overweight, using the efficacy estimand (-1.8 and -3.3 mmHg, respectively; TZP 10 mg: p<0.05, TZP 15 mg: p<0.001).

Diastolic blood pressure

Tirzepatide 10 and 15 mg significantly reduced DBP from baseline at 40 weeks compared with semaglutide 1 mg in the subpopulation of participants in SURPASS-2 with obesity or overweight, using the treatment-regimen estimand (-1.3 and -1.7 mmHg, respectively; TZP 10mg: p<0.05, TZP 15mg: p<0.01).

Tirzepatide 10 and 15 mg significantly reduced DBP from baseline at 40 weeks compared with semaglutide 1 mg in the subpopulation of participants in SURPASS-2 with obesity or overweight, using the efficacy estimand (-1.4 and -1.9 mmHg, respectively; TZP 10 mg: p<0.05, TZP 15 mg: p<0.01).

Percent change from baseline in fasting insulin

Tirzepatide 5, 10 and 15 mg significantly reduced fasting insulin from baseline at 40 weeks compared with semaglutide 1 mg, using the treatment-regimen estimand (-11.4, -13.5, and -19.9%, respectively; TZP 5 mg: p<0.05, TZP 10 mg: p<0.01, TZP 15 mg: p<0.001). Tirzepatide 10 and 15 mg significantly reduced fasting insulin from baseline at 40 weeks compared with semaglutide 1 mg, using the efficacy estimand (-14.9% and -19.7%, respectively; p<0.001).

Change from baseline in HbA1c (%)

Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 40 weeks compared with semaglutide 1 mg, using the treatment-regimen estimand (-0.15%, -0.38%, and -0.50%, respectively; TZP 5 mg: p<0.05, TZP 10 and 15 mg: p<0.001). Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 40 weeks compared with semaglutide 1 mg, using the efficacy estimand (-0.23%, -0.51%, and -0.64%, respectively; p<0.001).

Change from baseline in fasting serum glucose

Tirzepatide 5, 10, and 15 mg significantly reduced FSG from baseline at 40 weeks compared with semaglutide 1 mg, using the treatment-regimen (-0.32, -0.59, and -0.66 mmol/L, respectively; TZP 5 mg: p<0.05, TZP 10 and 15 mg, p<0.001) and efficacy (-0.44, -0.80, and -0.86 mmol/L, respectively; p<0.001) estimands.

Change in Patient-Reported Outcome Measures

IWQOL-Lite-CT

SURPASS-2 was the only SURPASS study providing primary support for the CWM indication that included the IWQOL-Lite-CT.

At Week 40, statistically significantly greater improvements in IWQOL-Lite-CT total score, Physical Function composite score, and Physical composite scores were observed for tirzepatide 5, 10, and 15 mg compared with semaglutide 1mg among participants with obesity or overweight with T2DM in SURPASS-2. The Psychosocial composite score improved significantly with tirzepatide 15 mg compared with semaglutide 1 mg in SURPASS-2.

SURPASS-3

Study Design

SURPASS-3 was a 52-week, Phase 3 study designed to examine the efficacy and safety of tirzepatide versus insulin degludec in participants with T2DM who had inadequate glycaemic control with metformin, with or without an SGLT-2i.

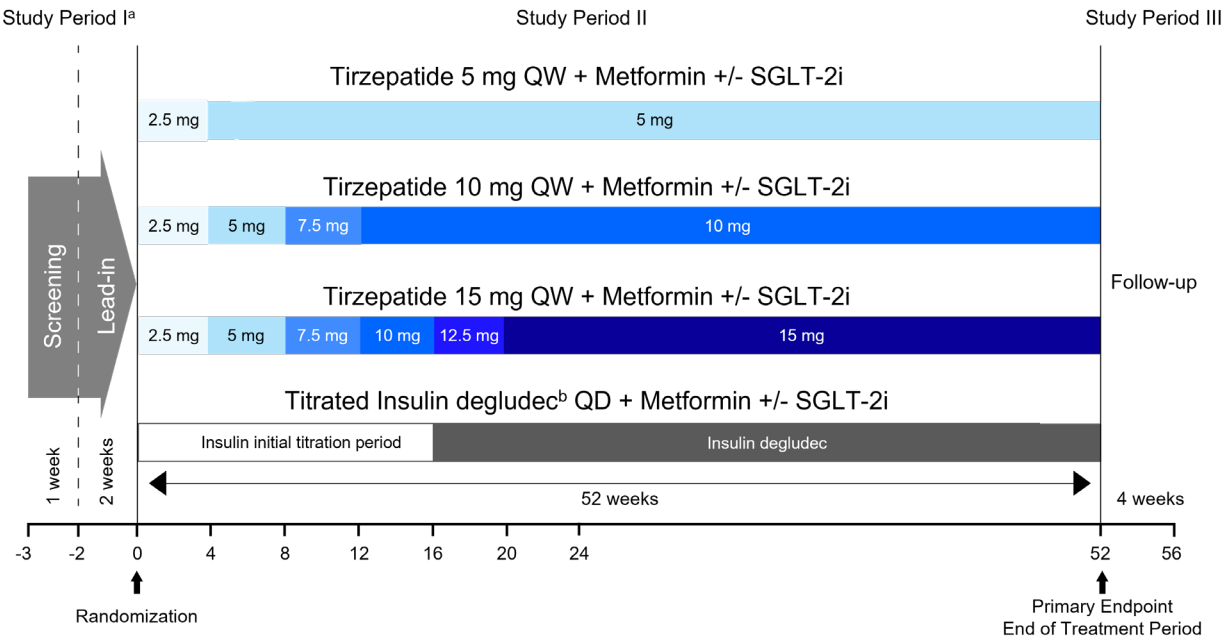
The design of SURPASS-3 included

- an approximately 3-week screening and lead-in period (Study Period I)
- a 52-week treatment period (Study Period II), and
- a 4-week safety follow-up period (Study Period III).

Participants enrolled in SURPASS-3 were required to be on stable doses of metformin ≥1500 mg/day and SGLT-2i (if used) for at least 3 months prior to Visit 1, during the screening and lead-in period, and throughout the treatment period. To ensure a valid comparison of the randomized study treatments, participants were required to titrate insulin degludec using a TTT algorithm. The initial dose of insulin degludec was 10 IU/day ideally at bedtime, titrated to a FBG <90 mg/dL (<5.0 mmol/L) (Philis-Tsimikas et al. 2013; Aroda et al. 2016; Pan et al. 2016).

The figure below illustrates the study design, including the dose-escalation scheme. The open-label design was used for this study because of the different dosing frequencies, dose-escalation (tirzepatide) or titration (insulin degludec) schemes, and injection devices for tirzepatide and insulin degludec.

Figure 19. Study design



Abbreviations: FBG = fasting blood glucose; QD = once-daily; QW = once weekly; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; TTT = treat-to-target.

a Stable doses of metformin (≥1500 mg/day) ± SGLT-2i for ≥3 months prior to Visit 1 and during the screening/lead-in period.

b The starting dose of insulin degludec was 10 IU/day ideally at bedtime, titrated to an FBG <90 mg/dL, following a TTT algorithm.

SURPASS-3 study design

Baseline Demographics and Clinical Characteristics

Table 36. Key Participant Demographics and Clinical Characteristics at Baseline in SURPASS-3; participants with Obesity or Overweight; all Randomized Population

Attribute	**Insulin Degludec (N=316)**	**TZP 5 mg (N=315)**	**TZP 10 mg (N=309)**	**TZP 15 mg (N=315)**	**Total (N=1255)**
Age (years), mean ± SD	57.2 ± 10.2	56.9 ± 10.1	57.0 ± 9.7	56.8 ± 9.8	57.0 ± 9.9
Age Category 1 (years), n (%)					
<65	237 (75.0)	241 (76.5)	236 (76.4)	235 (74.6)	949 (75.6)
≥65	79 (25.0)	74 (23.5)	73 (23.6)	80 (25.4)	306 (24.4)
Age Category 2 (years), n (%)					
<75	308 (97.5)	308 (97.8)	302 (97.7)	308 (97.8)	1226 (97.7)
≥75	8 (2.5)	7 (2.2)	7 (2.3)	7 (2.2)	29 (2.3)
Female, n (%)	129 (40.8)	144 (45.7)	147 (47.6)	139 (44.1)	559 (44.5)
Male, n (%)	187 (59.2)	171 (54.3)	162 (52.4)	176 (55.9)	696 (55.5)
Weight (kg), mean ± SD	97.03 ± 19.86	97.37 ± 17.87	97.15 ± 19.15	98.54 ± 19.57	97.52 ± 19.11
Height (cm), mean ± SD	167.46 ± 10.19	167.60 ± 10.02	167.29 ± 9.61	168.05 ± 9.72	167.60 ± 9.88
BMI (kg/m2), mean ± SD	34.50 ± 5.66	34.63 ± 5.46	34.66 ± 5.81	34.78 ± 5.70	34.64 ± 5.65
BMI category (kg/m2), n (%)					
<30	73 (23.1)	61 (19.4)	65 (21.0)	65 (20.6)	264 (21.0)
≥30 to <35	120 (38.0)	136 (43.2)	119 (38.5)	121 (38.4)	496 (39.5)
≥35 to <40	75 (23.7)	65 (20.6)	80 (25.9)	73 (23.2)	293 (23.3)
≥40	48 (15.2)	53 (16.8)	45 (14.6)	56 (17.8)	202 (16.1)
Duration of T2DM (years), mean ± SD	7.89 ± 5.89	8.00 ± 5.52	8.52 ± 6.70	8.23 ± 6.32	8.16 ± 6.12
Dyslipidaemia[a], n (%)	139 (38.6)	134 (37.4)	124 (34.4)	128 (35.7)	525 (36.5)
Hypertension[a], n (%)	240 (66.7)	247 (69.0)	257 (71.4)	262 (73.0)	1006 (70.0)
Systolic blood pressure (mmHg), mean ± SD	132.39 ± 13.52	130.66 ± 13.12	131.34 ± 13.35	132.34 ± 12.61	131.68 ± 13.16
Diastolic blood pressure (mmHg), mean ± SD	79.69 ± 9.21	78.58 ± 8.33	79.27 ± 8.78	80.10 ± 8.79	79.41 ± 8.79

Attribute	Insulin Degludec (N=316)	TZP 5 mg (N=315)	TZP 10 mg (N=309)	TZP 15 mg (N=315)	Total (N=1255)
Pulse rate (bpm), mean ± SD	75.38 ± 9.99	74.94 ± 9.78	75.10 ± 9.63	75.80 ± 9.37	75.31 ± 9.69
eGFR (CKD-EPI), (mL/min/1.73 m2), mean ± SD	94.53 ± 17.10	95.12 ± 17.62	93.89 ± 17.13	93.79 ± 16.69	94.34 ± 17.13

Abbreviations: BMI = body mass index; CKD-EPI = chronic kidney disease-epidemiology; eGFR = estimated glomerular filtration rate; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

a This parameter includes all study participants, not only those with obesity or overweight.

Disposition

The 1255 participants with obesity or overweight randomly assigned to treatment in SURPASS-3 received at least 1 dose of study drug and were included in the mITT population.

In the tirzepatide 5-, 10-, and 15-mg groups,

- 91.6% to 95.6% of participants completed the study, and
- 84.8% to 88.6% of participants completed study drug.

In the insulin degludec group, 91.8% and 88.3% of participants completed the study and study drug, respectively. Overall, the highest percentages of participants across the treatment groups discontinued from the study due to

- withdrawal by subject

-tirzepatide: 1.9% to 3.2%, and

-insulin degludec: 4.7%, and

- lost to follow-up

-tirzepatide: 0.9% to 2.2%, and
-insulin degludec: 1.6%.

The highest percentages of participants across the treatment groups discontinued from the study drug due to

- an AE

-tirzepatide: 6.3% to 10.2%, and

-insulin degludec, 1.6%, and

- withdrawal by subject

-tirzepatide: 2.2% to 4.2%, and

-insulin degludec: 7.3%.

Results Summary

Two participants from the mITT population (1 randomly assigned to tirzepatide 15 mg and 1 randomly assigned to insulin degludec) discontinued the study drug due to inadvertent enrollment and were not included in the efficacy analysis set or the full analysis set.

Change in Body Weight

Tirzepatide 5, 10, and 15 mg significantly reduced body weight from baseline at 52 weeks compared with insulin degludec, using the treatment-regimen and efficacy estimands. Participants treated with insulin degludec gained weight between baseline and the primary endpoint visit, likely due to the anabolic effects of insulin. Significantly higher percentages of participants randomly assigned to each dose of tirzepatide compared with insulin degludec achieved body weight reductions of ≥5%, ≥10%, ≥15%, and ≥20%, using both estimands.

Table 37. Summary of Body Weight Measures at Week 52 in SURPASS-3; participants with Obesity or Overweight; mITT Population; Full Analysis Set; Efficacy Analysis Set

Parameter	Insulin Degludec (N=315)	TZP 5 mg (N=315)	TZP 10 mg (N=309)	TZP 15 mg (N=314)
Body Weight at baseline (kg)				
Treatment-Regimen Estimand[a]	97.1	97.4	97.2	98.5
Efficacy Estimand[b]	97.4	97.5	97.5	98.6
Body Weight Change at Week 52 (%)				
Treatment-Regimen Estimand[a]				
Percent change from baseline	2.1†††	-7.7†††	-10.5†††	-12.0†††
Difference in percent change from insulin degludec (95% CI)	N/A	-9.8### (-10.9, -8.6)	-12.6### (13.8, -11.4)	-14.1### (-15.3, -12.9)
Efficacy Estimand[b]				
Percent change from baseline	2.5 †††	-8.0†††	-11.5†††	-13.5†††
Difference in percent change from insulin degludec (95% CI)	N/A	-10.5### (-11.5, -9.5)	-14.0### (-15.0, -13.0)	-16.0### (-17.0, -15.0)
Percentage of participants with Weight Reduction ≥5% at Week 52 (%)				
Treatment-Regimen Estimand[c]	8.8	61.0###	74.8###	78.9###
Efficacy Estimand[d]	6.5	64.8###	82.1###	87.7###
Percentage of participants with Weight Reduction ≥10% at Week 52 (%)				
Treatment-Regimen Estimand[c]	3.4	36.5###	51.0###	59.0###
Efficacy Estimand[d]	3.3	38.7###	54.3###	67.3###
Percentage of participants with Weight Reduction ≥15% at Week 52 (%)				
Treatment-Regimen Estimand[c]	0.5	11.6##	27.0###	34.8###
Efficacy Estimand[d]	0.0	11.9##	29.1###	40.1###
Percentage of participants with Weight Reduction ≥20% at Week 52 (%)				
Treatment-Regimen Estimand[c]	0.5	5.2#	12.4##	17.8###
Efficacy Estimand[d]	0.00	5.5##	12.6###	20.1###

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ISE = integrated summary of efficacy; 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, excluding participants who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide.

a ANCOVA with retrieved dropout imputation for missing body weight at 52 weeks.

b MMRM analysis.

c Logistic regression with missing body weight imputed using retrieved dropout imputation at 52 weeks.

d Logistic regression with missing body weight imputed using an MMRM analysis at 52 weeks.

Note: Shown are least squares means.

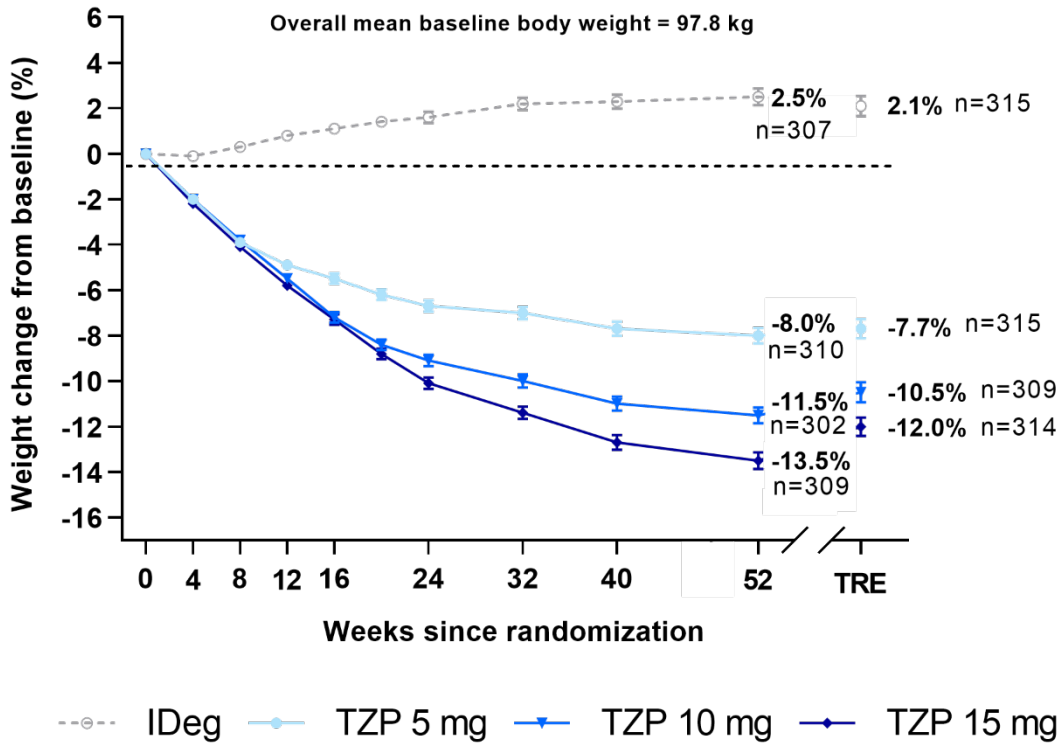
#p-Value <0.05, ##p-value <0.01, ###p-value <0.001 versus insulin degludec for objectives not controlled for type 1 error.

†††p-Value <0.001 versus baseline.

Body weight change over time

Steady decreases in body weight were observed over time for participants of the 3 tirzepatide dose groups in SURPASS-3, with participants of each dose group reaching near-plateaus by the time of the 52-week primary endpoint visit. These results show that participants with obesity or overweight with T2DM continue to have significant and clinically meaningful body weight reductions for at least 1 year from initiation of treatment. Participants treated with insulin degludec gained weight over the same time period.

Figure 20. SURPASS-3 body weight percent change over time (efficacy estimand) and at the primary endpoint visit (efficacy and treatment-regimen estimands)



Abbreviations: ISE = integrated summary of efficacy; MMRM = mixed model for repeated measures; n = number of participants in the modified intent-to-treat population with values at baseline; TRE = treatment-regimen estimand; TZP = tirzepatide.

Note: Values are least-squares means (error bars are standard error) from an MMRM analysis.

Change in Waist Circumference

Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with insulin degludec at 52 weeks, using the treatment-regimen estimand (-7.8, -9.5, and -10.4 cm, respectively; p<0.001). Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with insulin degludec at 52 weeks, using the efficacy estimand (-8.5, -10.8, and -12.0 cm, respectively; p<0.001).

Change in Lipid Parameters

Tirzepatide 10 and 15 mg significantly reduced triglycerides, non-HDL-C, and VLDL-C from baseline at 52 weeks compared with insulin degludec, using the treatment-regimen and efficacy estimands. Additionally, all 3 doses of tirzepatide significantly increased HDL-C at 52 weeks compared with insulin degludec, using both estimands. There was no significant difference in LDL-C and total cholesterol between any of the tirzepatide groups and the insulin degludec group.

Systolic blood pressure

Tirzepatide 5, 10, and 15 mg significantly reduced SBP from baseline at 52 weeks compared with insulin degludec in the subpopulation of participants in SURPASS-3 with obesity or overweight, using the treatment-regimen estimand (-5.6, -6.5, and -5.7 mmHg, respectively; p<0.001). Tirzepatide 5, 10, and 15 mg significantly reduced SBP from baseline at 52 weeks compared with insulin degludec in the subpopulation of participants in SURPASS-3 with obesity or overweight, using the efficacy estimand (-5.3, -7.6, and -6.3 mmHg, respectively; p<0.001).

Diastolic blood pressure

Tirzepatide 5, 10, and 15mg significantly reduced DBP from baseline at 52 weeks compared with insulin degludec in the subpopulation of participants in SURPASS-3 with obesity or overweight, using the treatment-regimen estimand (-2.6, -2.6, and -2.2 mmHg, respectively; TZP 5 and 10 mg: p<0.001, TZP 15 mg: p<0.01).

Tirzepatide 5, 10, and 15 mg significantly reduced DBP from baseline at 52 weeks compared with insulin degludec in the subpopulation of participants in SURPASS-3 with obesity or overweight, using the efficacy estimand (-2.3, -2.9, and -2.5 mmHg, respectively; p<0.001).

Percent change from baseline in fasting insulin

Fasting insulin was not analyzed in this study because some participants received insulin degludec which could confound the assessment of endogenous insulin.

Change from baseline in HbA1c (%)

Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 52 weeks compared with insulin degludec, using the treatment-regimen estimand (-0.57%, -0.78%, and -0.92%, respectively; p<0.001).

Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 52 weeks compared with insulin degludec, using the efficacy estimand (-0.55%, -0.88%, and -1.08%, respectively; p<0.001).

Change from baseline in fasting serum glucose

Tirzepatide 5, 10, and 15mg significantly reduced FSG from baseline at 52 weeks using the treatment-regimen (-2.63, -2.84, and -3.10 mmol/L, respectively; p<0.001) and efficacy (-2.69, -3.07, and -3.35 mmol/L, respectively; p<0.001) estimands. However, tirzepatide did not significantly reduce from baseline mean FSG at 52 weeks compared with insulin degludec.

SURPASS-4

Study Design

SURPASS-4 was designed to examine the efficacy and safety of tirzepatide versus insulin glargine in participants with T2DM and increased CV risk on stable treatment with at least 1 and no more than 3 OAMs comprising metformin, SGLT-2i, sulfonylurea, or a combination. No participants were excluded based on low eGFR values. Increased CV risk was defined as the presence of

- coronary heart disease
- peripheral arterial disease presumed to be of atherosclerotic origin
- cerebrovascular disease presumed to be of atherosclerotic origin
- age ≥50 years, history of chronic kidney disease, and an eGFR <60 mL/min/1.73 m2 (chronic kidney disease-epidemiology) on consecutive measurements (Visits 1 and 2), or
- age ≥50 years and congestive heart failure documented as a history of congestive heart failure, New York Heart Association Functional Classification II to III.

The design of SURPASS-4 included

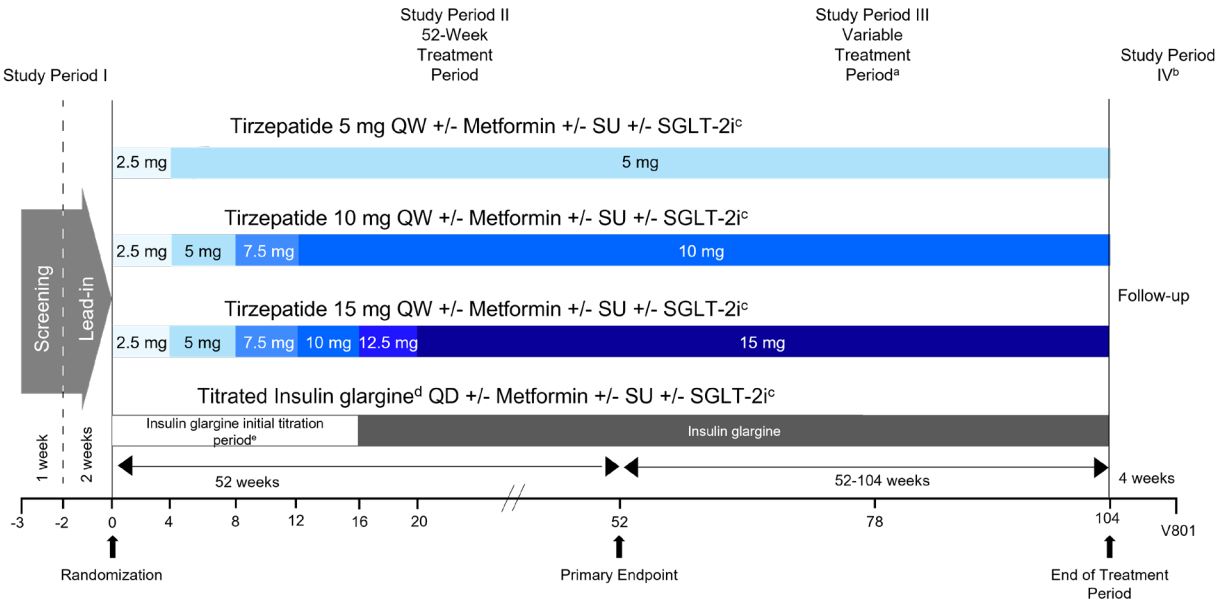
- an approximately 3-week screening and lead-in period (Study Period I)
- a 52-week treatment period (Study Period II)
- a variable treatment period of up to an additional 52 weeks (Study Period III), and
- a 4-week safety follow-up period (Study Period IV).

To ensure a valid comparison of the randomized study treatments, participants were required to titrate insulin glargine using a TTT algorithm. The initial dose of insulin glargine was 10 IU/day, ideally at bedtime, titrated to an FBG <100 mg/dL (<5.6mmol/L).

The figure below illustrates the study design, including dose-escalation scheme. The open-label design was used for this study because of the differences in

- dosing frequencies
- dose-escalation (tirzepatide) or titration (insulin glargine) schemes, and
- injection devices for tirzepatide and insulin glargine.

Figure 21. Study design



Abbreviations: FBG = fasting blood glucose; QD = once-daily; QW = once weekly; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TTT = titrated-to-treat; V = visit.

a The planned duration of treatment for the primary endpoint was 52 weeks, followed by a variable treatment duration of up to but not longer than 104 weeks.

b All participants performed a Visit 801 four weeks after their last treatment visit.

c Participants were on at least 1 and up to 3 oral antihyperglycaemic medications comprising metformin, SU, and SGLT-2i.

d The starting dose of insulin glargine was 10 IU/day at bedtime, titrated to an FBG <100 mg/dL, following a TTT algorithm (Riddle et al. 2003).

e Participants titrated insulin glargine dose in a weekly manner and made the dose decision with the investigator for the first 8 weeks (phone or clinic visit). From Weeks 8 to 16, participants continued the titration by a phone consultation or clinic visit every other week, with 3 weeks between Visits 13 (Week 12) and 14 (Week 15).

Note: // indicates the X-axis is not shown to scale from 20 to 52 weeks.

Baseline Demographics and Clinical Characteristics

Table 38. Key Participant Demographics and Clinical Characteristics at Baseline in SURPASS-4 Participants with Obesity or Overweight; all Randomized Population

Attribute	**Insulin Glargine (N=844)**	**TZP 5 mg (N=277)**	**TZP 10 mg (N=280)**	**TZP 15 mg (N=288)**	**Total (N=1689)**
Age (years), mean ± SD	63.3 ± 8.6	62.4 ± 8.4	63.3 ± 8.6	63.2 ± 8.5	63.2 ± 8.5
Age Category 1 (years), n (%)					

Attribute	Insulin Glargine (N=844)	TZP 5 mg (N=277)	TZP 10 mg (N=280)	TZP 15 mg (N=288)	Total (N=1689)
<65	457 (54.1)	163 (58.8)	148 (52.9)	162 (56.3)	930 (55.1)
≥65	387 (45.9)	114 (41.2)	132 (47.1)	126 (43.8)	759 (44.9)
Age Category 2 (years), n (%)					
<75	763 (90.4)	256 (92.4)	256 (91.4)	262 (91.0)	1537 (91.0)
≥75	81 (9.6)	21 (7.6)	24 (8.6)	26 (9.0)	152 (9.0)
Female, n (%)	313 (37.1)	113 (40.8)	107 (38.2)	117 (40.6)	650 (38.5)
Male, n (%)	531 (62.9)	164 (59.2)	173 (61.8)	171 (59.4)	1039 (61.5)
Weight (kg), mean ± SD	94.00 ± 17.91	93.93 ± 19.81	93.94 ± 17.45	93.32 ± 15.03	93.86 ± 17.70
Height (cm), mean ± SD	166.72 ± 9.78	166.05 ± 10.26	165.91 ± 9.39	166.40 ± 9.82	166.43 ± 9.80
BMI (kg/m2), mean ± SD	33.71 ± 5.12	33.94 ± 5.73	34.03 ± 5.03	33.67 ± 4.49	33.79 ± 5.11
BMI category (kg/m2), n (%)					
<30	223 (26.4)	67 (24.2)	61 (21.8)	61 (21.2)	412 (24.4)
≥30 to <35	342 (40.5)	121 (43.7)	126 (45.0)	132 (45.8)	721 (42.7)
≥35 to <40	181 (21.4)	58 (20.9)	59 (21.1)	69 (24.0)	367 (21.7)
≥40	98 (11.6)	31 (11.2)	34 (12.1)	26 (9.0)	189 (11.2)
Duration of T2DM (years), mean ± SD	11.37 ± 7.29	10.72 ± 7.14	11.57 ± 7.06	11.16 ± 7.02	11.26 ± 7.18
Dyslipidaemia[a], n (%)	546 (54.6)	184 (55.9)	175 (53.4)	183 (54.1)	1088 (54.5)
Hypertension[a], n (%)	884 (88.4)	286 (86.9)	298 (90.9)	296 (87.6)	1764 (88.4)
Systolic blood pressure (mmHg), mean ± SD	134.86 ± 15.63	133.26 ± 14.10	135.68 ± 15.89	134.59 ± 15.18	134.69 ± 15.36
Diastolic blood pressure (mmHg), mean ± SD	78.91 ± 9.63	79.10 ± 8.70	79.06 ± 9.30	78.54 ± 9.21	78.91 ± 9.35
Pulse rate (bpm), mean ± SD	72.80 ± 10.39	72.69 ± 11.04	72.80 ± 10.35	72.57 ± 10.60	72.74 ± 10.52
eGFR (CKD-EPI), (mL/min/1.73 m2), mean ± SD	81.41 ± 21.09	81.12 ± 22.12	81.74 ± 20.49	81.94 ± 20.73	81.51 ± 21.09

Abbreviations: CKD-EPI = chronic kidney disease-epidemiology; BMI = body mass index; eGFR = estimated glomerular filtration rate; N = number of participants in population; n = number of participants in the specified category; SD = standard deviation; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

[a] This parameter includes all study participants, not only those with obesity or overweight.

Disposition

1689 participants with obesity or overweight were randomly assigned to treatment in SURPASS-4, received at least 1 dose of study drug, and were included in the mITT population.

In the tirzepatide 5-, 10-, and 15-mg groups,

- 90.6% to 95.4% of participants completed the study, and
- 86.3% to 88.6% of participants completed study drug.

In the insulin glargine group, 88.6% and 86.4% of participants completed the study and study drug, respectively. Overall, the highest percentages of participants across the treatment groups discontinued from the study due to

- death (tirzepatide, 0.4% to 4.3%; insulin glargine, 3.1%), and
- withdrawal by subject (tirzepatide, 0.4% to 2.4%; insulin glargine, 3.7%).

The highest percentages of participants across the treatment groups discontinued from the study drug due to

- an AE (tirzepatide, 5.8% to 6.8%; insulin glargine, 2.0%), and
- withdrawal by subject (tirzepatide, 1.1% to 2.4%; insulin glargine 4.7%).

Results Summary

Overall, 6 participants from the mITT population discontinued the study drug due to inadvertent enrollment and were not included in the efficacy analysis set or the full analysis set:

- 1 randomly assigned to tirzepatide 5 mg
- 2 randomly assigned to tirzepatide 10 mg
- 1 randomly assigned to tirzepatide 15 mg, and
- 2 randomly assigned to insulin glargine.

Change in Body Weight

Tirzepatide 5, 10, and 15 mg significantly reduced body weight from baseline at the primary endpoint of 52 weeks compared with insulin glargine, using the treatment-regimen and efficacy estimands. Participants treated with insulin glargine gained weight between baseline and the primary endpoint visit, likely due to the anabolic effects of insulin.

The percent body weight reduction was significantly greater with all 3 tirzepatide dose groups compared with insulin glargine starting at Week 4 and persisted through 104 weeks. The insulin glargine group had increases from baseline in body weight at all time points assessed.

Significantly higher percentages of participants randomly assigned to each dose of tirzepatide compared with insulin glargine achieved body weight reductions of ≥5%, ≥10%, ≥15%, or ≥20%, using both estimands.

Table 39. Summary of Body Weight Measures at Week 52 in SURPASS-4; participants with Obesity or Overweight; mITT Population; Full Analysis Set; Efficacy Analysis Set

Parameter	Insulin Glargine (N=842)	TZP 5 mg (N=276)	TZP 10 mg (N=278)	TZP 15 mg (N=287)
Body Weight at baseline (kg)				
Treatment-Regimen Estimand[a]	94.0	93.9	93.9	93.3
Efficacy Estimand[b]	93.9	94.0	94.0	93.3
Body Weight Change at Week 52 (%)				
Treatment-Regimen Estimand[a]				
Percent change from baseline at Week 52	1.7†††	-7.3†††	-10.0†††	-12.2†††
Difference in percent change from insulin glargine (95% CI)	N/A	-9.1### (-10.0, -8.1)	-11.7### (-12.7, -10.7)	-13.9### (-14.8, -13.0)
Efficacy Estimand[b]				
Percent change from baseline at Week 52	2.0†††	-8.0†††	-10.4†††	-13.0†††
Difference in percent change from insulin glargine (95% CI)	N/A	-10.0### (-10.9, -9.1)	-12.5### (-13.4, -11.6)	-15.0### (-15.9, -14.1)
Percentage of participants with Weight Reduction ≥5% at Week 52 (%)				
Treatment-Regimen Estimand[c]	9.5	58.3###	72.9###	78.9###
Efficacy Estimand[d]	8.2	62.0###	75.9###	84.2###
Percentage of participants with Weight Reduction ≥10% at Week 52 (%)				
Treatment-Regimen Estimand[c]	1.8	33.3###	49.7###	60.8###
Efficacy Estimand[d]	1.6	36.9###	51.8###	65.6###
Percentage of participants with Weight Reduction ≥15% at Week 52 (%)				
Treatment-Regimen Estimand[c]	0.5	13.9###	23.1###	34.9###
Efficacy Estimand[d]	0.5	14.6###	23.4###	36.5###
Percentage of participants with Weight Reduction ≥20% at Week 52 (%)				
Treatment-Regimen Estimand[c]	0.3	2.9##	9.8###	19.0###
Efficacy Estimand[d]	0.2	3.3###	9.9###	19.7###

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; ISE = integrated summary of efficacy; 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, excluding participants who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide.

a ANCOVA with retrieved dropout imputation for missing body weight at 52 weeks.

b MMRM analysis.

c Logistic regression with missing body weight imputed using retrieved dropout imputation at 52 weeks.

d Logistic regression with missing body weight imputed using an MMRM analysis at 52 weeks.

Note: Shown are least squares mean.

##p-Value <0.01, ###p-value <0.001 versus insulin glargine for objectives not controlled for type 1 error.

†††p-Value <0.001 versus baseline.

Change in body weight over time

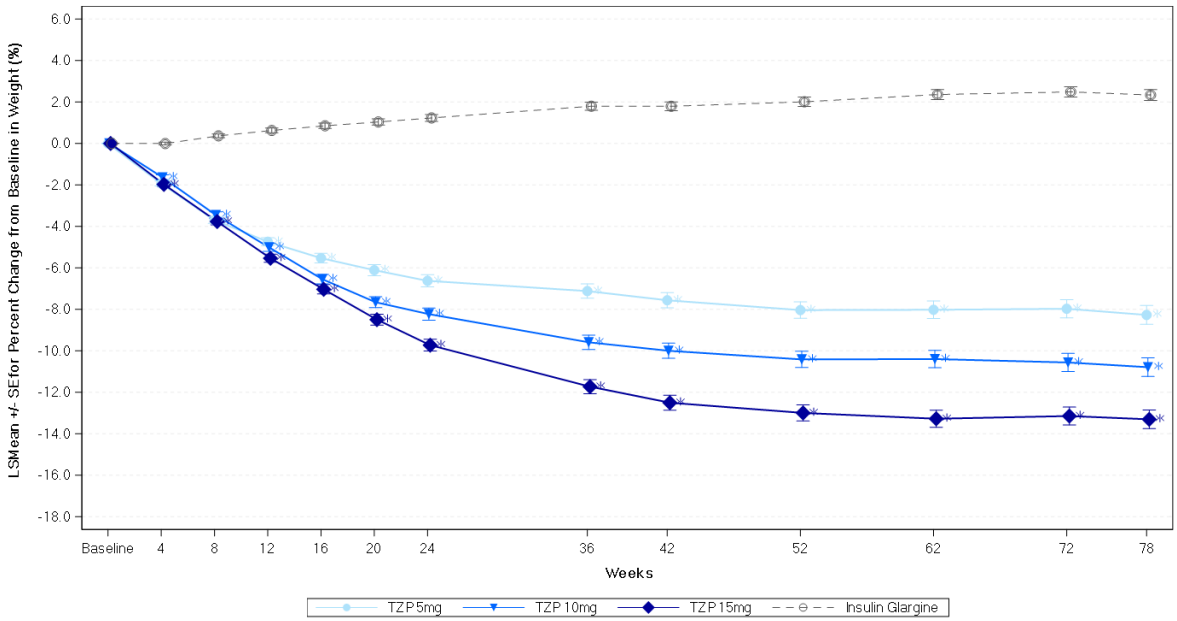
Steady decreases in body weight were observed over time for participants with obesity or overweight in in all dose groups. The effect plateaued at around 52 weeks for the tirzepatide 5- and 10-mg groups (-8.5% and -10.0%, respectively) and at around 62 weeks for the tirzepatide 15 mg group (-13.7%).

The significant reductions in body weight from baseline with tirzepatide compared with insulin glargine started at Week 4. In contrast, the body weight of participants treated with insulin glargine increased from baseline at all time points assessed.

For the subset of participants who reached **78 weeks** (n=1008 [59.7%]), the body weight reductions were maintained (see figure below):

- tirzepatide 5 mg: 166 participants (59.9%)
- tirzepatide 10 mg: 168 participants (60.0%), and
- tirzepatide 15 mg: 166 participants (57.6%).

Figure 22. Plot of estimated mean percent change (%) in body weight from baseline to 78 weeks in SURPASS-4: mITT population (in participants with obesity or overweight who completed 78-week visit), efficacy analysis set.



Abbreviations: LSMean = least squares mean; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; SE = standard error; TZP = tirzepatide.

Note: MMRM analysis.

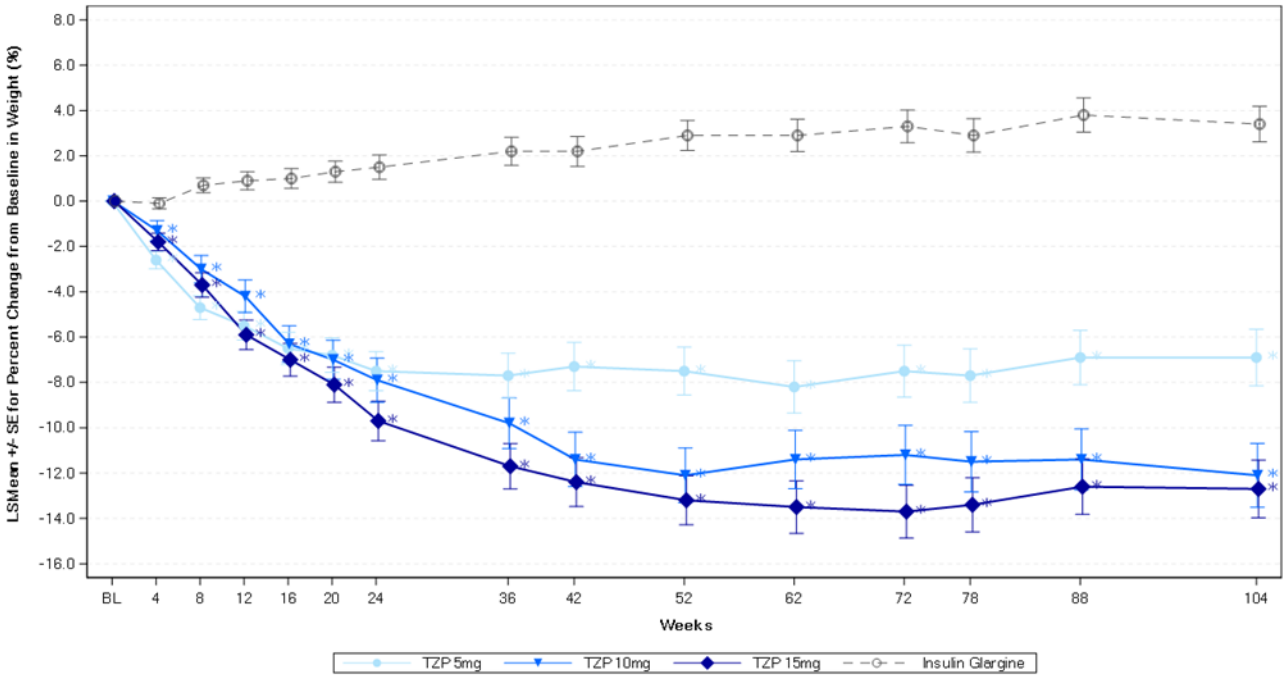
*p-Value <0.05 for tirzepatide versus insulin glargine.

Even fewer participants in SURPASS-4 completed the **104-week visit** (n=176 [10.4%]):

- tirzepatide 5 mg: 33 participants (11.9%)
- tirzepatide 10 mg: 26 participants (9.3%), and
- tirzepatide 15 mg: 32 participants (11.1%).

When percent body weight reduction over time was assessed from baseline to 104 weeks for this subpopulation of participants, steady decreases in body weight were observed over time for these participants with obesity or overweight in the 3 tirzepatide dose groups, with participants reaching a percent body weight reduction that was near-maximal at 62 weeks for the tirzepatide 5 mg group (-8.2%), at 52 weeks for the tirzepatide 10 mg group (-12.1%), and at 72 weeks for the tirzepatide 15-mg group (-13.7%); thereafter, weight loss plateaued or tended to increase slightly (in the 15 mg and 5 mg dose groups Participants treated with insulin glargine steadily gained weight).

Figure 23. Plot of estimated mean percent change (%) in body weight from baseline to 104 weeks in SURPASS-4: mITT population (in participants with obesity or overweight), efficacy analysis set.



Abbreviations: LS = least squares; mITT = modified intent-to-treat; MMRM = mixed model for repeated measures; SE = standard error; TZP = tirzepatide.

Note: MMRM analysis.

*p-Value <0.05 for tirzepatide versus insulin glargine.

Change in Waist Circumference

Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with insulin glargine at 52 weeks, using the treatment-regimen estimand (-7.8, -8.2, and -9.9 cm, respectively; p<0.001). Tirzepatide 5, 10, and 15 mg significantly reduced waist circumference from baseline compared with insulin glargine at 52 weeks, using the efficacy estimand (-8.1, -8.6, and -10.8 cm, respectively; p<0.001).

Change in Lipid Parameters

Tirzepatide 5, 10, and 15 mg significantly reduced triglycerides, non-HDL-C, VLDL-C, LDL-C, and total cholesterol from baseline at 52 weeks compared with insulin glargine, using the treatment-regimen and efficacy estimands. Additionally, tirzepatide 10 and 15 mg significantly increased HDL-C from baseline at 52 weeks compared with insulin glargine using the treatment-regimen estimand, whereas all 3 tirzepatide dose groups significantly increased HDL-C compared with insulin glargine using the efficacy estimand.

Systolic blood pressure

Tirzepatide 5, 10, and 15 mg significantly reduced SBP from baseline at 52 weeks compared with insulin glargine in the subpopulation of participants in SURPASS-4 with obesity or overweight, using the treatment-regimen estimand (-3.4, -4.4, and -5.7 mmHg, respectively; TZP 5 mg: p<0.01, TZP 10 and 15 mg: p<0.001).

Tirzepatide 5, 10, and 15 mg significantly reduced SBP from baseline at 52 weeks compared with insulin glargine in the subpopulation of participants in SURPASS-4 with obesity or overweight, using the efficacy estimand (-4.9, -5.7, and -6.5 mmHg, respectively; p<0.001).

Diastolic blood pressure

Tirzepatide 5, 10, and 15 mg significantly reduced DBP from baseline at 52 weeks compared with insulin glargine in the subpopulation of participants in SURPASS-4 with obesity or overweight, using the treatment-regimen estimand (-1.5, -1.2, and -1.9 mmHg, respectively; TZP 5 and 10 mg: p<0.05, TZP 15 mg: p<0.01).

Tirzepatide 5, 10, and 15 mg significantly reduced DBP from baseline at 52 weeks compared with insulin glargine in the subpopulation of participants in SURPASS-4 with obesity or overweight, using the efficacy estimand (-1.9, -1.2, and -1.7 mmHg, respectively; TZP 5 mg: p<0.001, TZP 10 mg: p<0.05, TZP 15 mg: p<0.01).

Percent change from baseline in fasting insulin

Fasting insulin was not analyzed in this study because some participants received insulin glargine which could confound the assessment of endogenous insulin.

Change from baseline in HbA1c (%)

Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 52 weeks compared with insulin glargine, using the treatment-regimen estimand (-0.76%, -0.96%, and -1.10%, respectively; p<0.001). Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline at 52 weeks compared with insulin glargine, using the efficacy estimand (-0.83%, -1.05%, and -1.20%, respectively; p<0.001).

Change from baseline in fasting serum glucose

Tirzepatide 15 mg significantly reduced FSG from baseline at 52 weeks compared with insulin glargine, using the treatment-regimen (-0.47 mmol/L, respectively; p<0.01) and efficacy (-0.55 mmol/L, respectively; p<0.001) estimands.

2.4.3. Discussion on clinical efficacy

Proposed change

With this type II variation the following indication is proposed to be added:

"…

Weight management

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

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

Design and conduct of the clinical studies

The efficacy of tirzepatide for CWM in adults with overweight (BMI>27kg/m^2) or obesity without T2DM has been investigated in one pivotal study (**SURMOUNT-1**). As supportive data, the 36-week open-label lead-in period data of **SURMOUNT-4**, a phase 3 randomised withdrawal study in participants with obesity or overweight without diabetes mellitus has been submitted. This study is ongoing. Post-hoc subgroup analyses of the patients with BMI above 27kg/m^2 included in the **SURPASS 1-5** studies, the pivotal studies for the T2DM indication, further support the CWM indication.

Study designs

SURMOUNT-1 was a phase 3, double-blind study that randomly assigned participants to receive once-weekly, injectable placebo or tirzepatide 5, 10, or 15 mg to investigate weight loss. Randomisation was stratified based on glycaemic status at baseline (normoglycaemia or pre-diabetes). Results of the 72-week double-blind treatment period have been reported with this submission. The double-blind period was followed by a 4-week follow-up period for patients without prediabetes at baseline and a 2-year additional treatment period followed by a 17-week safety follow-up in patients with prediabetes at randomisation (*ongoing; data not included in this submission*).

Two addenda have been completed during the 72-week study period:

- The DXA addendum was designed to assess changes in body composition from baseline to week 72.
- The ABPM addendum was designed to assess mean change in 24-hour blood pressure and heart rate from baseline to week 36.

The study design is considered adequate and generally in line with the recommendations in Guideline EMA/CHMP/311805/2014. The randomised treatment period of 72 weeks is adequate. Blinding may have been compromised due to the occurrence of gastrointestinal side effects or pronounced weight loss in the intervention arms.

A longer treatment period for patients with pre-diabetes is considered adequate to capture a potential delay in onset of T2DM. It is in line with the recommendation in Guideline EMA/CHMP/311805/2014, section 6.3. ("*To document the effect on some weight related outcomes, e. g. delay in onset of type 2 diabetes mellitus, longer study durations may be needed*…"). No claim with respect to diabetes prevention is made.

SURMOUNT-4 is a multicentre, double-blind, placebo-controlled study that was designed to assess the efficacy and safety of once-weekly tirzepatide maximal tolerated dose (MTD; 10 or 15mg) compared with once-weekly placebo for maintenance of weight reduction. 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. The 52- week post-randomization double-blind phase of the study is ongoing. Conduction of a study using a randomized withdrawal design is endorsed as it will provide information on the duration of effect (Guideline EMA/CHMP/ 311805/2014: *"A randomised withdrawal design, randomising patients on active drug to continue treatment or switch to placebo may give some useful information on the duration of the effect."*)

Post-hoc analyses from SURPASS 1-5 excluding patients with baseline BMI<27m^2/kg have been submitted; these analyses included 86% of patients included in the overall SURPASS program which had been conducted for the T2DM indication. The SURPASS1-5 studies lack important design elements of chronic weight management studies. For instance, weight reduction was investigated as secondary endpoint and patients were not required to have at least one failed attempt to reduce weight by lifestyle modification. Lifestyle interventions in SURPASS 1-5 were tailored to T2DM (e. g. counselling dealt with hypoglycaemia). No calorie restriction was recommended on a regular basis; patients were

asked "*to continue their usual exercise habits and follow a healthy meal plan*" (CSR SURPASS-1). However, the study results of SURMOUNT-1 and the SURPASS studies are similar; therefore, the differences in counselling did not have a major impact.

Of note, in SURPASS 2 the active comparator semaglutide was administered at a dose of 1 mg, which is below the dose licensed for weight reduction (2.4 mg; see the SmPC of Wegovy); effect sizes have to be evaluated bearing this in mind.

Overall, the SURPASS 1-5 post-hoc analyses add information on the efficacy of tirzepatide in overweight/obese patients with T2DM and patients from EU countries/the UK as well as for elderly, patient populations not or not well represented in SURMOUNT-1; these studies are considered supportive for efficacy.

Doses and dose escalation scheme (SURMOUNT-1)

The doses were selected based on body weight reduction observed in Study I8F MC GPGB, which had been performed for the T2DM indication. In this study, the weight reduction and HbA1c dose-response patterns were similar. Selection of the 5 mg, 10 mg and 15 mg doses is considered reasonable. Like in the SURPASS studies, an up-titration regimen (dose-escalation until week 20) was used in SURMOUNT-1 with the aim to ameliorate gastrointestinal side effects. Forced up-titration is adequate for study purposes and eases evaluation of dose-response. However, it does not reflect the mode of up-titration in clinical practice based on tolerability and therapeutic needs. No changes to the posology were introduced with this variation, which is adequate.

Background therapy (SURMOUNT-1)

For all participants, lifestyle modification was advised. This consisted of a hypocaloric diet with a 500-calorie deficit that was individually calculated, and an increase in physical activity by 150 minutes per week. Lifestyle counseling was administered throughout the entire study. Lifestyle modification was in line with Guideline recommendations as regards calorie deficit and amount of physical activity (e. g. AACE/ ACE Guideline, Garvey et al, 2016). Regular enforcement through counseling throughout the study is endorsed.

With the availability of new anti-obesity drugs, the contribution of lifestyle modifications to weight loss may become less. Interestingly, even more aggressive regimens seem not to confer greater benefit: in the STEP-3 study with semaglutide 2.4 mg, in which more aggressive lifestyle management ("intensive behavioral therapy") add-on semaglutide was investigated, this did not lead to a more pronounced weight loss (compared to STEP-1 with standard recommendations; Wadden T. A. et al. 2021). Nevertheless, a healthier lifestyle contributes to weight loss, improves its sustainability and improves overall cardiovascular, metabolic and mental health. The indication wording adequately reflects that tirzepatide should be administered in addition to a calorie-reduced diet and exercise.

Concomitant medication (SURMOUNT-1)

Per protocol, participants were permitted to use concomitant medications that they required during the study (e. g. anti-emetics, hypertensive drugs, lipid lowering agents).

Endpoints in SURMOUNT-1

The co-primary endpoints for assessment of efficacy in SURMOUNT-1 were percent change in body weight and percentage of participants reaching ≥5% body weight reduction, measured from randomization to week 72. Additional efficacy measures studied included percent of participants reaching ≥10%, ≥15%, and ≥20% total body weight reduction, change in waist circumference, change in lipid levels, change in BP and change in glycaemic measures. To include the patient`s perspective the generic SF-36v2 physical functioning domain score was investigated as a key secondary endpoint

with control of type I error (change from baseline to week 72); the other seven domains of SF-36 were also evaluated. In addition, results of a responder analysis had been submitted.
The IWQOL-Lite CT was developed and validated to assess weight-related changes in physical and psychosocial functioning in subjects with overweight or obesity. No clinically relevant differences (neither for mean changes from baseline nor for within-patient changes) had been pre-defined in the CSR. Overall, PRO results have to be seen in the light of potential unblinding of patients who might have become aware of their treatment assignment (due to pronounced weight loss or gastrointestinal intolerance).

In a subgroup of patients a validated method (DEXA) was applied to estimate body fat.

Primary and secondary endpoints were in accordance with regulatory guidance (Guideline on clinical evaluation of medicinal products used in weight management 2016, EMA/CHMP/311805/2014).

Endpoints in SURPASS 1-5

In SURPASS 1-5, the primary objective was related to glycaemic control; however, mean change from baseline in body weight was a key secondary objective controlled for type 1 error. Percentage of participants reaching ≥5% body weight reduction was an additional secondary objective not controlled for type 1 error.

Population studied (SURMOUNT-1)

Patients with a body mass index (BMI) ≥30 kg/m^2, or a BMI ≥27 kg/m^2 and at least one weight related comorbidity with at least one self-reported unsuccessful dietary effort to lose weight were included. The patient population included in SURMOUNT-1 represents the intended target population for tirzepatide as CWM treatment. The average baseline BMI was 38.0 kg/m^2. Approximately 32% of the participants had a BMI of at least 40 kg/m^2. Patients with BMI below 30kg/m^2 made up only 5.5% of the study population.

Acceptable weight-related comorbidities for participants with BMI ≥27 kg/m2 and <30 kg/m2 included obstructive sleep apnoea, hypertension, dyslipidaemia, or cardiovascular disease. Nearly two-thirds of the participants had at least one weight-related comorbidity at baseline. While the diagnosis of diabetes was exclusionary, about 41% of the participants had prediabetes diagnosed at baseline, based on HbA1c, FSG, and oral glucose tolerance test assessment during screening. The average HbA1c was 5.6% at baseline.

Inclusion and exclusion criteria are considered adequate. The BMI cut-offs of 30kg/m^2 and 27 kg/m^2 (requirement of at least one weight-related co-morbidity) had likewise been applied to characterize the target population for GLP-1 agonists for the treatment of overweight and obesity (EPAR Saxenda, EMEA/H/C/003780; EPAR Wegovy EMEA/H/C/005422).

Overall, demographic and baseline characteristics were comparable across the treatment groups.

No European patients were included in the SURMOUNT studies. The Guideline EMA/CHMP/311805/2014 states that "*a relevant number of patients should be included from EU countries with baseline characteristics, lifestyle and non-pharmacological obesity interventions similar to those of EU countries*". This deficiency is countered by the SURPASS 3, 4 and 5 studies which included a considerable proportion of European patients (53.9%, 29.0% and 79.1%, respectively). Further, in SURMOUNT-1 44.9% of patients were from North America where lifestyle and non-pharmacological obesity interventions are similar to the EU.

The average age in SURMOUNT 1 was 44.9 years; the patients were on average about 10-15 years younger compared to the SURPASS 1-5 studies (53.0 to 63.2 years). The younger age in SURMOUNT 1 reflects a somewhat distinct clinical population; the prevalence of obesity, particularly severe obesity,

is highest among 40- to 59-year-old individuals (NCHS 2020), and across age groups, the use of anti-obesity medication is lowest among those who are >65 years (MacEwan et al. 2021).

In SURMOUNT-1, across treatment groups, 152 participants (6.0%) were >65 years old, and eight participants (0.3%) were >75 years old. The low number of patients older than 75 years in SURMOUNT-1 may be partly compensated by a greater representation of this age group in the SURPASS 1-5 studies (148 patients, 3.3% older than 75 years). A pooled analysis including all obese/overweight patients from SURMOUNT-1 and SURPASS1-5 above 75 years was requested and further performed by the MAH to further elucidate efficacy in the elderly. Percent change in body weight from baseline was assessed in 243 participants having body weight measurement available at baseline (134 treated with tirzepatide [any dose], and 109 participants from control groups [either placebo or active comparators]). Percent change in body weight from baseline in elderly participants treated with tirzepatide was -9.9% (comparator-adjusted: -9.7%) at Week 40, -10.3% (comparator-adjusted: -10.2%) at Week 52, and -10.1% (comparator-adjusted: -10.3%) at Week 72. Decreases in body weight at all time points were statistically significant from baseline, and when compared to changes in body weight in participants in control groups. Body weight reductions were clinically relevant in patients above 75 years of age. Hence, the wording in section 4.2 which points at sparse data in patients above 85 years is acceptable and can remain unchanged (it has been shifted with this variation from SmPC section 4.4 to SmPC section 4.2).

Few patients with moderate (n=44) and no patients with severe renal impairment had been included. The wording in section 4.2 of the SmPC applicable to the T2DM indication is limited to severe renal impairment and no change is proposed with this variation: "*Renal impairment: no dose adjustment is required for patients with renal impairment including end stage renal disease (ESRD). Experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with tirzepatide (see section 5.2*)." To further justify this wording, a subgroup analysis for the primary endpoint for the 44 patients with moderate renal impairment was requested during the procedure . Efficacy was maintained in this subgroup with effect sizes comparable to the overall population. TEAE were presented for the safety analysis set for patients with moderate renal impairment. It is acknowledged that the total number of participants in the eGFR category ≥30 to <60 mL/min/1.73 m2 is considerably lower than in the higher eGFR categories. Moreover, the absolute number of cases within each event is relatively low and it is difficult to establish a plausible causal relationship with tirzepatide treatment. Based on these considerations, the applicant concluded that the observed increase in OR with decreasing kidney function may rather be a chance finding without clinical relevance.

Statistical methods

Two estimands of interest were defined for SURMOUNT-1 and SURPASS-1 to -5.

The treatment-regimen estimand targets the treatment effect regardless of adherence to randomised treatment (treatment policy strategy). Analyses related to the treatment-regimen estimand were conducted using all available data obtained during treatment period regardless of adherence to study drug (for SURMOUNT-1 and SURPASS studies) or initiation of rescue antihyperglycaemic medication (for SURPASS studies). Analysis of continuous data used an analysis of covariance model adjusted for baseline value and stratification factors. Analysis of proportion of participants achieving target thresholds was performed by dichotomizing the continuous outcome, followed by a logistic regression that was adjusted for baseline value and stratification factors. In SURMOUNT-1, missing data were imputed using hybrid imputation: Missing data due to exceptional circumstances (i.e., pandemics or natural disasters) were imputed using all non-missing data of the outcome measurement from the

same treatment arm (missing at random) and missing data due to all other intercurrent events other than previously defined exceptional circumstances were imputed based on retrieved dropouts defined as observed outcome measurements from participants in the same treatment group who had their outcome measurement collected after early discontinuation of study drug. A sensitivity analysis for the co-primary endpoints was conducted where all missing data were imputed from retrieved dropouts only. In SURPASS-1 to -5, missing data were imputed using retrieved dropout (active controlled trials; SURPASS-2, -3, and -4) or placebo imputation (placebo-controlled trials; SURPASS-1 and -5).

The efficacy estimand targets the on-treatment efficacy not confounded by discontinuation of study drug (for SURMOUNT-1 and SURPASS studies) or initiation of rescue antihyperglycaemic therapy (for SURPASS studies), which reflects the treatment effect for patients who are willing and able to take the drug as prescribed (hypothetical strategy). Analyses related to the efficacy estimand were conducted using data obtained during treatment period, excluding data after early, permanent discontinuation of study drug (last dose date + 7 days; for SURMOUNT-1 and SURPASS studies) or initiating rescue antihyperglycaemic medication (for SURPASS studies). Analysis of longitudinal continuous variables used a mixed model for repeated measures (MMRM) using restricted maximum likelihood estimation under missing at random. Analysis of proportion of participants achieving target thresholds used a logistic regression model. 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. For continuous outcomes collected only once postbaseline, the last observation carried forward approach was applied to impute the missing endpoint, unless specified otherwise.

As the guideline (EMA/CHMP/311805/2014) recommends to follow-up all patients for the duration of the trial to get a measure of weight change regardless of adherence to randomised treatment, the treatment-regimen estimand is considered more relevant for regulatory decision making than the efficacy estimand. The dataset used for analyses related to the treatment-regimen estimand and handling of missing data are acceptable.

In SURMOUNT-1, the type 1 error was controlled at 5% two-sided for evaluating the primary and key secondary efficacy objectives within each estimand, which is considered appropriate. The results of the SURPASS-1 to -5 studies presented are all post hoc analyses which were not controlled for type 1 error.

Conduct of SURMOUNT-1

In general, this study was well-conducted. Treatment compliance was defined as taking at least 75% of the required doses of study drug. Overall, study drug compliance during the entire treatment period was high (2473 participants, 97.4%) and did not differ across the treatment groups.

Patient retention during the primary, double-blind period of the study was high, with 88-90% of patients on tirzepatide doses completed the double-blind period (77% on placebo); likewise, adherence to study drug was high. Compared to previous studies for CWM with only 50-70% of patients completing the studies (Greenway et al, 2010, Pi-Sunyer et al., 2015), retention rates in SURMOUNT-1 were high. COVID-19 related disruptions did not have a meaningful impact on study discontinuations and/or study drug discontinuations, or collection of efficacy measures.

Results

SURMOUNT-1 *(pivotal phase 3 study; figures refer to the treatment-regimen estimand)*

In comparison with placebo, tirzepatide 5, 10, and 15 mg each achieved superiority with both the treatment-regimen and efficacy estimands on the *co-primary endpoints*:

- mean percent change (reduction) in body weight from baseline at 72 weeks, and
- percentage of participants achieving ≥5% body weight reduction from baseline to 72 weeks.

Tirzepatide treatment led to clinically meaningful weight reductions across doses. The mean percent weight reduction for tirzepatide 5, 10, and 15 mg at 72 weeks was 15%, 19.5%, and 20.8%, respectively. With placebo, weight reduction from baseline was 3.1%. Effect sizes are considered large; the effect sizes for tirzepatide 10 mg and 15 mg approached those achieved with bariatric surgery for which weight reduction of approximately 25 to 30% at 1 to 2 years had been reported (Aminian A et al, 2021; van Rijswijk et al, 2021).

All doses of tirzepatide demonstrated superiority to placebo for the percentage of participants achieving ≥5% weight reduction from baseline to 72 weeks (85.1% , 88.9%, and 90.9% with tirzepatide 5 mg, 10 mg and 15 mg, respectively; placebo 34.5%). A body weight reduction of 5% is considered clinically relevant as it translates in an improvement of cardiovascular health (Ryan and Yockey, 2017). Results for percent change in body weight were consistent across all subgroups, including ethnicity. Albeit only 5.5% of patients had baseline body weight below BMI 30kg/m2, the subgroup analysis for percent change in body weight clearly indicated benefit for overweight patients (BMI>27kg/m2).

Other weight reduction related endpoints

Tirzepatide was superior to placebo in achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to 72 weeks. Across tirzepatide dose groups, a weight loss ≥10% was observed in 68.5%, 78.1% and 83.5% of patients, compared to 18.8% with placebo; weight loss ≥15% was observed in 48.5%, 66.6% and 70.6% of patients compared with 8.8% with placebo; a weight loss ≥20% was achieved in 30.0%, 50.1% and 56.7% of patients compared with 3.1% with placebo. Weight reductions of at least 10%, 15% and 20% often are a desired goal in the target population, especially in patients with very high BMI. Improvement of some weight related complications (reduce inflammation in NASH; reduce fat burden in obstructive sleep apnoea, knee pain, and osteoarthritis) seem to require higher weight loss than 5% (Ryan and Yockey, 2017).

Body weight change at 20 weeks was evaluated as a measure of *early* efficacy of tirzepatide. Clinically relevant effect sizes for body weight reduction were shown at week 20 for the pooled 10 mg and 15 mg tirzepatide group. Data on *early* non-response had not been submitted initially; no stopping rules are proposed in the label. According to the Guideline EMA/CHMP/311805/2014 "*the predictive value of weight loss after short-term treatment (e.g. 12 weeks treatment on target treatment dose) with respect to long-term efficacy should be documented, in order to better identify a population with expected long-term benefit and include a potential stopping rule for non-responders in the product label*". Therefore, the Applicant was requested to determine the predictive value of response (> 5% weight loss) and non-response (< 5% weight loss) at week 12, 16 and week 20 for response or non-response at week 72; to perform this analysis for all doses separately and to propose a stopping rule, if appropriate. In addition, the applicability of a stopping rule for exaggerated response should be discussed. As requested the Applicant performed analyses in early non-responders (less than 5% weight loss, less than 3% weight loss at Week 12 and Week 24). Selection of the 24-week time-point is accepted, as due to up-titration dose-related response cannot be assessed at earlier timepoints. The analyses exploring the predictive value of early non-response showed that considerable proportions of patients who did not respond at week 24, responded (=achieved more than 5% body weight reduction) at week 72. For example: of those who did not achieve 5% body weight reduction at week 24, 53% on tirzepatide 5mg, 67.7% on tirzepatide 10 mg, and 71.9% on tirzepatide 15 mg (compared

to 13.4% on placebo) achieved over 5% body weight reduction at week 72. In clinical practise, response rates may be higher than those achieved with 5 mg (53%), as a patient on 5 mg with good tolerability but insufficient weight loss is expected to be up-titrated (which was not possible in SURMOUNT-1 in patients allocated to the 5 mg treatment arm). The analyses performed with a lower cut-off for non-response (>3% body weight reduction) likewise showed that about half of the early non-responders (43-57%) had response at week 72. It is agreed with the MAH, that the value of assessment of non-response at week 12 is limited, as patients had not achieved their target dose. In contrast, the predictive value of short-term *response* (in contrast to non-response) on response at day 72 is high. Since the overall percentage achieving ≥5% weight loss at week 72 is 89% to 96%, and the percentage of non-responders at Week 24 achieving ≥5% weight loss at Week 72 is 53% to 72%, more than 90% of short-term responders achieved ≥5% weight loss at Week 72, as such meeting the responder criterion. Overall, it is agreed that -in the light of the high early and late response rates- the predictive value of early response (>5% weight loss) or non-response (<5% weight loss, <3% weight loss) for response or non-response at week 72 is limited and does not justify introducing stopping rules for tirzepatide for weight management.

Results for waist circumference supported the results of the co-primary endpoints. Losses in waist circumferences were -14.0 cm, -17.7 cm, and -18.5 cm across tirzepatide dose groups, compared with -4.0 cm with placebo; this is considered beneficial, as central adiposity is associated with cardiovascular risk (Huxley et al., 2010). Results from the DXA sub-study demonstrated that mean percent reduction from baseline in total body fat mass was significantly greater for pooled tirzepatide 5, 10, and 15 mg (-33.9%) compared with placebo (-8.2%). Hence, weight loss was associated with loss of fat mass (as distinct from body water or muscle mass), which is desirable.

Cardiovascular risk factors and cardiovascular benefit

Tirzepatide improved cardiovascular risk factors beyond overweight/obesity. Clinically meaningful improvements were shown for lipid parameters, blood pressure and measures of glycaemic control. In addition to reductions in HbA1c, 95.3% (726 out of 762 patients) of tirzepatide-treated participants with prediabetes at baseline reverted to normoglycemia at week 72, compared with 61.9% (167 out of 270 patients) of placebo-treated participants. Stopping progress to T2DM is considered relevant.

To determine how improvements in cardiovascular risk factors translate into reduced morbidity and mortality in overweight/obese adults, a phase 3 Study (I8F MC GPIJ; SURMOUNT-MMO) is ongoing. SURMOUNT-MMO is a long-term, double-blind, placebo controlled, event-driven study that will determine if tirzepatide is better than placebo in reducing obesity-related disease and death in adults living with obesity and established CVD or CVD risk factors, excluding diabetes. Completion of SURMOUNT MMO is projected for 2027. In addition, results from SURPASS-CVOT, in participants with T2DM, may provide further insights. Completion of SURPASS-CVOT is projected for 2024 (*please refer to safety part of this AR for assessment of cardiovascular safety*).

Body weight change over time and sustainability of action

The percent body weight changes showed separation from placebo starting at week 4 for all three tirzepatide groups. The body weight for participants in the tirzepatide 5 mg group continued to decrease through week 60 and plateaued by week 72. In the higher dose groups, weight reduction attenuated but seemed to continue through week 72. Upon availability, the Applicant should provide data of the four week safety follow-up period to further characterise the time course of weight reduction across tirzepatide doses.

Patient reported outcomes

Compared with placebo all doses of tirzepatide led to small improvements (changes from baseline to

week 72) in SF-36V2 scores measuring overall HrQoL and functioning, physical function and the psychosocial composite score. Score differences in the IWQOL-Lite-CT scores were shown for tirzepatide compared to placebo. No clinically relevant differences (neither for mean changes from baseline nor for within patient changes) had been pre-defined in the CSR. Overall, tirzepatide showed consistent small benefits on how overweight/obese patients feel and function. The small effect sizes may partly be caused by high baseline scores. The clinical relevance of the effect size is insufficiently established. This is accordingly reflected in the revised SmPC.

Concomitant medication

As expected, more patients in the tirzepatide compared to the placebo group used antidiarrhoeal and antiemetic medication. Use of anti-hypertensive drugs was reduced in the interventions arms during the study, while lipid lowering drugs were slightly reduced to a comparable extent in all treatment arms.

Results of supportive studies

At the completion of the 36-week open-label tirzepatide lead-in period of **SURMOUNT-4**, participants treated with tirzepatide reduced body weight from baseline by 20.9%. During this open-label period, 88% of patients had been up-titrated to 15 mg. In addition, the percentages of participants achieving body weight reduction targets of ≥5% were 98.2%, ≥10% (93.1%), ≥15% (78.7%), or ≥20% (57.0%) by the end of the 36-week tirzepatide lead-in period. Improvements from baseline were also observed for cardio-metabolic and PRO-related measures. Overall, the SURMOUNT-4 open-label lead-in period results were well in line with the outcome of SURMOUNT-1.

*Post-hoc subgroup analyses from **SURPASS 1-5** in patients with BL BMI>27kg/m^2 and T2DM (results presented for the treatment regimen estimand)*

All tirzepatide doses led to a clinically meaningful improvement in percent reduction in body weight in the subgroup analyses of all studies. In SURPASS-1 the percent change from baseline was -1.3% with placebo and -7.3%, -8.6% and -9.3% with 5 mg, 10 mg and 15 mg tirzepatide, respectively. In SURPASS-5 the percent change from baseline was -1.6% with placebo and -5.8%, -8.1% and -9.4% with 5 mg, 10 mg and 15 mg tirzepatide, respectively. In SURPASS-2 the percent change from baseline was -6.1% with semaglutide 1 mg (dose below licensed semaglutide dose for CWM) and -8.2%, -10.2% and -12.0 % with 5 mg, 10 mg and 15 mg tirzepatide, respectively. In SURPASS-3 the percent change from baseline was 2.1kg with insulin degludec, and -7.7%, -10.5% and -12.0% with 5 mg, 10 mg and 15 mg tirzepatide, respectively. In SURPASS-4 the percent change from baseline was 1.7% with insulin glargine and –7.3%, -10.0% and -12.2% with 5 mg, 10 mg and 15 mg tirzepatide, respectively. Other weight related endpoints (waist circumference, percentage of patients reaching weight reduction targets) supported the results on percent reduction in body weight. In addition, for patients with overweight/obesity in SURPASS 1-5 tirzepatide showed improvements in lipid profile, BP, HbA1c, and HrQoL consistent with the effects in SURMOUNT-1 in patients without T2DM.

In contrast to the SURMOUNT-1 study, patients from the EU/UK had been included in the SURPASS 3, 4 and 5 studies and subgroup analyses did not hint at differences in weight loss between ethnic groups.

Albeit cross-study comparison has to be done cautiously (as the SURPASS studies were not designed as CWM studies), body weight reductions were greater in participants with obesity or overweight without T2DM than in participants with obesity or overweight with T2DM (without T2DM 15.0% to 20.9%, with T2DM 5.8% to 12.2%). This may partly be due to anti-hyperglycaemic medication (SU, insulin). An additive effect of the more eagerly supervised lifestyle management in SURMOUNT-1 might

have contributed. Nevertheless, the effect size of weight loss observed in patients with T2DM is clearly clinically relevant.

For the longer-term studies SURPASS-3 and SURPASS-4, results for the change in percent body weight over time had been submitted. Mean percent body weight change seemed to plateau earlier in participants with T2DM as compared to those without. While in SURMOUNT-1 body weight reduction seemed to be maintained at 72 weeks for the 10 mg and 15 mg tirzepatide doses (this will undergo further evaluation when data from the 4-week safety follow-up are available), weight reduction plateaued in SURPASS-3 by 52 weeks in all dose groups. Similarly, near plateaus were reached for all doses in SURPASS-4 by week 52. Few participants in SURPASS-4 completed the 104 week visit (n=176, 10.4%). No further weight loss (and even a slight increase with tirzepatide 10 mg and 15 mg) was observed during this longer-term observation.

2.4.4. Conclusions on the clinical efficacy

SURMOUNT-1 demonstrated statistically superior and clinically meaningful weight loss compared with placebo in overweight and obese patients without T2DM. The weight loss benefit was supported by improvements in other weight related and non-weight related parameters reflecting cardio-metabolic health like waist circumference, body fat mass, blood lipids, blood pressure and measures of glycaemic control. The patient perspective was taken into account by PRO assessment. Post-hoc analyses from the SURPASS studies confirmed the weight loss benefit in patients with T2DM, albeit the weight loss and sustainability of action were somewhat less pronounced.

Overall, tirzepatide is considered a valuable asset for weight management.

2.5. Clinical safety

Introduction

Data from 25 Phase 1, 2, and 3 studies (submission data cut-off date: 10 June 2022) are included in this application for the adult chronic weight management (CWM) indication. The primary safety data for tirzepatide (TZP) comes from 2 phase 2 (GPGB, GPGF) and 10 phase 3 studies (global: GPHK, GPHN, GPGK, GPGL, GPGH, GPGM, GPGI and GPHO; regional: GPGO, GPGP). Only the data from study GPHK (SURMOUNT-1) and GPHN (SURMOUNT-4) are new data specific for this chronic weight management application. The SURMOUNT-1 study is completed. The safety data from SURMOUNT-4 comprise only the initial 36-week open-label period, while the double-blinded treatment is still ongoing. Studies GPGK, GPGL, GPGH, GPGM and GPGI were already part of the previous T2DM procedure, but a new analysis is now presented for the subgroup of patients with BMI ≥ 27 kg/m^2. Study GPHO (SURPASS-AP combo) is also a T2DM study, but the results had not yet been submitted in the previous T2DM application. From study GPHO, also only safety data for a BMI ≥ 27 kg/m^2 are included.

The safety population comprises patients who took at least one dose of study drug. The safety assessments were based on all available data through the treatment period and subsequent 4-week safety follow-up, regardless of adherence to study drug. The applicant presents four integrated analysis sets (**Table 40**). Due to different dose escalation schemes, the phase 2 and 3 studies were analysed separately from each other.

Table 40: Analysis sets presented by the applicant

Analysis Set	Studies	Time period	Treatment Groups (only BMI ≥ 27)*	Treatment comparison	Analyses
AS1C (Phase 3 placebo-controlled) N= 3317	SURMOUNT-1 (GPHK), GPGK, GPGI	First dose of treatment to end of safety follow-up visit or date of study withdrawal	Placebo: 827 TZP 5 mg: 832 TZP 10 mg: 830 TZP 15 mg: 828 TZP_ALL: 2490 SURMOUNT-1: 76.5% of total	TZP 5 mg, 10 mg, 15 mg, TZP_ALL *vs.* placebo	Full set of safety analyses**
AS2C (Phase 3 dose-effect) N = 6326	SURMOUNT-1 (GPHK), GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, GPGP, GPHO		TZP 5 mg: 2109 TZP 10 mg: 2095 TZP 15 mg: 2122 Total: 6326 SURMOUNT-1: 30.0% of total	TZP dose arm: 10 mg vs. 5 mg 15 mg vs. 5 mg 15 mg vs. 10 mg	
AS3C (Phase 2/3) N = 10065	GPHK, GPGB, GPGF, GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, GPHO, GPHN, GPGP		TZP_ALL: 7354 SURMOUNT-1 and -4: 36.4% of total	Summary only, no comparison	Exposure, demographics, TEAEs, SAEs, DCAEs, special safety topics (incl. AESIs), labs shift to high/low, vital signs, ECG threshold
AS4C (Phase 2/3 comparator-controlled) N = 9083	GPHK, GPGB, GPGF, GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, GPHO	First dose of treatment to end of safety follow-up visit or date of study withdrawal***.	Comp: 2711 TZP_ALL: 6372 SURMOUNT-1: 28.0% of total	TZP_ALL *vs.* comparators	Exposure, demographics, TEAEs, SAEs, DCAEs, AESIs

*All subjects in SURMOUNT-1 and-4, but only a part of the study population from the T2DM programme, had BMI ≥ 27. For details on the T2DM programme, please see original T2DM application.
**includes exposure, demographics, medical history, concomitant medications, TEAEs, SAEs, DCAEs, AESIs, labs, vital signs, ECGs.
*** 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.

The following discussion will mainly refer to SURMOUNT-1, AS1C (TZP *vs.* placebo, phase 3) and AS4C (TZP *vs.* comparators, phase 2/3). If AS4C is not available, AS2C (phase 3 dose-effect) will be discussed instead.

Patient exposure

In total, 10 065 participants with overweight/obesity received study drug in the 12 phase 2 and 3 studies. Of these, 7354 participants received TZP in the Phase 2 and 3 studies (AS3C) for 7071 patient-years (**Table 41**). A total of 3492 participants received TZP for at least 52 weeks in the phase 2 and 3 studies, with 2027 receiving TZP for at least 72 weeks. In addition, 2711 participants received comparator (active or placebo) for 2905 participant-years. Of the 10 065 participants with overweight/obesity, 6744 also had T2DM (TZP_ALL: n=4676 [4167 patient-years]; comparator: n=2068 [2142 patient-years]), and 3321 participants had overweight/obesity without T2DM (TZP_ALL: n=2678 [2904 patient-years]; comparator; n=643 [763 patient-years]).

In the phase 2/3 study program (previous T2DM studies and SURMOUNT-1; analysis set AS3C), a total of 7354 patients (TZP_ALL group) was exposed to TZP for a mean (SD) exposure time of 50.2 (20.61) weeks (min: 1 week, max: 106 weeks; Q1: 39.9 weeks; Q3: 72.0 weeks). An overview of the patient numbers and patient-years per time period is shown in **Table 41** for analysis set AS3C.

Table 41: Patient numbers and patient-years of exposure (TZP_ALL, AS3C) according to treatment intervals

Weeks of exposure*	TZP_ALL (N = 7354) n (%)	Patient-years**
>0	7354 (100.0)	7071.3
≥4 weeks	7254 (98.6)	7068.0
≥8 weeks	7135 (97.0)	7055.3
≥12 weeks	7038 (95.7)	7037.9
≥16 weeks	6881 (93.6)	6999.1
≥20 weeks	6790 (92.3)	6969.4
≥24 weeks	6732 (91.5)	6945.9
≥36 weeks	6338 (86.2)	6725.1
≥48 weeks	3672 (49.9)	4719.1
≥52 weeks	3492 (47.5)	4543.7
≥72 weeks	2027 (27.6)	2957.4
≥104 weeks	13 (0.2)	26.1
>0 to <4 weeks	100 (1.4)	3.3
≥4 to <8 weeks	119 (1.6)	12.6
≥8 to <12 weeks	97 (1.3)	17.4
≥12 to <16 weeks	157 (2.1)	38.8
≥16 to <20 weeks	91 (1.2)	29.7
≥20 to <24 weeks	58 (0.8)	23.5
≥24 to <36 weeks	394 (5.4)	220.8
≥36 to <48 weeks	2666 (36.3)	2006.0
≥48 to <52 weeks	180 (2.4)	175.4
≥52 to <72 weeks	1465 (19.9)	1586.3
≥72 to <104 weeks	2014 (27.4)	2931.4
≥104 weeks	13 (0.2)	26.1
*duration of study treatment exposure is defined as time in days from date of first dose of study treatment to date of last dose of study treatment plus 7 days. **patient-year is calculated as sum of duration of exposure in days for all participants at specific time point / 365.25.		

During the primary study period of SURMOUNT-1, the mean treatment exposure was similar across treatment groups (placebo: 61.9 weeks; TZP groups: 65.4 to 66.8 weeks). In the integrated biopharmaceutic and clinical pharmacology studies, 623 healthy participants, participants with T2DM, and participants in special populations (for example, renally or hepatically impaired) received at least one dose of either TZP or placebo. Of these, 546 received at least one dose of TZP.

Adverse events

Overview

A TEAE (treatment-emergent adverse event) was defined as an event first occurring or worsening in severity post-baseline. The maximum severity during the baseline period was used as baseline. Events with missing severity during the baseline period were treated as "mild". Events with a missing severity during the post-baseline period were treated as "severe". Hypoglycaemic events meeting the criteria of severe AEs were reported as SAE. Non-severe events were not recorded as TEAEs.

In AS1C (TZP vs. placebo, phase 3; **Table 42**, upper part), the percentage of patients with TEAEs and discontinuations of study treatment due to AE was higher with TZP as compared to placebo. The percentage of patients with discontinuations from study due to an AE was similar across all treatment groups (TZP dose groups and placebo), with slightly less SAEs in TZP_ALL as compared to placebo. There was a weak trend towards fewer deaths in TZP-treated patients as compared to placebo. Similar results were obtained in SURMOUNT-1 (**Table 42**, middle part) and AS4C (TZP_ALL vs. comparator for phase 2/3 studies; **Table 42**, lower part).

Table 42: Overview of AEs, Safety Population, Phase 3 Placebo-controlled analysis set (**AS1C**), the SURMOUNT-1 study , and the Phase 2/3 comparator-controlled analysis set (**AS4C**)

AS1C					
Category[a]	**Placebo (N=827) n (%)**	**TZP 5 mg (N=832) n (%)**	**TZP 10 mg (N=830) n (%)**	**TZP 15 mg (N=828) n (%)**	**TZP_ALL (N=2490) n (%)**
Deaths[b]	4 (0.48)	4 (0.48)	2 (0.24)	1 (0.12)	7 (0.28)
SAEs	53 (6.41)	51 (6.13)	57 (6.87)	41 (4.95)	149 (5.98)
Discontinuation from study due to AE	18 (2.18)	19 (2.28)	19 (2.29)	23 (2.78)	61 (2.45)
Discontinuation from study treatment due to AE	26 (3.14)	38 (4.57)	56 (6.75)	54 (6.52)	148 (5.94)
TEAEs	589 (71.22)	654 (78.61)	648 (78.07)	643 (77.66)	1945 (78.11)

SURMOUNT-1 (mITT population)				
Category[a]	**Placebo (N=643) n (%)**	**TZP 5 mg (N=630) n (%)**	**TZP 10 mg (N=636) n (%)**	**TZP 15 mg (N=630) n (%)**
Deaths[b]	4 (0.6)	4 (0.6)	2 (0.3)	1 (0.2)
SAEs	44 (6.8)	40 (6.3)	44 (6.9)	32 (5.1)
Discontinuation from study due to AE	17 (2.6)	16 (2.5)	18 (2.8)	21 (3.3)
Discontinuation from study treatment due to AE	21 (3.3)	30 (4.8)	46 (7.2)	40 (6.3)
TEAEs	463 (72.0)	510 (81.0)	520 (81.8)	497 (78.9)
TEAEs related to study treatment[c]	196 (30.5)	350 (55.6)	395 (62.1)	386 (61.3)

AS4C		
Adverse event[a]	**Comparator (N=2711) n (%)**	**TZP_ALL (N=6372) n (%)**
Deaths[b]	32 (1.18)	39 (0.61)
SAEs	262 (9.66)	450 (7.06)
Discontinuation from study due to AE	61 (2.25)	130 (2.04)
Discontinuation from study drug due to AE	102 (3.76)	436 (6.84)
TEAEs	1836 (67.72)	4721(74.09)

Abbreviations: AE = adverse event; N = number of patients in treatment group; n = number of patients with at least 1 AE per event type; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TZP = tirzepatide.
[a]Patients may be counted in more than 1 category.
[b]Deaths are also included as SAEs and discontinuations due to AEs.
[c]Includes events that were considered related to study treatment as judged by the investigator.

In the AS2C phase 3 dose effect analysis set (not shown here), an incremental increase with higher dose groups was visible for "*Discontinuations from study treatment due to AE"* and with regard to TEAEs.

AEs according to MedDRA Terms

Except for COVID-19, headache, and nasopharyngitis, the majority of frequently reported TEAEs were reported at higher frequency in TZP_ALL as compared to placebo, specifically in the SOCs "Gastrointestinal disorders" (TZP_ALL: 54.0%; placebo: 28.5%) and "General disorders and administration site conditions" (TZP_ALL: 16.6%; placebo: 9.6%). As shown in **Table 43**, among TEAEs occurring at ≥5% in AS1C, SURMOUNT-1 and AS4C, the percentage of the gastrointestinal AEs like nausea, diarrhoea and vomiting was higher in TZP-treated patients than in the control groups. TZP-treated patients in SURMOUNT-1 exhibit a higher incidence of nausea, vomiting, diarrhoea and constipation than the patients in the corresponding dosing groups of AS1C.

Table 43: TEAEs with an incidence of **≥5%** in any treatment group in the overweight/obesity population of the placebo-controlled analysis set AS1C , SURMOUNT-1 , and AS4C

AS1C					
Preferred term	**Placebo (N=827) n(%)**	**TZP 5 mg (N=832) n(%)**	**TZP 10 mg (N=830) n(%)**	**TZP 15 mg (N=828) n(%)**	**TZP_ALL (N=2490) n(%)**
Nausea	69 (8.34)	184 (22.12)	239 (28.80)	231 (27.90)	654 (26.27)
Diarrhoea	66 (7.98)	141 (16.95)	160 (19.28)	180 (21.74)	481 (19.32)
Constipation	38 (4.59)	118 (14.18)	120 (14.46)	87 (10.51)	325 (13.05)
COVID-19	94 (11.37)	94 (11.30)	100 (12.05)	84 (10.14)	278 (11.16)
Vomiting	15 (1.81)	64 (7.69)	75 (9.04)	94 (11.35)	233 (9.36)
Decreased appetite	23 (2.78)	70 (8.41)	87 (10.48)	74 (8.94)	231 (9.28)
Dyspepsia	32 (3.87)	72 (8.65)	76 (9.16)	82 (9.90)	230 (9.24)
Headache	51 (6.17)	51 (6.13)	48 (5.78)	46 (5.56)	145 (5.82)
Eructation	5 (0.60)	31 (3.73)	38 (4.58)	43 (5.19)	112 (4.50)
Injection site reaction	2 (0.24)	23 (2.76)	42 (5.06)	34 (4.11)	99 (3.98)
Nasopharyngitis	43 (5.20)	35 (4.21)	28 (3.37)	27 (3.26)	90 (3.61)
Hyperglycaemia	42 (5.08)	6 (0.72)	4 (0.48)	2 (0.24)	12 (0.48)

SURMOUNT -1 (mITT population)				
Preferred term	**Placebo (N=643) n (%)**	**TZP 5 mg (N=630) n (%)**	**TZP 10 mg (N=636) n (%)**	**TZP 15 mg (N=630) n (%)**
Nausea	61 (9.5)	155 (24.6)	212 (33.3)	195 (31.0)
Diarrhoea	47 (7.3)	118 (18.7)	135 (21.2)	145 (23.0)
COVID-19	90 (14.0)	94 (14.9)	98 (15.4)	82 (13.0)
Constipation	37 (5.8)	106 (16.8)	109 (17.1)	74 (11.7)
Dyspepsia	27 (4.2)	56 (8.9)	62 (9.7)	71 (11.3)
Vomiting	11 (1.7)	52 (8.3)	68 (10.7)	77 (12.2)
Decreased appetite	21 (3.3)	59 (9.4)	73 (11.5)	54 (8.6)
Headache	42 (6.5)	41 (6.5)	43 (6.8)	41 (6.5)
Abdominal pain	21 (3.3)	31 (4.9)	34 (5.3)	31 (4.9)
Alopecia	6 (0.9)	32 (5.1)	31 (4.9)	36 (5.7)
Dizziness	15 (2.3)	26 (4.1)	35 (5.5)	26 (4.1)
Eructation	4 (0.6)	24 (3.8)	33 (5.2)	35 (5.6)
Injection site reaction	2 (0.3)	18 (2.9)	36 (5.7)	29 (4.6)

AS4C		
Preferred term	**TZP_ALL (N=6372) n (%)**	**Comparator (N=2711) n(%)**
Nausea	1411 (22.14)	199 (7.34)
Diarrhoea	1199 (18.82)	193 (7.12)
Decreased appetite	665 (10.44)	56 (2.07)
Vomiting	546 (8.57)	75 (2.77)
Constipation	545 (8.55)	86 (3.17)
Dyspepsia	474 (7.44)	70 (2.58)

COVID-19	334 (5.24)	155 (5.72)
Headache	284 (4.46)	118 (4.35)
Nasopharyngitis	248 (3.89)	149 (5.50)

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

Numerical imbalances disfavouring TZP with regard to less frequent AEs (incidence ≥1% and <5%) in safety datasets **AS1C, SURMOUNT-1 and AS4C** are compiled in **Table 44** (limited to those increased by ≥0.2% in TZP_ALL compared to placebo). As expected, a relevant number of AEs in the gastrointestinal disorders SOC were increased by TZP. Moreover, pancreatic AEs like "lipase increased" or "amylase increased" are reported. TZP also increased the frequency of unspecific AEs like dizziness, asthenia or fatigue.

Table 44: TEAEs with an incidence of **≥1% and <5%** in either treatment group and with incidence in the ***TZP_ALL group by >0.2% higher than in the control group***. Overweight/obesity population of the placebo-controlled analysis set AS1C (upper part), placebo-controlled dataset of SURMOUNT-1 (middle part), and the comparator-controlled safety dataset AS4C (lower part)

AS1C					
Preferred term	**Placebo (N=827) n(%)**	**TZP 5 mg (N=832) n(%)**	**TZP 10 mg (N=830) n(%)**	**TZP 15 mg (N=828) n(%)**	**TZP_ALL (N=2490) n(%)**
Abdominal pain	22 (2.66)	37 (4.45)	38 (4.58)	35 (4.23)	110 (4.42)
Alopecia	6 (0.73)	32 (3.85)	31 (3.73)	36 (4.35)	99 (3.98)
Dizziness	17 (2.06)	28 (3.37)	39 (4.70)	32 (3.86)	99 (3.98)
Gastrooesophageal reflux disease	15 (1.81)	30 (3.61)	31 (3.73)	35 (4.23)	96 (3.86)
Flatulence	13 (1.57)	24 (2.88)	23 (2.77)	32 (3.86)	79 (3.17)
Abdominal pain upper	13 (1.57)	22 (2.64)	27 (3.25)	26 (3.14)	75 (3.01)
Abdominal distension	11 (1.33)	23 (2.76)	24 (2.89)	25 (3.02)	72 (2.89)
Fatigue	14 (1.69)	20 (2.40)	22 (2.65)	23 (2.78)	65 (2.61)
Asthenia	10 (1.21)	12 (1.44)	21 (2.53)	20 (2.42)	53 (2.13)
Abdominal discomfort	12 (1.45)	16 (1.92)	12 (1.45)	23 (2.78)	51 (2.05)
Early satiety	6 (0.73)	20 (2.40)	16 (1.93)	12 (1.45)	48 (1.93)
Gastroenteritis	12 (1.45)	14 (1.68)	16 (1.93)	15 (1.81)	45 (1.81)
Injection site erythema	0	6 (0.72)	14 (1.69)	21 (2.54)	41 (1.65)
Lipase increased	6 (0.73)	10 (1.20)	12 (1.45)	17 (2.05)	39 (1.57)
Anaemia	6 (0.73)	11 (1.32)	11 (1.33)	14 (1.69)	36 (1.45)
Overdose	6 (0.73)	13 (1.56)	12 (1.45)	5 (0.60)	30 (1.20)
Amylase increased	1 (0.12)	7 (0.84)	12 (1.45)	8 (0.97)	27 (1.08)
Migraine	3 (0.36)	6 (0.72)	11 (1.33)	10 (1.21)	27 (1.08)
Osteoarthritis	6 (0.73)	14 (1.68)	10 (1.20)	2 (0.24)	26 (1.04)
Myalgia	6 (0.73)	9 (1.08)	9 (1.08)	7 (0.85)	25 (1.00)
Haemorrhoids	5 (0.60)	8 (0.96)	9 (1.08)	7 (0.85)	24 (0.96)
Injection site pruritus	0	4 (0.48)	6 (0.72)	14 (1.69)	24 (0.96)
Neck pain	6 (0.73)	10 (1.20)	8 (0.96)	6 (0.72)	24 (0.96)
Pruritus	5 (0.60)	8 (0.96)	6 (0.72)	10 (1.21)	24 (0.96)
Hypotension	1 (0.12)	6 (0.72)	5 (0.60)	12 (1.45)	23 (0.92)
Dry mouth	1 (0.12)	5 (0.60)	11 (1.33)	4 (0.48)	20 (0.80)
Hypersensitivity	1 (0.12)	4 (0.48)	6 (0.72)	9 (1.09)	19 (0.76)
Herpes zoster	3 (0.36)	5 (0.60)	9 (1.08)	4 (0.48)	18 (0.72)
Ovarian cyst	0	2 (0.37)	6 (1.18)	1 (0.19)	9 (0.58)
SURMOUNT -1 (mITT population)					
Preferred term	**Placebo (N=643) n (%)**	**TZP 5 mg (N=630) n (%)**	**TZP 10 mg (N=636)**	**TZP 15 mg (N=630) n (%)**	**TZP_ALL (N=1896) n(%)**

			n (%)		
Back pain	23 (3.6)	24 (3.8)	22 (3.5)	28 (4.4)	74 (3.90)
Gastrooesophageal reflux disease	14 (2.2)	27 (4.3)	25 (3.9)	31 (4.9)	83 (4.38)
Injection site reaction	2 (0.3)	18 (2.9)	36 (5.7)	29 (4.6)	83 (4.38)
Flatulence	13 (2.0)	21 (3.3)	19 (3.0)	25 (4.0)	65 (3.43)
Abdominal distension	11 (1.7)	22 (3.5)	19 (3.0)	23 (3.7)	64 (3.38)
Abdominal pain upper	10 (1.6)	17 (2.7)	25 (3.9)	23 (3.7)	65 (3.43)
Fatigue	14 (2.2)	16 (2.5)	20 (3.1)	18 (2.9)	54 (2.85)
Asthenia	10 (1.6)	10 (1.6)	19 (3.0)	19 (3.0)	48 (2.53)
Early satiety	6 (0.9)	20 (3.2)	16 (2.5)	11 (1.7)	47 (2.48)
Abdominal discomfort	7 (1.1)	13 (2.1)	10 (1.6)	21 (3.3)	44 (2.32)
Gastroenteritis	11 (1.7)	13 (2.1)	13 (2.0)	12 (1.9)	38 (2.00)
Injection site erythema	0	6 (1.0)	13 (2.0)	20 (3.2)	39 (2.06)
Anaemia	6 (0.9)	9 (1.4)	11 (1.7)	10 (1.6)	30 (1.58)
Overdose	5 (0.8)	13 (2.1)	11 (1.7)	5 (0.8)	29 (1.53)
Migraine	3 (0.5)	6 (1.0)	11 (1.7)	8 (1.3)	25 (1.32)
Myalgia	5 (0.8)	8 (1.3)	8 (1.3)	7 (1.1)	23 (1.21)
Pruritus	5 (0.8)	6 (1.0)	6 (0.9)	10 (1.6)	22 (1.16)
Haemorrhoids	4 (0.6)	5 (0.8)	9 (1.4)	6 (1.0)	20 (1.05)
Injection site pruritus	0	4 (0.6)	6 (0.9)	13 (2.1)	23 (1.21)
Rash	2 (0.3)	6 (1.0)	7 (1.1)	6 (1.0)	19 (1.00)
Dry mouth	1 (0.2)	5 (0.8)	10 (1.6)	4 (0.6)	19 (1.00)
Hypersensitivity	1 (0.2)	4 (0.6)	6 (0.9)	9 (1.4)	19 (1.00)
Hypotension	0	4 (0.6)	5 (0.8)	10 (1.6)	19 (1.00)
Procedural pain	6 (0.9)	6 (1.0)	3 (0.5)	4 (0.6)	13 (0.69)
Amylase increased	0	2 (0.3)	12 (1.9)	4 (0.6)	18 (0.95)
Lipase increased	0	4 (0.6)	9 (1.4)	5 (0.8)	18 (0.95)
Bronchitis	3 (0.5)	7 (1.1)	4 (0.6)	3 (0.5)	14 (0.74)
Irritable bowel syndrome	2 (0.3)	1 (0.2)	7 (1.1)	7 (1.1)	15 (0.79)
Blood bicarbonate decreased	1 (0.2)	4 (0.6)	5 (0.8)	6 (1.0)	15 (0.79)
Erythema	1 (0.2)	6 (1.0)	3 (0.5)	5 (0.8)	14 (0.74)
Fall	2 (0.3)	7 (1.1)	4 (0.6)	2 (0.3)	13 (0.69)
Oropharyngeal pain	1 (0.2)	6 (1.0)	3 (0.5)	4 (0.6)	13 (0.69)
Gastrointestinal disorder	0	1 (0.2)	5 (0.8)	6 (1.0)	12 (0.63)
Tooth infection	2 (0.3)	1 (0.2)	7 (1.1)	2 (0.3)	10 (0.53)
Dysgeusia	0	0	7 (1.1)	2 (0.3)	9 (0.47)
Dermatitis	0	6 (1.0)	0	2 (0.3)	8 (0.42)
Ovarian cyst	0	2 (0.5)	5 (1.2)	1 (0.2)	8 (0.42)

AS4C

Preferred term	Comparator (N=2711) n(%)	TZP_ALL (N=6372) n (%)
Abdominal Pain	69 (2.55)	257 (4.03)
Lipase increased	47 (1.73)	239 (3.75)
Dizziness	66 (2.43)	213 (3.34)
Abdominal distension	36 (1.33)	234 (3.67)
Flatulence	31 (1.14)	230 (3.61)
Eructation	13 (0.48)	244 (3.83)
Abdominal pain upper	40 (1.48)	187 (2.93)
Gastrooesophageal reflux disease	30 (1.11)	186 (2.92)
Fatigue	34 (1.25)	146 (2.29)
Injection site reaction	14 (0.52)	157 (2.46)
Asthenia	19 (0.70)	142 (2.23)
Abdominal discomfort	24 (0.89)	124 (1.95)
Gastroenteritis	28 (1.03)	105 (1.65)
Hyperuricaemia	36 (1.33)	94 (1.48)
Alopecia	9 (0.33)	113 (1.77)
Insomnia	32 (1.18)	89 (1.40)
Amylase incrased	16 (0.59)	104 (1.63)

Gastritis	30 (1.11)	86 (1.35)
Hypotension	18 (0.66)	66 (1.04)
Weight decreased	7 (0.26)	75 (1.18)
Early satiety	7 (0.26)	64 (1.00)
Osteoarthritis	45 (0.71)	27 (1.00)
Abbreviation: N = number of patients in treatment group; n = number of patients with at least 1 treatment-emergent adverse event; TZP = tirzepatide.		

AEs of special interest (AESIs)

Gastrointestinal Adverse Events

In the placebo-controlled dataset AS1C, 1581 participants experienced TEAEs in the gastrointestinal disorders SOC, affecting more TZP- than placebo-treated subjects (TZP_ALL: 54.02%; placebo: 28.54%). In comparison to placebo, the fraction of moderate and severe GI AEs became higher with TZP. Accordingly, the fraction of mild GI AEs was reduced in TZP-treated patients (**Table 45**).

Table 45: Summary of TEAEs by maximum severity in the GI SOC in the safety population of dataset AS1C

AS1C					
Maximum Severity	**n (%)**				
	Placebo (N=827)	**TZP 5 mg (N=832)**	**TZP 10 mg (N=830)**	**TZP 15 mg (N=828)**	**TZP_ALL (N=2490)**
with ≥1 GI TEAE	236 (28.54)	427 (51.32)	458 (55.18)	460 (55.56)	1345 (54.02)
Mild	172 (72.88)	290 (67.92)	279 (60.92)	279 (60.65)	848 (63.05)
Moderate	56 (23.73)	123 (28.81)	159 (34.72)	157 (34.13)	439 (32.64)
Severe	8 (3.39)	13 (3.04)	20 (4.37)	24 (5.22)	57 (4.24)
Abbreviations: GI = gastrointestinal; N = number of patients who were randomized and received ≥1 dose of study drug; n = number of patients with events meeting the specified criteria; TEAE = treatment-emergent adverse event; TZP = tirzepatide.					

The overall frequency of GI AEs in the overweight/obese population was higher than in the original T2DM application (TZP_ALL: 40.1%; placebo: 20.4%). Also, the frequency of severe/serious GI TEAEs in TZP_ALL in dataset AS1C (2.37%) was numerically higher than in the original T2DM placebo-controlled analysis set (1.1%), which is mainly driven by SURMOUNT-1, which accounted for 59 (TZP_ALL: 52; placebo: 7) of the 69 affected patients in AS1C.

Nausea, vomiting and diarrhoea

Severity of nausea, vomiting and diarrhoea

AS1C, AS2C: The majority of events of nausea, vomiting, and diarrhoea were mild to moderate in severity. Less than 2% of participants in TZP_ALL reported a maximum severity of 'severe' for nausea, vomiting, or diarrhoea, which is consistent with the data in the original T2DM application.

Development over time of nausea, vomiting and diarrhoea

AS2C (Phase 3, T2DM programme and SURMOUNT-1):

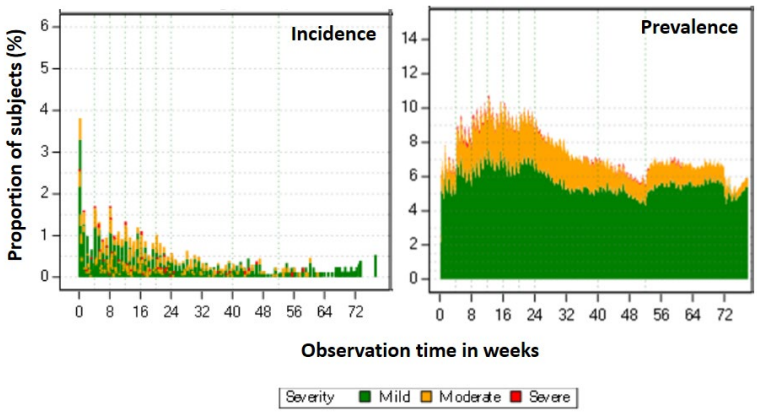
Probability of onset appeared highest during the first 4 weeks after TZP treatment start (all on 2.5 mg dose) and seemed to decrease in steady state, i.e., after 4 weeks on maintenance dose. The probability of onset of nausea and diarrhoea for TZP 10- and 15-mg groups was similar, but higher than for the TZP 5-mg group. These findings are consistent with the data presented in the original T2DM application.

Incidence: The combined (**Figure 24**, 15 mg TZP as example) and individual incidence of nausea, vomiting, and diarrhoea after initiation of study drug was highest in the TZP 15-mg group, followed by

TZP 10 mg and TZP 5 mg. This trend was consistent, irrespectively of event severity. Like in the original T2DM application, the majority of events occurred during dose-escalation and stabilized over time. At any TZP dose, ≤1.6% of patients reported a maximum severity of 'severe' in AS2C for the composite of nausea, vomiting, and diarrhoea during the entire study period.

Prevalence: The combined (**Figure 24**, 15 mg TTZP as example) prevalence of nausea, vomiting, and diarrhoea after initiation of study drug was highest in the TZP 10-mg group, followed by TZP 15 mg and TZP 5 mg. This trend was mainly driven by the nausea component (increased with TZP 10 mg as compared to 15 mg and 5 mg). According to the applicant, the secondary peak in the prevalence of nausea, vomiting, and diarrhoea after Week 52 (**Figure 24**, right graph) is due to SURMOUNT-1, which showed a higher prevalence of nausea, vomiting, and diarrhoea as compared to the T2DM clinical program. Another figure (not shown here) suggests that, among the individual components, this secondary peak is most prominent for the AE of nausea.

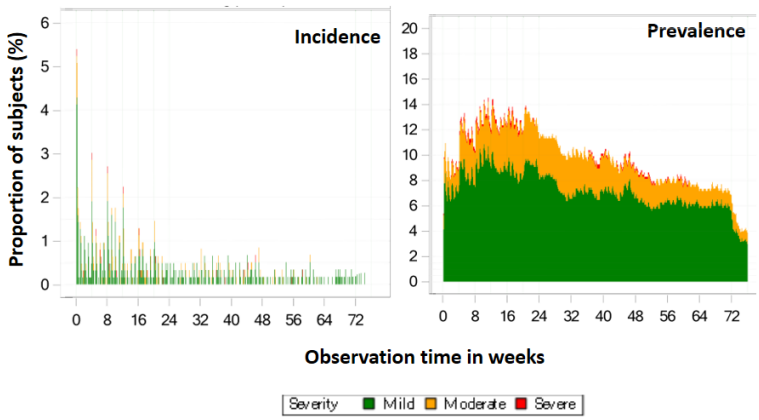
Figure 24: Overall incidence (left) and prevalence (right) of the composite of nausea, vomiting, and diarrhoea by maximum severity in participants with overweight/obesity in the TZP 15 mg group (n=2122) of the AS2C dataset.



SURMOUNT-1 study:

To allow a direct comparison with the AS2C dataset discussed in the preceding section, the incidence and prevalence of the composite of nausea, vomiting, and diarrhoea by maximum severity are shown in **Figure 25** for the TZP 15 mg group of SURMOUNT-1. Incidence and prevalence of the composite of nausea, vomiting and diarrhoea are higher in SURMOUNT-1 as compared to AS2C.

Figure 25: Overall incidence (left) and prevalence (right) of the composite of nausea, vomiting, and diarrhoea by maximum severity in participants with overweight/obesity in the TZP 15 mg group (n=630) of SURMOUNT-1 .



Constipation

Constipation was frequently reported in the TZP groups of the phase 2/3 studies (mostly mild to moderate in severity; more frequently than in original T2DM application). In the phase 3 studies, 0.13 % of TZP-treated participants reported severe constipation events (no dose dependency visible). Constipation resulted in study drug discontinuation in 0.09% of the patients.

Dehydration

In AS1C, dehydration was reported by 7 participants [placebo: 1 (0.12%); TZP 10 mg: 4 (0.48%), TZP 15 mg: 2 (0.24%); TZP_ALL: 6 (0.24%)]. All 7 cases (including one severe case) were from SURMOUNT-1 study. Of the 6 dehydration cases in the TZP group, 2 reported infection shortly before the event, 1 had chronic kidney disease at baseline, and 3 reported gastrointestinal TEAEs at the time of dehydration. None of the dehydration events was serious.

In dataset AS4C , 19 subjects (0.3%) in the TZP_ALL group and 6 subjects (0.2 %) in the pooled comparator groups were affected by dehydration. Sub-differentiation according to severity did not reveal major group differences (TZP_ALL *vs.* comparator: moderate: 11 [0.2%] *vs.* 2 [0.1%]; mild: 6 [0.1%] *vs.* 2 [0.1%], and severe: 2 [0.0%] *vs.* 2 [0.1%]). A total of 4 (0.06%) vs. 2 (0.07%) of TZP vs. comparator-treated participants reported serious or severe events.

It is noted that among the AEs associated with discontinuation from TZP treatment (see section below, *"Discontinuation due to AEs"*), several PTs are listed that may be related to dehydration: fatigue, asthenia, malaise, fall, muscular weakness, orthostatic hypotension, deep vein thrombosis, and vertigo.

Renal Safety

In AS1C (**Table 46)** slightly more patients reported renal TEAEs for TZP_ALL (n=21 [0.84%], 14 from SURMOUNT-1) than for placebo (n=4 [0.48%]; 3 from SURMOUNT-1), without TZP dose dependency. This is similar to the previous results from the original T2DM application. The frequency of dehydration observed in TZP-treated patients of AS1C is confirmed in the dose effect analysis set AS2C (0.91 to 1.56% in TZP-treated patients). Of note, among 55 (0.87%) participants in AS2C with an event of "Acute renal failure", 13 showed an association with dehydration, vomiting or diarrhoea.

Table 46: Renal TEAEs MedDRA PT by decreasing frequency within SMQ safety population (AS1C)

SMQ 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)
Patients with ≥1 TEAE	4 (0.48)	11 (1.32)	5 (0.60)	5 (0.60)	21 (0.84)
Acute renal failure	2 (0.24)	7 (0.84)	4 (0.48)	5 (0.60)	16 (0.64)
Acute kidney injury	1 (0.12)	4 (0.48)	2 (0.24)	4 (0.48)	10 (0.40)
Renal failure	1 (0.12)	2 (0.24)	1 (0.12)	0	3 (0.12)
Renal impairment	0	1 (0.12)	1 (0.12)	1 (0.12)	3 (0.12)
Chronic kidney disease	3 (0.36)	6 (0.72)	2 (0.24)	0	8 (0.32)
Chronic kidney disease	1 (0.12)	4 (0.48)	1 (0.12)	0	5 (0.20)
Renal failure	1 (0.12)	2 (0.24)	1 (0.12)	0	3 (0.12)
Kidney fibrosis	1 (0.12)	0	0	0	0

Severity and seriousness:

7 participants in AS1C (TZP_ALL: n=6 [0.24%]; placebo: n=1 [0.12%]), experienced ≥1 severe or serious renal event. All affected participants were from SURMOUNT-1. In the phase 2/3 comparator-

controlled analysis set (AS4C), a total of 14 (0.22%) TZP- *vs.* 10 (0.37%) comparator-treated participants reported ≥1 serious or severe renal event.

Estimated glomerular filtration rate (eGFR)

At 40 weeks (primary endpoint for SURPASS-1 and -5), 72 weeks (primary endpoint for SURMOUNT-1) and safety follow-up, the mean eGFR reductions from baseline did not show clinically meaningful differences between TZP and placebo. The mean eGFR reduction (in ml/min/1.73 m^2) was more pronounced after 40 weeks (TZP 5 mg: -2.2; TZP 10 mg: -1.8; TZP 15 mg: -0.5) as compared to 72 weeks (TZP 5 mg: -0.6; TZP 10 mg: -0.5; TZP 15 mg: 0.6 mg).

The percentage of patients shifting to lower eGFR categories in AS1C was numerically higher in TZP- as compared to placebo-treated patients in AS1C (placebo: 19.3%; TZP: 22.9%). A further differentiation of the shifts to lower categories in AS1C is shown in **Table 47**.

Table 47: eGFR minimum baseline to minimum post-baseline shifts in AS1C dataset

Shift	**Placebo** (N=827) n (%)	**TZP 5 mg** (N=832) n (%)	**TZP 10 mg** (N=830) n (%)	**TZP 15 mg** (N=828) n (%)
Baseline ≥30 mL/min/1.73 m^2 → Post-baseline <30 mL/min/1.73 m^2 *	0 (0.0)	3 (0.36)	3 (0.36)	2 (0.24)
Baseline ≥45 mL/min/1.73 m^2 → post-baseline ≥30 to<45mL/min/1.73 m^2	9 (1.09)	8 (0.96)	8 (0.96)	4 (0.48)
Baseline ≥60 mL/min/1.73 m^2 → post-baseline ≥45 to <60mL/min/1.73m^2	25 (3.02)	34 (4.09)	32 (3.86)	36 (4.35)
*6 of the 8 TZP-treated patients shifting to <30 mL/min/1.73 m^2 post-baseline were from SURMOUNT-1. The most pronounced shift in this category occurred in the SURMOUNT-1 patient GPHK-120-01897 (71 → 14 mL/min/1.73 m^2) with no related medical history reported.				

Urine albumin/creatinine ratio (UACR)

In AS1C, mean UACR (% change from baseline) decreased with TZP, while it increased with placebo. After 40 weeks (primary endpoint of SURPASS-1 and -5), in comparison to baseline, UACR increased by 5.5% in the placebo group, but decreased with TZP (5 mg: -14.8%; 10 mg: -25.2%; 15 mg: -15.5%).

The changes were less pronounced after 72 weeks (primary endpoint for SURMOUNT-1: placebo: +0.2%; TZP 5 mg: -8.2%; TZP 10 mg: -9.2%; TZP 15 mg: -6.0%). These observations were confirmed by the AS2C dataset (reduction of mean UACR in TZP groups; dose-dependency at 40 and 52 weeks).

In AS1C, fewer patients shifted to higher and more patients to lower UACR categories with TZP as compared to placebo. This trend was confirmed by the isolated SURMOUNT-1 dataset.

Metabolic Acidosis

In the phase 2/3 T2DM programme (AS2C and AS3C, excluding SURMOUNT-1 and -4), three (3) events of metabolic acidosis (1 x ketonuria, 1 x ketoacidosis, and 1 x lactic acidosis) occurred. No TEAEs of metabolic acidosis were reported in the SURMOUNT-1 study.

Exocrine Pancreas Safety

Pancreatitis

In AS1C, 15 (0.60%) TZP-treated participants with 24 events and 2 (0.24%) placebo-treated participants with 2 events of suspected pancreatitis were sent for CEC-adjudication (**Table 48**). All CEC-confirmed cases of acute pancreatitis (TZP_ALL: n=3; Placebo: n=1) in dataset AS1 occurred in the SURMOUNT-1

study. However, the percentage of cases in the group of TZP-treated patients was the same as in the placebo group (0.12%).

In dataset AS4C, 4 events (0.06%; incidence rate [IR] = 0.06) of acute pancreatitis were adjudication-confirmed for the TZP-ALL group, while 1 event (0.04%; IR = 0.03) was reported for pooled comparator.

Table 48: Summary of adjudicated pancreatic events in AS1C

Events	n (%); 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-assessed pancreatitis	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
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

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

Pancreatic enzymes

AS1C:

p-amylase was ≤1×ULN at baseline in 88% of the placebo group and in 79.2% of TZP_ALL. The levels shifted from ≤1×ULN to higher categories more frequently with TZP than with placebo:

- Shift to >1 x ULN: placebo: 36 (4.4%); TZP 5 mg: 105 (12.6%); 10 mg: 134 (16.1%); TZP 15 mg: 117 (14.1%)
- Shift to >3 x ULN: placebo: 0; TZP_ALL: n=15 (0.64%)

Of the 15 TZP-treated patients, who shifted from baseline p-amylase ≤1×ULN to >3 ×ULN, 1 participant (from SURMOUNT-1) had adjudication-confirmed acute pancreatitis.

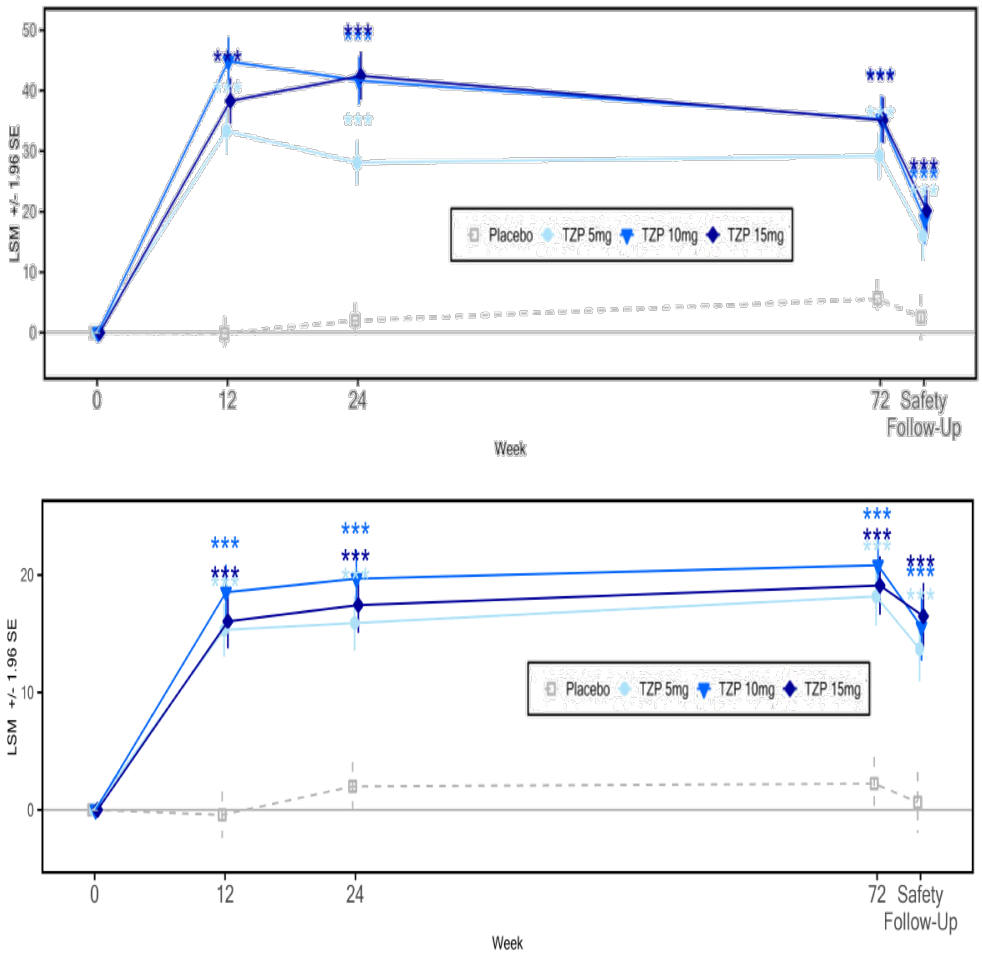
Serum lipase was ≤1×ULN at baseline in 89.5% of the placebo group and in 82.0% of TZP-ALL. The levels shifted from ≤1×ULN to higher categories more frequently with TZP than with placebo:

- Shift to >1 x ULN: placebo: 37 (4.5%); TZP 5 mg: 92 (11.0%); 10 mg: 113 (13.5%); 15 mg: 100 (12.1%)
- Shift to >3 ×ULN: placebo: 3 (0.4%); TZP_ALL: 36 (1.4%)

Of the 36 TZP-treated patients, who shifted from baseline lipase ≤1×ULN to >3 ×ULN, 2 participants (both from SURMOUNT-1) had adjudication-confirmed acute pancreatitis.

Figure 26 shows the time course for pancreas lipase and p-amylase in the SURMOUNT-1 dataset, which constitutes 76.5% of the AS1C dataset. The lipase levels (**Figure 26**, upper graph) reached a maximum at 12 weeks (5 mg and 10 mg) or at 24 weeks (15 mg dose), and remained higher than baseline, even at the time of safety follow-up. The time course of amylase (**Figure 26**, lower graph) is constantly slightly increasing in all three TZP dosing groups and also does not reach baseline levels at safety follow-up. Both lipase and amylase were negligibly affected in the placebo group.

Figure 26: Lipase (upper) and p-amylase (lower) percent change from baseline over time (SURMOUNT-1).

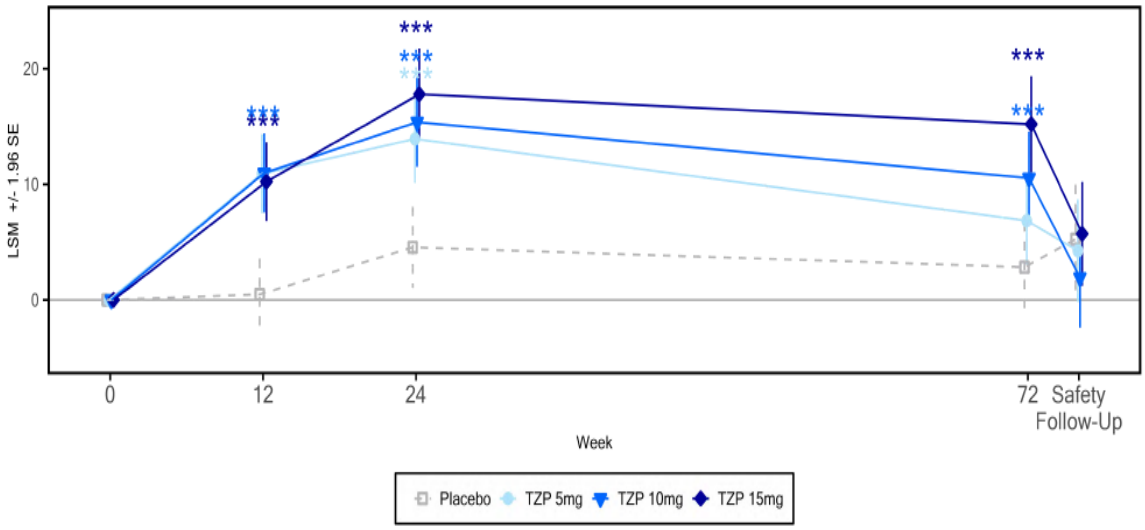


Thyroid Safety

Calcitonin levels

In SURMOUNT-1 (GPHK), 17 participants reported "blood calcitonin increased" with no relevant differences between study arms. Nevertheless, as shown in **Figure 27**, a clear correlation between TZP dose and percentage of calcitonin increase (compared to baseline) was visible. The levels peaked at week 24 in all study arms and slightly decreased until week 72. Nevertheless, at week 72, the percent change from baseline was still higher with TZP as compared to placebo, with a clearly visible dose dependency (placebo: 2.8%; TZP 5 mg: 6.9%; TZP 10 mg: 10.5% and TZP 15 mg: 15.2%).

Figure 27: Blood calcitonin levels over time in the SURMOUNT-1 study



Categorical shifts in calcitonin in SURMOUNT-1:
Shifts from maximum baseline ≤20 ng/L to maximum post-baseline >20 ng/L occurred in 30 patients: Placebo: 7 (1.1%); TZP 5 mg: 6 (0.95%); TZP 10 mg: 8 (1.26%); TZP 15 mg: 9 (1.43%). One patient (placebo group) reached a calcitonin level of >100 ng/L.

Thyroid malignancies
In contrast to the previous T2DM procedure, where no thyroid malignancy was reported in phase 2/3, the new data show 5 cases of *papillary* thyroid cancer (for details, see **Table 49**).

Table 49: Details on the patients reporting papillary thyroid cancer in studies GPHO and GPHK

Study	Treat-ment	Further information on case
GPHO	TZP 5 mg	Female 50-60 year old; pre-existing condition of thyroid nodules; normal calcitonin levels at baseline and throughout study; severe event of papillary thyroid cancer reported on D225; resolved on D242; considered related to study drug; study drug discontinued.
GPHO	TZP 10 mg	Male 50-60 year old; pre-existing condition of thyroid nodules; normal calcitonin levels at baseline and throughout study; event was moderate in severity, resolving at study completion; not considered related to study drug; study drug discontinued.
GPHO	TZP 10 mg	Female 60-70 year old; pre-existing condition of thyroid nodules and thyroid solid mass; biopsy on D166 suggests papillary thyroid carcinoma; event was considered severe; resolved on D175; not considered related to study drug; study drug discontinued;
GPHK	TZP 15 mg	Male 50-60; considered moderate in severity, no treatment discontinuation, resolved (thyroidectomy), not considered related to study drug

No events of medullary thyroid cancer were reported in AS3C (dataset comprising all TZP-treated patients from phase 2 and phase 3).

Hypoglycaemia

SURMOUNT-1

Unlike the T2DM studies, SURMOUNT-1 did not include the routine use of glucometers to capture hypoglycaemia systematically. Glucometers were mainly provided to participants who developed diabetes during the study, or who reported symptoms suggestive of hypoglycaemia requiring BG confirmation. Participants who were given glucometers were also provided diaries to record relevant information.

Severe Hypoglycaemia (severe cognitive impairment requiring assistance of another person to actively perform resuscitative actions)

Of the 1896 participants exposed to TZP in SURMOUNT-1, one episode of severe hypoglycaemia was reported by 1 (0.05%) participant in the hospital. The event was associated with multiple organ failure, including acute hepatic failure, eventually leading to death.

Blood glucose <54 mg/dL or severe hypoglycaemia

In SURMOUNT-1, the percentages and rates of TZP-treated participants reporting hypoglycaemia with BG<54 mg/dL or severe hypoglycaemia were low, but higher than in placebo-treated participants (**Table 50**). For the majority (26 of 34 [76%]) of hypoglycaemic events in TZP-treated participants in SURMOUNT-1 no symptoms were reported.

Table 50: Incidence and rate of hypoglycaemia with *BG <54 mg/dL or severe hypoglycaemia* in SURMOUNT-1 (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 TZP/placebo (95% CI)	--	9.9 (1.2, 78.4)	12.6 (1.6, >100)	10.6 (1.4, 83.4)
BG = blood glucose; CI = confidence interval; N = number of participants in population with baseline and post-baseline value at specified time point; n = number of participants with hypoglycaemia; TZP = tirzepatide.				

Overweight/obese patients from T2DM studies

The safety results regarding hypoglycaemia with *blood glucose <54 mg/dL or severe hypoglycaemia* (excluding events after initiation of new anti-hyperglycaemic therapy) from patients with baseline BMI ≥27 in the global phase 3 studies of the T2DM programme are shown in **Table 51**.

Table 51: Hypoglycaemia with *blood glucose <54 mg/dL or severe hypoglycaemia* (excluding events after initiation of new anti-hyperglycaemic therapy) - Modified Intent-to-Treat – Safety Analysis Set, Participants with Baseline BMI ≥27 kg/m^2 .

Study (comparator)		TZP, 5 mg N; n (%)	TZP, 10 mg N; n (%)	TZP, 15 mg N; n (%)	Comparator N; n (%)
GPGK (placebo)	Baseline	97; 0 (0.00)	92; 0 (0.00)	94; 1 (1.06)	85; 0 (0.00)
	Post-baseline	97; 0 (0.00)	92; 0 (0.00)	94; 0 (0.00)	85; 0 (0.00)
GPGL (Sema 1 mg)	Baseline	415; 3 (0.72)	417; 0 (0.00)	416; 0 (0.00)	422; 1 (0.24)
	Post-baseline	415; 4 (0.96)	417; 1 (0.24)	416; 8 (1.92)	422; 1 (0.24)
GPGH (degludec)	Baseline	313; 0 (0.00)	309; 0 (0.00)	315; 1 (0.32)	314; 0 (0.00)
	Post-baseline	313; 4 (1.28)	309; 3 (0.97)	315; 6 (1.90)	314; 24 (7.64)
GPGM (Ins. glargine)	Baseline	277; 1 (0.36)	280; 1 (0.36)	288; 0 (0.00)	844; 3 (0.36)
	Post-baseline	277; 19 (6.86)	280; 20 (7.14)	288; 21 (7.29)	844; 149 (17.65)
GPGI (placebo)	Baseline	105; 0 (0.00)	100; 0 (0.00)	103; 3 (2.91)	99; 0 (0.00)
	Post-baseline	105; 16 (15.24)	100; 20 (20.00)	103; 15 (14.56)	99; 10 (10.10)
N = number of subjects in the population with baseline and post-baseline value at the specified time point; n = number of subjects with hypoglycaemia; TZP = tirzepatide.					

TEAEs of hypoglycaemia in AS4C, with severity and seriousness

Hypoglycaemia was reported in TZP_ALL by 9 (0.14%) patients (severe: n=5; mild: n=4; moderate: n=1), and by 13 (0.48%) patients in the pooled comparator group (all events severe). Six (6) events in TZP_ALL (0.1%) and 12 events in the pooled comparator group (0.4%) were deemed serious.

Cardiovascular Safety

AS1C and AS2C will be discussed, with reference to SURMOUNT-1, where considered necessary. In some cases, the applicant has not submitted analyses for AS4C. The results of the ABPM (Ambulatory Blood Pressure Monitoring) sub-study in SURMOUNT-1 are provided in the separate section "ABPM sub-study in SURMOUNT-1" at the end of this section.

Blood pressure

Sitting blood pressure: systolic (SBP) and diastolic (DBP)

In AS1C, the baseline values were similar in all treatment groups (placebo, and TZP doses) for both SBP (125.4 to 126.2 mmHg) and DBP (79.4 to 80.0 mmHg). Maximal mean decreases were greater with TZP than with placebo for SBP (TZP: -7.4 to -9.2 mmHg; placebo: -2.1 mmHg) and DBP (TZP -4.5 to -5.2 mmHg; placebo: -1.7 mmHg). **AS2C** confirms these observations, but with slightly lower TZP-induced SBP and DBP reductions.

Sitting SBP in AS1C was by more than 5 mmHg lower than in the corresponding dataset of the original T2DM application, but the range of sitting DBP values was comparable. The maximum mean decreases in SBP and DBP were slightly stronger than in the previous T2DM dataset.

Abnormal blood pressure reductions and hypotension events

In AS1C, a more patients on TZP as compared to placebo fell into the category of

- DBP ≤50 and change from baseline ≤-10 mmHg (TZP_ALL: 20 [0.81%]; placebo: 2 [0.24%])
- SBP ≤90 and change from baseline ≤-20 mmHg (TZP_ALL: 66 [2.67%]; placebo: 2 [0.24%])

The abnormal blood pressure reductions by TZP were more pronounced than in the previous T2DM application.

A cluster analysis in AS1C for hypotension-related PTs (hypotension, syncope, orthostatic hypotension, pre-syncope, blood pressure decreased, and dizziness postural) revealed more TEAEs of hypotension in TZP- than in placebo-treated patients (TZP_ALL: 62 [2.49%]; placebo: 6 [0.73%]). The majority of affected TZP-treated patients was from SURMOUNT-1 (52 out of 62 participants). Analysis of the *hypotension_narrow* cluster (hypotension, orthostatic hypotension, blood pressure decreased) confirmed the above results (TZP_ALL: 35 [1.41%]; placebo: (1 [0.12%]. Again, the majority of TZP-treated participants with events were from SURMOUNT-1 (30 out of 35 participants).

Severity and seriousness of hypotension events (AS2C)

Ten (10, 0.16%) participants reported 11 serious or severe events in AS2C (**Table 52**). It is noted that 4 of these patients were from SURMOUNT-1 (all randomized to 10 or 15 mg of TZP).

Table 52. Participants with serious or severe AEs within broad cluster of hypotension, Safety Population, AS2C

Study	Reported Term for AE	Severity/Serious (Yes/No)
GPHK	Hypotension	Moderate/Yes
GPHK	Hypotension	Severe/Yes
GPHK	Lipothymia	Severe/No
GPHK	Syncopal episode	Severe/No
GPGK	Syncope	Severe/Yes

GPGL	Vasovagal syncope	Severe/Yes
GPGL	Syncope	Severe/Yes
GPGL	2 x Postural hypotension	First severe/Yes; Second severe/No
GPGL	Arterial hypotension	Severe/No
GPGM	Syncope	Severe/Yes

Pulse rate

In AS1C, baseline mean sitting pulse rate was similar between placebo and TZP (72.3 – 73.4 bpm), but increased in all TZP groups at week 4, reaching the maximum value during dose escalation (maximal increase for TZP: 2.7 – 5.2 bpm; placebo: 0.8 bpm). The mean pulse rate gradually decreased throughout the treatment period. At 72 weeks, the differences from placebo were TZP 5 mg: 0.5 bpm; TZP 10 mg: 2.2 bpm, TZP 15 mg: 2.5 bpm. At safety follow-up, the mean pulse rate for all TZP groups was by ~2 bpm *lower* than placebo and baseline. Dataset AS2C confirms these observations.

The findings are consistent with the observations in the previous T2DM application. In addition, an analysis of the subpopulation of patients from Japan in AS2C confirms the finding from the original T2DM application that TZP induces higher increases in mean pulse in patients from Japan.

Abnormal pulse rate

In AS1C, a higher percentage of patients treated with TZP than with placebo met threshold criteria for abnormal pulse rate, e.g., for the criterion "*change from baseline >20 bpm at any visit*" (TZP groups: 7.48 - 13.21% vs. placebo: 4.37%). The strongest effects were seen in the TZP 10 mg and 15 mg groups. The difference between the percentages of affected patients in the TZP groups and the placebo group were consistent with the original T2DM application. However, the percentage of affected patients in the different abnormal pulse rate categories was lower in all treatment groups in the chronic weight management application as compared to the original T2DM data.

The AS2C dataset revealed similar results. The percentage of participants affected by abnormal increases in pulse rate was incrementally increasing across TZP doses in almost all of the analysed categories. The findings are consistent with those observed in the dose-effect analysis set of the original T2DM application.

Electrocardiogram Intervals and Heart Rate

In analogy to pulse rate, the mean ECG-derived heart rate was increased from baseline with increasing TZP dose in AS1C and AS2C. No other notable effects with TZP were observed in the other ECG parameters (PR interval, QRS interval, QT, QTcF). These results are consistent with those observed in the original T2DM application.

Treatment-emergent arrhythmias and cardiac conduction disorders

AS1C:

A similar proportion of participants in TZP_ALL (3.53%) and placebo (3.26%) experienced TEAEs of arrhythmia and cardiac conduction disorders in AS1C, which is consistent with the placebo-controlled analysis set in the original T2DM application.

Seven (7) participants experienced at least 1 *serious or severe* TEAE of arrhythmia and cardiac conduction disorders in AS1C with similar frequency in TZP_ALL (0.20%) and placebo (0.24%). 6 events were experienced by 5 TZP-treated participants (3 events in 3 participants from SURMOUNT-1).

AS2C:

239 (3.8%) participants across TZP dose groups reported TEAEs of arrhythmia and cardiac conduction disorders in AS2C. Of these, 65 were from SURMOUNT-1. As in the original T2DM application, similar

percentages of participants across the TZP dose groups were affected (TZP 5 mg: 89 [4.22%]; TZP 10 mg: 69 [3.29%]; TZP 15 mg: 81 [3.82%]).
30 participants (0.48%) experienced *serious or severe* events in AS2C. Of these, 3 were from SURMOUNT-1. A total of 6 fatal events occurred in the SURPASS studies.

Major adverse cardiovascular events (CV safety meta-analysis)
An external clinical events committee (CEC) adjudicated the MACE events listed in **Table 53** in a blinded fashion throughout the phase 2 and 3 studies.

AS1C: CEC-confirmed MACE-related events occurred in 23 participants at similar percentages in the placebo- and TZP_ALL (placebo: 6 [0.73%]; TZP 5 mg: 7 [0.84%]; TZP 10 mg: 8 [0.96%]; TZP 15 mg: 2 [0.24%]; TZP_ALL: 17 [0.68%]). 9 patients in the TZP group and 5 in the placebo group were from SURMOUNT-1.

AS4C: CEC-confirmed MACE events occurred numerically more frequently with pooled comparator than with TZP (TZP_ALL: 100 [1.57%]; comparator: 74 [2.73%]). Details are provided in **Table 53**.

Table 53: Composite MACE, its components, and all-cause death in phase 2/3 comparator-controlled dataset AS4C; CEC-confirmed; Modified Intent-to-Treat Population

	TZP_ALL N=6372 n(%)	**Pooled Comparator N=2711 n(%)**
MACE	100 (1.57)	74 (2.73)
Death Due to CV Cause	23 (0.36)	18 (0.66)
MI	30 (0.47)	24 (0.89)
Hospitalization for Unstable Angina	5 (0.08)	7 (0.26)
Hospitalization for Heart Failure	11 (0.17)	7 (0.26)
Coronary Interventions	40 (0.63)	34 (1.25)
CABG	8 (0.13)	8 (0.30)
PCI	31 (0.49)	27 (1.00)
Cerebrovascular Events	25 (0.39)	15 (0.55)
Stroke	19 (0.30)	14 (0.52)
TIA	6 (0.09)	1 (0.04)
All Cause Death	39 (0.61)	32 (1.18)
Abbreviations: CABG = coronary artery bypass graft; CV = cardiovascular; MACE = major adverse cardiovascular events; MI = myocardial infarction; N = number of participants in the analysis population; n = number of subjects in the specified category; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; TZP = tirzepatide.		

A CV meta-analysis had been previously performed for the original T2DM application. In short, 142 participants experienced the primary endpoint (adjudicated MACE-4: composed of (i) death from CV or undetermined causes, (ii) myocardial infarction (iii) stroke, and (iv) hospitalisation for unstable angina pectoris) across all seven Phase 3 clinical studies for T2DM. Comparison of pooled TZP vs. pooled comparators revealed a hazard ratio of 0.80 (95% CI, 0.57 to 1.11).

ABPM (ambulatory blood pressure monitoring) sub-study in SURMOUNT-1
SURMOUNT-1 included a multinational, blinded ABPM sub-study in 494 participants, who received at least 1 dose of study treatment and wore the ABPM device for baseline and post-baseline measurements. As shown in **Table 54**, mean 24-hour SBP decreased from baseline with TZP and increased from baseline with placebo. Mean 24-hour DBP decreased from baseline only for TZP 5 mg and 10 mg and was similar to baseline for placebo. Mean 24-hour pulse rate increased from baseline only for TZP 15 mg and decreased for placebo.

Table 54 : Change from baseline in mean 24-hour blood pressure and pulse rate at week 36 SURMOUNT-1 ABPM addendum (least square means)

Parameter	Placebo (N=131)	TZP 5 mg (N=116)	TZP 10 mg (N=123)	TZP 15 mg (N=124)
Mean 24-hour SBP (mmHg)				
Baseline	123.8	125.8	124.5	124.4
Change from baseline at 36 weeks	1.8	-5.6††	-8.8†††	-6.2†††
Change difference from placebo (95% CI)	N/A	-7.4*** (-10.0, -4.7)	-10.6*** (-13.2, -8.0)	-8.0*** (-10.6, -5.4)
Mean 24-hour DBP (mmHg)				
Baseline	71.4	72.9	71.6	72.5
Change from baseline at 36 weeks	0.5	-1.5†	-2.4†††	0.0
Change difference from placebo (95% CI)	N/A	-2.0* (-3.6, -0.3)	-2.9*** (-4.5, -1.3)	-0.5 (-2.0, 1.1)
Mean 24-hour Pulse rate (bpm)				
Baseline	76.8	77.8	77.2	78.0
Change from baseline at 36 weeks	-1.8††	0.3	0.5	3.6†††
Change difference from placebo (95% CI)	N/A	2.1* (0.3, 3.9)	2.3* (0.6, 4.1)	5.4*** (3.6, 7.1)

Abbreviations: ABPM = ambulatory blood pressure monitoring; CI = confidence interval; DBP = diastolic blood pressure; N = number of participants with baseline and post-baseline values; N/A = not applicable; SBP = systolic blood pressure; TZP = tirzepatide.

*p-value <0.05, ***p-value <0.001 versus placebo
†p-value <0.05, †† p-value <0.01, ††† p-value <0.001 versus baseline

The SURMOUNT-1 ABPM data were additionally analysed for treatment-emergent abnormally high BP and pulse rate at 36 weeks:

- A lower percentage of participants in TZP groups than in the placebo group had abnormally high mean daytime SBP, mean nighttime SBP, and mean 24-hour SBP
- A lower percentage of participants in the TZP 10 mg group as compared to placebo and the other TZP groups had abnormally high mean daytime DBP and mean 24-hour DBP.
- Abnormally high mean nighttime DBP was observed in a higher percentage of participants in the TZP 15-mg group compared with placebo and other TZP groups.
- One participant randomized to TZP 15 mg had abnormally high mean 24-hour pulse rate.

Amputation or Peripheral Revascularization (only applicable to T2DM studies)

12 patients with overweight/obesity underwent *amputations* in phase 3 (TZP: n=9; insulin glargine: n=2; insulin degludec: n=1); no case was identified in the phase 2 T2DM studies. 6 of these 12 patients had pre-existing peripheral vascular disease and 6 reported tobacco use. Of the 9 TZP-treated patients with amputations (5 mg: n=2; 10 mg: n=4; 15 mg: n=3), 6 (0.13%) had an amputation considered non-accidental (diabetic foot, peripheral ischemia, infection), b 3 of these 6 patients had pre-existing peripheral vascular disease.

9 patients with overweight/obesity (TZP_ALL: n=6; semaglutide 1 mg: n=1; insulin glargine: n=2) in the T2DM studies underwent *peripheral revascularization* (8 of these had pre-existing peripheral vascular disease).

Hypersensitivity Reactions

Immediate (within 24 h of drug administration)

SURMOUNT-1:
49 (1.9%) participants experienced TEAEs of potential immediate hypersensitivity reactions within 24 h following study drug administration (**Table 55**). The reactions occurred more frequently with TZP as compared to placebo.

Table 55: Event queries for potential immediate treatment-emergent hypersensitivity reactions - Modified Intent-to-Treat – Safety Analysis Set - I8F-MC-GPHK (SURMOUNT-1)

Event Category or Term – Narrow search	Placebo (N=643) n (%)	TZP 5 mg (N=630) n (%)	TZP 10 mg (N=636) n (%)	TZP 15 mg (N=630) n (%)
On Day of Drug Administration	2 (0.3)	11 (1.7)	19 (3.0)	17 (2.7)
SMQ Anaphylactic reaction	0	0	1 (0.2)	0
SMQ Hypersensitivity*	2 (0.3)	11 (1.7)	19 (3.0)	17 (2.7)
SMQ Angioedema**	2 (0.3)	1 (0.2)	0	1 (0.2)
SMQ Severe cutaneous adverse reactions	0	0	0	0
*includes Hypersensitivity, Injection site rash, Dermatitis contact, Dermatitis allergic, Injection site hypersensitivity, Rash, Eczema, Urticaria, Dermatitis, Drug hypersensitivity, Rhinitis allergic, Anaphylactic reaction, Application site rash, Injection related reaction and Urticaria popular **includes Urticaria and Urticaria papular				

One patient in SURMOUNT-1 reported a severe immediate hypersensitivity reaction, later followed by a moderate anaphylactic reaction – please see below, section on "*Severe or serious immediate reactions (SURMOUNT-1, AS1C, AS2C datasets)*". None of the participants reported serious immediate hypersensitivity reactions.

AS1C:
A higher proportion of participants in the TZP arms reported immediate hypersensitivity reactions as compared to placebo (placebo: 3 [0.36%]; TZP 5 mg: 13 [1.56%]; TZP 10 mg: 19 [2.29%]; TZP 15 mg: 19 [2.29%]; TZP_ALL: 51 [2.05%]). Of the 51 affected TZP-treated participants, 47 were from SURMOUNT-1 **(Table 54)**. One (1) severe event of hypersensitivity occurred in SURMOUNT-1 (see details below).

AS2C:
In the phase 3 dose-effect analysis set AS2C, 91 (1.44%) TZP-treated participants reported treatment-emergent immediate hypersensitivity reactions with no clear relationship to TZP dose. The most frequently reported events were hypersensitivity (15 [0.24%]), rash (11 [0.17%]), urticaria (10 [0.16%]), eczema (8 [0.13%]), injection site rash (8 [0.13%]), and dermatitis (7 [0.11%]).

No serious event was reported; one (1) severe event of hypersensitivity occurred in SURMOUNT-1 (see details below). Remaining events were mild or moderate in severity. One participant (TZP 15 mg) discontinued the study drug due to a moderately severe immediate hypersensitivity reaction.

Severe or serious immediate reactions (SURMOUNT-1, AS1C, AS2C datasets)
No serious immediate hypersensitivity reactions occurred.
One severe event was reported (TZP 10 mg): from SURMOUNT-1, female 40-50 year old prediabetes; immediate severe hypersensitivity reaction on day 114 (resolved within same day, considered related to study drug). Separate anaphylactic reaction reported on day 505 (moderate, not considered related to study drug). The participant completed the 72-week treatment period on study drug 3 days later.

Comparison with previous T2DM data

The difference between TZP_ALL and placebo in the occurrence of immediate hypersensitivity reactions was more pronounced in the previous T2DM application as compared to the overweight/obese patients (overweight/obese: TZP_ALL, 2.05% *vs.* placebo, 0.36%; T2DM: TZP_ALL, 0.6% *vs.* placebo, 0.4%).

Non-immediate (>24 h after drug administration, but prior to next administration)

SURMOUNT-1:
86 participants experienced TEAEs of potential (mostly cutaneous) non-immediate hypersensitivity reactions (**Table 56**), occurring more frequently with TZP (TZP_ALL: 72 [3.80%]) as compared to placebo (placebo: 14 [2.2%]).

Table 56: Event queries for potential non-immediate treatment-emergent hypersensitivity reactions - Modified Intent-to-Treat – Safety Analysis Set - I8F-MC-GPHK (SURMOUNT-1)

Event Category or Term – Narrow search	Placebo (N=643) n (%)	TZP 5 mg (N=630) n (%)	TZP 10 mg (N=636) n (%)	TZP 15 mg (N=630) n (%)
Beyond Day of Drug Administration	14 (2.2)	22 (3.5)	22 (3.5)	28 (4.4)
SMQ Anaphylactic reaction	0	0	0	0
SMQ Hypersensitivity*	14 (2.2)	22 (3.5)	22 (3.5)	28 (4.4)
SMQ Angioedema**	2 (0.3)	5 (0.8)	3 (0.5)	4 (0.6)
SMQ Severe cutaneous adverse reactions***	0	0	0	1 (0.2)
*includes Rash, Hypersensitivity, Dermatitis contact, Urticaria, Dermatitis, Injection site rash, Rhinitis allergic, Eczema, Drug hypersensitivity, Conjunctivitis allergic, Injection site hypersensitivity, Angioedema, Application site hypersensitivity, bronchospasm, cutaneous vasculitis, Dermatitis allergic, Dermatitis infected, Eye swelling, Lip swelling, Mast cell activation syndrome, Mouth swelling, Perioral dermatitis, Rash pruritic, Swelling face, Urticaria cholinergic. **includes Urticaria, Angioedema, Eye swelling, Lip swelling, Mouth swelling, Swelling face, Urticaria cholinergic ***Cutaneous vasculitis				

No serious non-immediate hypersensitivity reactions were reported.
Severe non-immediate hypersensitivity reactions were reported by 2 (0.1%) participants (rash in GPHK [TZP 10 mg] and dermatitis in GPHK [TZP 15 mg]. 4 participants discontinued the study drug due to non-immediate hypersensitivity reactions.

Additional hypersensitivity reaction (not identified by pre-specified search criteria):
One event of leukocytoclastic vasculitis in the lower limbs (TZP 15 mg group) on day 515; patient had pharyngotonsilitis on day 510 and was treated with amoxicillin/clavulanic acid from day 512 to 516. The AE was of moderate severity and resolved on Study Day 560.

AS1C:
Non-immediate hypersensitivity reactions occurred more frequently in the TZP groups as compared to the placebo groups (placebo: 16 [1.93%]; TZP 5 mg: 28 [3.37%]; TZP 10 mg: 26 [3.13%]; TZP 15 mg: 33 [3.99%]; TZP_ALL: 87 [3.49%]). Of the 87 affected patients, 72 were from SURMOUNT-1.

No serious event was reported. For the 2 severe events, please see above, SURMOUNT-1 section. The remaining events were considered mild or moderate in severity. 4 participants (SURMOUNT-1), discontinued the study drug due to non-immediate hypersensitivity reactions.

AS2C:
In the phase 3 dose-effect analysis set AS2C, 193 (3.05%) TZP-treated participants reported treatment-emergent non-immediate hypersensitivity reactions. A slight dose dependency was visible (5 mg: 2.70%; 10 mg: 3.05%; 15 mg: 3.39%). Most frequently reported were rash (36 [0.57%]), urticaria (26 [0.41%]), dermatitis contact (20 [0.32%]), hypersensitivity (19 [0.30%]), rhinitis allergic (17 [0.27%]), and eczema (16 [0.25%]).

No serious event was reported. A total of 3 (0.05%) TZP-treated participants (1 per TZP dose group; 2 from SURMOUNT-1) reported severe non-immediate hypersensitivity reactions (SURMOUNT-1: rash with 10 mg, and dermatitis with 15 mg; GPGL: rhinitis allergic with 5 mg). The remaining events were considered mild or moderate in severity. 8 TZP-treated participants in AS2C (4 from SURMOUNT-1) discontinued the study drug due to non-immediate hypersensitivity reactions.

Comparison with previous T2DM data

In the overweight/obese patients, non-immediate hypersensitivity reactions occurred more frequently than in the previous T2DM dataset, but the % difference between TZP_ALL and placebo was comparable (overweight/obese: placebo, 1.93%; TZP_ALL, 3.49%; T2DM: placebo: 1.3%, TZP_ALL, 2.6%).
Treatment-emergent non-immediate hypersensitivity reactions were reported more frequently in the phase 3 dose-effect analysis set of the current weight reduction application as compared to the previously analysed T2DM dataset (3.05% vs. 2.75%).

Injection Site Reactions

MedDRA high-level terms "Injection site reaction", "Administration site reaction" and "Infusion site reactions"

SURMOUNT-1

173 (6.8%) participants (more TZP- than placebo-treated patients) experienced injection site reactions based on the pre-defined MedDRA search **(Table 57)**. No severe or serious events were identified.

Table 57: Summary of treatment-emergent injection site reactions in SURMOUNT-1 - mITT population – safety analysis set

	Placebo (N=643) n (%)	TZP 5mg (N=630) n (%)	TZP 10mg (N=636) n (%)	TZP 15mg (N=630) n (%)
Subjects with >= 1 TEAE of Injection Site Reactions	14 (2.2)	36 (5.7)	62 (9.7)	61 (9.7)
Injection site reactions (HLT)	14 (2.2)	36 (5.7)	62 (9.7)	61 (9.7)
Injection site reaction	2 (0.3)	18 (2.9)	36 (5.7)	29 (4.6)
Injection site erythema	0	6 (1.0)	13 (2.0)	20 (3.2)
Injection site pruritus	0	4 (0.6)	6 (0.9)	13 (2.1)
Injection site bruising	5 (0.8)	2 (0.3)	5 (0.8)	4 (0.6)
Injection site pain	2 (0.3)	5 (0.8)	3 (0.5)	1 (0.2)
Injection site rash	0	1 (0.2)	5 (0.8)	4 (0.6)
Injection site haematoma	4 (0.6)	1 (0.2)	1 (0.2)	0
Injection site hypersensitivity	0	1 (0.2)	3 (0.5)	1 (0.2)
Injection site haemorrhage	1 (0.2)	0	2 (0.3)	0
Injection site paraesthesia	1 (0.2)	0	1 (0.2)	0
Injection site swelling	0	0	1 (0.2)	1 (0.2)
Injection site induration	0	0	0	1 (0.2)
Injection site inflammation	0	1 (0.2)	0	0
Injection site irritation	0	1 (0.2)	0	0
Injection site oedema	0	0	0	1 (0.2)

Abbreviations: HLT = high level term; N = number of subjects in the analysis population; n = number of subjects in the specified category; NA = not applicable; TEAE = treatment-emergent adverse event; TZP = tirzepatide.

Two TZP-treated participants discontinued study drug due to injection site reactions:

- GPHK (TZP 10 mg): injection site rash, mild, 5 events
- GPHK (TZP 15 mg): injection site reaction, mild, 2 events.

Data from dedicated electronic case report forms (eCRFs) in SURMOUNT-1

998 events in 176 (6.9%) participants (154 overlap with MedDRA search above) were retrieved (placebo: 8 events; TZP groups: 990 events). Most injection site reactions in TZP-treated patients occurred >6 hours after TZP administration (5 mg: 156 [70.6%]; 10 mg: 300 [71.8%]; 15 mg: 235 [67.0%]).
From 24 hours to 14 days post-administration, 25.9 to 41.1% of the injection site reactions in the TZP groups were reported (5 mg: 82 [37.1%]; 10 mg: 172 [41.1%]; 15 mg: 91 [25.9%]. Most TZP-treated patients reported erythema and pruritus, followed by induration, oedema and pain.

AS1C:
The frequency of injection site reactions was higher with TZP than with placebo (TZP_ALL: 7.19%; placebo: 1.81%), and the difference between TZP_ALL and placebo was larger than in the original T2DM population (previous T2DM data: TZP_ALL: 3.2%; placebo: 0.4%).

No events were serious, and all were mild or moderate in severity. Regarding the 2 TZP-treated subjects who discontinued the study drug, please see preceding section.

AS2C:
The percentage of participants reporting treatment-emergent injection site reactions was increased in the higher dose groups (5 mg: 3.03%; 10 mg: 5.01%; 15 mg: 5.28%). In most participants, the first injection site reaction occurred during dose escalation. No events were serious, and all were mild or moderate in severity. 5 (0.08%) TZP-treated participants (including 2 from SURMOUNT-1) discontinued study drug due to injection site reactions.

In the eCRFs, 1775 events were reported in 296 patients (258 overlap with above MedDRA search). The number of affected participants was higher with 10 mg and 15 mg of TZP as compared to the 5 mg dose (5 mg: 65 [3.08%]; 10 mg: 111 [5.30%]; 15 mg: 120 [5.66%]). Specifically, the percentage of TZP-treated participants reporting 2 to 5 and >5 events increased with increasing TZP dose. Most events (72.6%) occurred more than 6 hours after study drug administration, with approximately one third of events (35.1%) occurring from 24 hours to 14 days after study drug administration.

Immunogenicity

A patient was defined as "TE ADA Evaluable" if there is at least one non-missing test result for TZP ADA for each of the baseline period and the post-baseline period.

Definition of ADA+ status:
- *Treatment-induced:* new ADA post-baseline (titer ≥2x minimum required dilution [MRD])
- *Treatment-boosted:* ADA at least 4-fold increased as compared to baseline
- *TE ADA Inconclusive*: ≥20% of the pre-dose post-baseline samples are ADA inconclusive and the patient is not otherwise TE ADA+.

Treatment-emergent TZP ADA status

SURMOUNT-1
Baseline TE ADA status was comparable across treatment groups, but post-baseline TE ADA+ status was considerably increased with TZP as compared to placebo (**Table 58**). Out of 2489 TE-ADA evaluable participants, 179 (7.2%) had ADA at baseline (titres from 1:10 to 1:2560; median 1:20). Of the 1858 TZP-treated TE-ADA evaluable patients, 1226 (66.0%) were treatment-emergent ADA positive, out of which 1145 (61.6%) were classified as treatment-induced, and 81 (4.4%) as treatment-boosted. Maximum titres for TZP-treated TE-ADA-positive participants ranged from 1:20 to 1:20,480 (median 1:320).

Table 58: Summary of TE ADA status in SURMOUNT-1

Category	n (%)				
	Placebo (N=643)	TZP 5mg (N=630)	TZP 10mg (N=636)	TZP 15mg (N=630)	TZP_ALL (N=1896)
Patients Evaluable for TE ADA	631 [98.1]	619 [98.3]	624 [98.1]	615 [97.6]	1858 [98.0]
ADA Present at Baseline	47 (7.4)	46 (7.4)	36 (5.8)	50 (8.1)	132 (7.1)
Post-baseline TE ADA+	22 (3.5)	396 (64.0)	407 (65.2)	423 (68.8)	1226 (66.0)
Treatment-Induced TE ADA+	20 (3.2)	372 (60.1)	381 (61.1)	392 (63.7)	1145 (61.6)
Treatment-Boosted TE ADA+	2 (0.3)	24 (3.9)	26 (4.2)	31 (5.0)	81 (4.4)
Post-baseline TE ADA Inconclusive	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Post-baseline TE ADA-	609 (96.5)	222 (35.9)	217 (34.8)	192 (31.2)	631 (34.0)
Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide.					

AS2C

Baseline TE ADA status was comparable across TZP dosing groups (**Table 59**). TZP treatment considerably increases ADA post-baseline. Out of 6206 TE ADA evaluable TZP-treated patients, 3484 (56.1%) were post-baseline TE ADA$^+$, with no relevant differences between dosing groups. Maximum ADA titers in TE ADA$^+$ participants ranged from 1:20 to 1:81920 (median 1:160).

Table 59: Summary of TE ADA status in AS2C

Category	n (%)			
	TZP 5 mg (N=2109)	TZP 10 mg (N=2095)	TZP 15 mg (N=2122)	TZP_ALL (N=6326)
Patients Evaluable for TE ADA	2070 (98.2)	2057 (98.2)	2079 (98.0)	6206 (98.1)
ADA Present at Baseline	144 (7.0)	136 (6.6)	147 (7.1)	427 (6.9)
Post-baseline TE ADA+	1126 (54.4)	1159 (56.3)	1199 (57.7)	3484 (56.1)
Post-baseline TE ADA Inconclusive	1 (0.05)	0	0	1 (0.02)
Post-baseline TE ADA-	943 (45.6)	898 (43.7)	880 (42.3)	2721 (43.8)

In 43.1 % of the assessed patients, TE ADAs were persistent (ADAs present for ≥16 weeks). Neutralizing antibodies against TZP activity on the glucose dependent insulinotropic polypeptide (GIP) receptor were developed by 2.2% of the TE ADA evaluable patients, and against TZP activity on the glucagon-like peptide 1 (GLP 1) receptor by 2.4%. Neutralising antibodies against native GIP and GLP 1 were developed by 0.8 % and 0.3 %, respectively.

The percentage of post-baseline TE ADA+ patients in the TZP-treated population was lower in AS2C than in SURMOUNT-1 (compare **Tables 56** and **57**).

Specific TEAEs by TE ADA

In the pooled TZP-treated groups of dataset AS2C, the following percentages of TE ADA+ and TE ADA- patients experienced hypersensitivity- or injection site reactions:

- *Hypersensitivity reaction:*
  TE ADA+: 170 (4.9%) *vs.* TE ADA-: 82 (3.0%)

  The 170 TE ADA+ participants with hypersensitivity reactions had ADA titres from 1:20 to 1:10240. Out of 137 TE ADA+ participants with a maximum ADA titre of ≥1:5120, 17 experienced mild or moderate hypersensitivity reactions. No pattern of temporal relationship was observed. Most events were mild or moderate. 3 of the 4 participants with a severe or serious hypersensitivity reaction were TE ADA$^-$. One participant from SURMOUNT-1 (TZP 10 mg), who reported severe rash on study day 80, was TE ADA$^+$ (treatment-induced; peak titre of 1:1280 on study day 84). The TZP-treated patient with an anaphylactic reaction (from SURMOUNT-1) was TE ADA-.

- *Injection site reactions:*
  TE ADA+: 256 (7.3%) *vs.* TE ADA-: 21 (0.8%)

The difference in the percentages of TE ADA$^+$ and TE ADA$^-$ patients with injection site reactions is larger than in the previous T2DM application (previous data: TE ADA$^+$: 2.32%; TE ADA-: 0.35%). Of the 256 affected TE ADA+ participants, the titre ranged from 1:20 to 1:81920 during the treatment period. Of 137 TE ADA+ participants with a maximum ADA titre of ≥1:5120, 28 experienced mild or moderate injection site reactions (highest titre: 1:81920). No pattern of temporal relationship was observed. 38 additional participants with TEAEs of injection site reactions were identified in the eCRF; 37 of these participants were TE ADA+ (titres 1:20 to 1:20480).

One participant (TZP 5 mg; from a T2DM study; not captured by MedDRA search for injection site reactions) reported moderate cellulitis on study day 107 and a severe SAE of cellulitis at the injection site on study day 124 (resolved on study day 148). She was TE ADA$^+$ at study day 84 (treatment-induced; titre of 1:640) and remained TE ADA$^+$ throughout the study.

Diabetic Retinopathy Complications (only applicable to T2DM studies)

21 (0.36%) TZP-treated patients and 6 (0.25 %) comparator-treated patients reported *worsening of fundoscopic examination results* (retinopathy eCRF) in the phase 3 studies (SURPASS 1 to 5, SURPASS J-Mono, SURPASS J-Combo and SURPASS AP-Combo).

Search for MedDRA PTs related to diabetic retinopathy complications:

AS1C: none with TZP *vs.* 2 (1.09%) patients with placebo (PT of "vision blurred").

AS2C (without SURMOUNT-1): TEAE of diabetic retinopathy complications in 34 (0.77%) of TZP-treated patients, with similar percentages across dose groups (5 mg: 0.81%; 10 mg: 0.82%; 15 mg: 0.67%). Five patients (0.11%; all treated with TZP) experienced ≥1 serious/severe TEAE of potential diabetic retinopathy (TZP 5 mg: 2 x retinal vein occlusion; 1 x retinal detachment; TZP 10 mg: 1 x retinal detachment; TZP 15 mg: 1 x macular oedema).

AS4C: Five (5) TZP-treated (0.11%) and 2 (0.10%) comparator-treated participants reported ≥1 serious or severe TEAE of potential diabetic retinopathy.

Hepatobiliary Disorders

Hepatobiliary events

General comment: The most frequently reported hepatobiliary TEAEs in SURMOUNT-1, AS1C and AS2C pertained to increases of various hepatic enzymes and to the PT "hepatic steatosis".

- SURMOUNT-1: 52 (2.0%) patients with hepatic TEAEs; similar frequency across treatment groups (placebo: 2.2%; TZP groups: 1.7% - 2.4%)
- AS1C: 72 (2.17%) participants with hepatic TEAEs; similar frequency across treatment groups (placebo: 2.06%; TZP groups: 1.57% to 2.16%). To these 72 participants, SURMOUNT-1 contributed 38 TZP- and 14 placebo-treated patients.
- AS2C: 151 (2.39%) TZP-treated participants (38 from SURMOUNT-1) experienced hepatic TEAEs; similar frequency across TZP groups (2.24% to 2.59%).

Severe or serious hepatic events (AESI):

- SURMOUNT-1/AS1C: 4 patients in AS1C (all TZP-treated and from SURMOUNT-1) reported serious or severe events of transaminases increased, hepatic failure, aspartate aminotransferase increased, or liver function test increased.
- AS4C: 7 (0.11%) TZP-treated patients in AS4C (4 from SURMOUNT-1), and 2 (0.07%) comparator-treated patients reported serious or severe events.

Hepatic analytes (ALT, AST, ALP, bilirubin)

AS1C:

- Maximum post-baseline ALT: A higher percentage of TZP- as compared to placebo-treated patients was in the categories ≥5 x ULN and ≥10 x ULN (**Table 60**). SURMOUNT-1 contributed 6 of the 7 TZP-treated patients in category ≥10 x ULN. In 6 cases, the strong ALT elevation was explained by medical reasons (i.e., hepatitis, autoimmune disorder, biliary duct obstruction, cholelithiasis, pancreatitis).
- Maximum post-baseline AST: Higher percentages of patients with TZP than with placebo were in the categories ≥3 x ULN, ≥5 x ULN and ≥10 x ULN (**Table 60**). This imbalance did not occur in the previous T2DM application. Of note, all 5 patients with post-baseline AST ≥10 x ULN were from SURMOUNT-1, but in most cases, a medical explanation was available (1 x hepatitis B; 1 x cholelithiasis with hepatic steatosis; 2 x vigorous exercise; 1 x isolated elevation).
- Maximum post-baseline ALP ≥2 x ULN: An imbalance occurred for TZP_ALL (9 [0.4%]) vs. placebo (0). SURMOUNT-1 contributed 8 of the 9 cases in TZP_ALL.
- Maximum post-baseline bilirubin ≥2 x ULN: Similar imbalance as for ALP (TZP_ALL: 9 [0.4%] vs. placebo: 1 [0.1%]). All 9 cases in TZP_ALL were from SURMOUNT-1.
- ALT, AST, ALP and bilirubin over time: ALT, AST and ALP decreased from baseline to week 40 and 72 in each TZP group. This trend was more pronounced with TZP than with placebo.
  At week 40, 72 and safety follow-up, bilirubin increased slightly, but more pronounced in TZP- as compared to placebo-treated patients.
- TEAEs of hepatic enzyme abnormalities: Most events were from SURMOUNT-1 (39 of 42 TZP-treated and 11 of 12 placebo-treated patients). Of the 42 events in TZP-treated participants, 20 (48%) were mild, 19 (45%) moderate, and 3 (7%) severe. Of the 12 events in placebo-treated participants, 10 (83%) were mild and 2 (17%) moderate.

AS2C:

AS2C is discussed in the following, as the applicant has not provided the results for dataset AS4C.

- Maximum post-baseline ALT and AST: No clear dose-effect relationship (**Table 60**). The absolute number of TZP-treated patients with maximum post-baseline ALT or AST levels ≥10 x ULN is almost the same as in AS1C, i.e., it can be assumed that these cases mostly come from SURMOUNT-1.
- Maximum post-baseline bilirubin ≥2 x ULN: TZP_ALL: 14 (0.2%) - of these, 2 had already values ≥2 x ULN at baseline.
- Maximum post-baseline ALP ≥2 x ULN: TZP_ALL: 20 (0.3%) - of these, 3 had already values ≥2 x ULN at baseline.
- Development of ALT, AST, ALP and bilirubin over time: In each TZP group, ALT, AST and ALP decreased from baseline to week 40, 52 and 72, with a more pronounced effect in higher dose groups. Bilirubin slightly increased in TZP-treated patients as compared to baseline.
- TEAEs of hepatic enzyme abnormalities: 85 (1.34%) TZP-treated participants reported a TEAE in the Liver-related investigations, signs, and symptoms SMQ (no dose-effect relationship); SURMOUNT-1 contributed 28 of these cases. No event was serious, but 3 events in SURMOUNT-1 were severe. Four (4) participants (2 from SURMOUNT-1) discontinued study drug.

Table 60: Maximum post-baseline laboratory values for ALT and AST in safety analysis sets AS1C and AS2C

		AS1C	**n(%)**		
Maximum post-baseline	Placebo (N=805)	TZP 5 mg (N=822)	TZP 10 mg (N=810)	TZP 15 mg (N=810)	TZP_ALL (N=2442)

Alanine aminotransferase (ALT)					
≥ 3 x ULN	11 (1.4)	8 (1.0)	12 (1.5)	12 (1.5)	32 (1.3)
≥ 5 x ULN	3 (0.4)	3 (0.4)	8 (1.0)	3 (0.4)	14 (0.6)
≥ 10 x ULN	0	1 (0.1)	4 (0.5)	2 (0.2)	7* (0.3)
Aspartate aminotransferase (AST)					
≥ 3 x ULN	5 (0.6)	11 (1.3)	8 (1.0)	5 (0.6)	24 (1.0)
≥ 5 x ULN	1 (0.1)	6 (0.7)	5 (0.6)	2 (0.2)	13 (0.5)
≥ 10 x ULN	0	2 (0.2)	2 (0.2)	1 (0.1)	5** (0.2)
		AS2C	**n(%)**		
Maximum post-baseline		TZP 5 mg (N=2085)	TZP 10 mg (N=2064)	TZP 15 mg (N=2093)	TZP_ALL (N=6242)
Alanine aminotransferase (ALT)					
≥ 3 x ULN		19 (0.9)	22 (1.1)	28 (1.3)	69 (1.1)
≥ 5 x ULN		7 (0.3)	10 (0.5)	9 (0.4)	26 (0.4)
≥ 10 x ULN		1 (0.0)	5 (0.2)	2 (0.1)	8 (0.1)
Aspartate aminotransferase (AST)					
≥ 3 x ULN		16 (0.8)	14 (0.7)	13 (0.6)	43 (0.7)
≥ 5 x ULN		8 (0.4)	6 (0.3)	6 (0.3)	20 (0.3)
≥ 10 x ULN		2 (0.1)	2 (0.1)	2 (0.1)	6 (0.1)
*6 of these patients were from SURMOUNT-1 **all from SURMOUNT-1 n = number of patients with at least 1 observation in both the baseline and post-baseline category TZP = tirzepatide; ULN = upper level of normal					

Drug-induced serious hepatotoxicity (eDISH plot)

- Hy's law: Three (3) TZP-treated participants from SURMOUNT-1 were in Hy's law range (ALT and total bilirubin of >3×ULN and >2×ULN, respectively; **Figure 28**). However, all three cases could be explained by medical reasons, and therefore did not meet all criteria for Hy's law:
  - GPHK: TZP 15 mg group; Choledocholithiasis
  - GPHK: TZP 5 mg group; Cholecystitis, cholelithiasis, hepatic steatosis
  - GPHK: TZP 10 mg group; Hepatitis B
- Hyperbilirubinaemia: 15 (0.21%) TZP-treated *vs.* 2 (0.07%) comparator-treated patients
- ALT≥3 x ULN: 77 (1.06%) TZP-treated *vs.* 30 (1.12%) comparator-treated patients

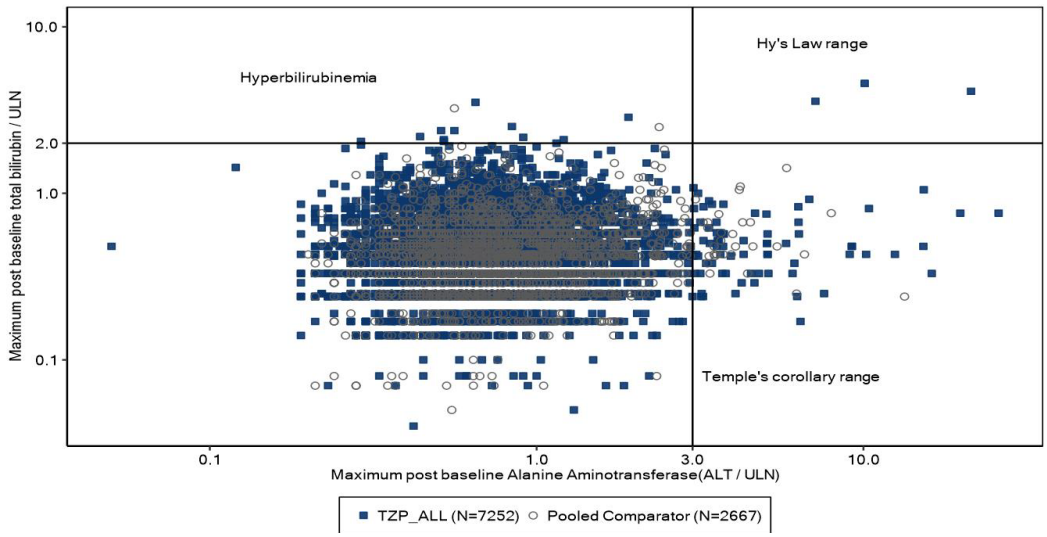


Figure 28: eDISH plot: maximum total bilirubin vs. maximum ALT in participants with overweight/obesity in the TZP Phase 2 and 3 studies (safety population).

Potentially clinically important cases:

Twelve (12) participants (9 from SURMOUNT-1) had an increase in hepatic enzymes ≥10 x ALT and ≥10 x AST. Three (3) of the "SURMOUNT-1 cases" are listed above in the section "*Drug-induced serious hepatotoxicity (eDISH plot)*". The other 6 cases from SURMOUNT-1 are listed as follows, along with potential medical explanations:

- TZP 10 mg group; ALT- and AST elevation on day 85; antinuclear antibodies titre (1:40) with speckled pattern on day 92, but no final diagnosis ➔ cause of ALT/AST increase unknown. Study drug permanently discontinued; ALT, AST, ALP, and total bilirubin back to normal on day 225.
- TZP 10 mg group; single isolated ALT/AST increase with unknown cause on day 84; no AEs reported around the date of the event; participant completed study on study drug.
- TZP 5 mg group; AE of gallstones reported on day 54; cholecystectomy on day 84 (TZP administration interrupted; last injection prior to hospitalization on day 78); acute pancreatitis reported on day 88 (end date: day 95). On day 112, ALT and AST had returned to normal. Study drug reinitiated on day 117.
- TZP 10 mg; ALT/AST elevation on day 337. AE of cholelithiasis on day 337; study drug interrupted (last injection on day 351); AE of acute cholecystitis on day 370 → cholecystectomy performed. On day 389, ALT levels were 122 U/L and AST levels were 98 U/L. During the remainder of the study, ALT and AST levels further decreased. Study drug reinitiated on day 395.
- TZP 5 mg group and TZP 15 mg group: ALT and/or AST elevations were presumably due to vigorous physical exercise.

Gallbladder-related disorders

SURMOUNT-1: As SURMOUNT-1 constitutes the major part of the AS1C dataset, please see AS1C section below. Reference to SURMOUNT-1 is included, where considered appropriate.

AS1C: Treatment-emergent gallbladder disease occurred more frequently in TZP- as compared to placebo-treated patients (placebo: 8 [0.97%]; TZP_ALL: 40 [1.61%]). All affected placebo-treated participants and 37 of the 40 TZP-treated participants were from SURMOUNT-1. The % patients affected in TZP and placebo groups are higher than in the original T2DM application (T2DM: placebo: 0%; TZP_ALL: 0.6%).

The most frequently reported events were cholelithiasis (TZP_ALL: 22 [0.88%]; placebo: 6 [0.73%]) and cholecystitis (including cholecystitis and acute cholecystitis) (TZP_ALL: 13 [0.52%]; placebo: 0%). All cholecystitis-related events occurred in SURMOUNT-1.

An evaluation of gallbladder-related TEAEs in relation to maximum weight reduction (**Table 61**) revealed a higher incidence of gallbladder-related events with increased weight reduction in the TZP group. This trend was also visible with placebo, but only few patients on placebo reached a weight reduction ≥20%.

Table 61: Summary of treatment-emergent acute gallbladder disease by maximum weight reduction categories in AS1C

Maximum Weight Reduction Category	Participants		Any Gallbladder-Related Event	
	Placebo n	TZP_ALL n	Placebo m (%)	TZP_ALL m (%)
Any category	827	2490	8 (1.0)	40 (1.6)
≥0% to <10%	599	653	6 (1.0)	6 (0.9)
≥10% to <20%	105	815	2 (1.9)	10 (1.2)
≥20 % to ≤30%	11	663	0	14 (2.1)
>30%	2	310	0	10 (3.2)

Abbreviations: n = number of participants in treatment group for each category; m = number of participants with at least 1 treatment-emergent adverse event; TZP = tirzepatide.

A total of 22 (0.88%) TZP-treated participants and 5 (0.60%) placebo-treated participants reported serious or severe gallbladder-related events in AS1C (most frequently with TZP: cholelithiasis, cholecystitis acute and cholecystitis). All 27 participants with serious or severe gallbladder-related events were from SURMOUNT-1. Of these, 20 (0.80%) TZP-treated and 5 (0.60%) placebo-treated participants had at least 1 serious gallbladder related TEAE.

AS4C: A total of 83 (1.30%) TZP-treated and 22 (0.81%) comparator-treated participants reported TEAEs of gallbladder disease. Cholecystitis was reported by 32 (0.50%) TZP-treated (18 from SURMOUNT-1) *vs.* 9 (0.33%) comparator-treated participants (3 from SURMOUNT-1).

A total of 36 (0.56%) TZP-treated *vs.* 10 (0.37%) comparator-treated participants reported serious or severe events of gallbladder disease. Serious or severe events of cholecystitis were reported by 17 (0.27%) TZP-treated (10 from SURMOUNT-1) *vs.* 6 (0.22%) comparator-treated patients (3 from SURMOUNT-1).31 of the 36 participants with serious or severe gallbladder disease reported SAEs of cholelithiasis (n=15) or cholecystitis (n=16).

Malignancy

SURMOUNT-1 dataset

Overall, 24 (0.9%) participants reported malignancies **(Table 62)**; 15 of these reported serious malignancies (placebo: 7 [1.1%]; TZP 5 mg: 4 [0.6%]; TZP 10 mg: 1 [0.2%]; TZP 15 mg: 3 [0.5%]). There is a slight numerical imbalance disfavouring TZP with regard to malignancies of the skin (basal cell carcinoma, malignant melanoma, squamous cell carcinoma, highlighted in **Table 62**).

Table 62: Summary of treatment-emergent malignancies (skin malignancies highlighted in table) - mITT Population – Safety Analysis Set

Event Category or Term	Placebo (N=643) n (%)	TZP 5 mg (N=630) n (%)	TZP 10 mg (N=636) n (%)	TZP 15 mg (N=630) n (%)
Subjects with >= 1 TEAE of malignancies	7 (1.1)	9 (1.4)	3 (0.5)	5 (0.8)
Malignant tumours (SMQ)	7 (1.1)	8 (1.3)	2 (0.3)	4 (0.6)
Narrow	7 (1.1)	8 (1.3)	2 (0.3)	4 (0.6)
Prostate cancer[a]	1 (0.5)	2 (1.0)	0	0
Basal cell carcinoma	0	2 (0.3)	0	0
Intraductal proliferative breast lesion	1 (0.2)	1 (0.2)	0	0
Malignant melanoma	0	1 (0.2)	1 (0.2)	0
Papillary thyroid cancer	1 (0.2)	0	0	1 (0.2)
Adenocarcinoma of the cervix[b]	1 (0.2)	0	0	0
Adenosquamous carcinoma of the cervix[b]	0	0	0	1 (0.2)
Endometrial cancer[b]	0	1 (0.2)	0	0
Ovarian cancer[b]	1 (0.2)	0	0	0
Ovarian germ cell endodermal sinus tumour stage I[b]	0	1 (0.2)	0	0
Breast cancer	0	0	0	1 (0.2)
Invasive ductal breast carcinoma	0	1 (0.2)	0	0
Lung adenocarcinoma	0	0	0	1 (0.2)
Pancreatic carcinoma metastatic	1 (0.2)	0	0	0
Plasma cell myeloma	1 (0.2)	0	0	0
Renal cancer	1 (0.2)	0	0	0
Squamous cell carcinoma[c]	0	0	1 (0.2)	0

Tumours of unspecified malignancy (SMQ)	0	1 (0.2)	1 (0.2)	1 (0.2)
Narrow	0	1 (0.2)	1 (0.2)	1 (0.2)
Colon neoplasm	0	1 (0.2)	0	0
Ear neoplasm	0	0	1 (0.2)	0
Prolactin-producing pituitary tumour	0	0	0	1 (0.2)

AESI = adverse events of special interest; N = number of subjects in the analysis population; n = number of subjects in the specified category; NA = not applicable; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event; TZP = tirzepatide.

[a] Denominator adjusted (only males): N=207 (Placebo), N=204 (TZP 5 mg), N=209 (TZP 10 mg), N=205 (TZP 15 mg).
[b] Denominator adjusted (only females): N=436 (Placebo), N=426 (TZP 5 mg), N=427 (TZP 10 mg), N=425 (TZP 15 mg).
[c] of the skin, affecting the right ankle

AS4C dataset

Most types of malignancies were reported by only 1 or 2 participants. Only basal cell carcinoma, prostate cancer, papillary thyroid cancer, and squamous cell carcinoma were reported by ≥2 TZP-treated patients. In the completed Phase 2/3 studies (AS3C), no cases of MTC or C-cell hyperplasia were reported. **Table 63** shows the number of treatment-emergent malignancies according to cancer location. The imbalance regarding skin malignancies in SURMOUNT-1 noted in the preceding section) is confirmed.

Table 63: Treatment-emergent malignancies according to cancer location in participants with overweight/obesity, phase 2/3 comparator-controlled analysis set (AS4C).

Location of Cancer	**TZP_ALL (N=6372) n (%)[a]**	**Pooled Comparator (N=2711) n (%)[a]**
Participants with ≥1 TEAE of Malignancy	62 (0.97)	31 (1.14)
Skin	16 (0.25)	3 (0.11)
Breast	8 (0.13)	3 (0.11)
Gastrointestinal	7 (0.11)	2 (0.07)
Renal	7 (0.11)	2 (0.07)
Reproductive neoplasms female	6 (0.09)	2 (0.07)
Reproductive neoplasms male	6 (0.09)	4 (0.15)
Thyroid	4 (0.06)	1 (0.04)
Lung	3 (0.05)	3 (0.11)
Hepatobiliary	2 (0.03)	3 (0.11)
Nervous system neoplasms	1 (0.02)	1 (0.04)
Musculoskeletal and connective tissue	2 (0.03)	0 (0.00)
Endocrine neoplasms	3 (0.05)	0 (0.00)
Blood and lymphatic system	1 (0.02)	5 (0.18)
Ear, nose, throat	1 (0.02)	2 (0.07)
Bladder	0 (0.00)	2 (0.07)
Other	3 (0.05)	1 (0.04)

[a]frequencies were calculated in relation to the total number of participants, denominator was not adjusted in cases of gender-specific conditions

Two (2) cases of **pancreatic cancer** were reported in participants with overweight/obesity in AS4C; (SURPASS-1, TZP; SURMOUNT-1, placebo). One additional case of pancreatic cancer (not included in above analysis) occurred in a patient with BMI <27 kg/m^2 (SURPASS-4, TZP). In addition, a non-malignant pancreatic cyst (reported as pancreatic neoplasm) occurred in a TZP-treated participant in SURPASS-4.

Four (4) TZP-treated and 1 placebo-treated participant reported **papillary thyroid cancer**. 3 of the 4 affected TZP-treated participants were from SURPASS-AP-Combo and had pre-existing thyroid mass/nodules at study entry; the fourth participant was from SURMOUNT-1 (TZP 15 mg) and had no

history of thyroid neoplasm, but was diagnosed with papillary thyroid cancer ~4 months after starting study drug.

Major Depressive Disorder/Suicidal Ideation or Behaviour

SURMOUNT-1

Columbia-Suicide severity rating scale (C-SSRS)

C-SSRS captures occurrence, severity, and frequency of suicidal ideation and/or behavior. Ten categories are assessed by Y/N responses, yielding three possible composite endpoints: "Suicidal ideation", "Suicidal behavior" and "Suicidal ideation or behavior". In SURMOUNT-1, 12 (0.6%) TZP- and 6 (0.9%) placebo-treated patients experienced suicidal ideation events. Two (2) TZP-treated participants experienced suicidal behavior events (2 events per participant). There were no completed suicide events.

PHQ-9

PHQ-9 is a validated self-reported screening tool that assesses presence and intensity of depressive symptoms in a primary care setting. It uses the 9 DSM IV depression criteria, which are scored from 0 (not at all) to 3 (nearly every day). The total scores are categorized into "not depressed", "mild", "moderate", "moderately severe" and "severe". **Table 64** summarizes the changes in PHQ-9 categories from baseline to Week 72 in SURMOUNT-1. The majority (>65%) of participants in all groups had PHQ-9 scores indicative of no depression at baseline. More placebo- than TZP-treated participants moved to a higher category, and more TZP-treated than placebo-treated patients moved to a lower category.

Table 64. Shift Table Summary PHQ-9 from Maximum Baseline to Maximum Postbaseline from Baseline to 72 Weeks, Safety Analysis Set SURMOUNT-1

	n (%)			
	Placebo (N=643)	**TZP 5 mg (N=630)**	**TZP 10 mg (N=636)**	**TZP 15 mg (N=630)**
Remained in the same category	400 (62.2)	410 (65.1)	400 (62.9)	394 (62.5)
Moved to a higher category	145 (22.6)	113 (17.9)	106 (16.7)	118 (18.7)
Moved to a lower category	82 (12.8)	97 (15.4)	116 (18.2)	107 (17.0)
Had no postbaseline result	16 (2.5)	10 (1.6)	14 (2.2)	11 (1.7)

AS1C:

Major depressive disorder or suicidal ideation occurred in 67 patients (TZP_ALL: 1.81%; placebo: 2.66%). All but 4 participants were from SURMOUNT-1. **Table 65** further differentiated according to "Depression (excluding suicide and self-injury)" (n=65; all but 4 from SURMOUNT-1) and "Suicide/self-injury" (all from SURMOUNT-1).

Table 65: Treatment-emergent major depressive disorder/suicidal ideation or behavior by decreasing frequency within SMQ; phase 3 placebo-controlled analysis set AS1C.

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)**
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

AS1C analysis according to severity/seriousness:
Five (5) (0.20%) TZP-treated patients (all SURMOUNT-1) experienced severe or serious TEAEs of major depression disorder or suicidal ideation events in (placebo: 0; TZP 5 mg: 1; TZP 10 mg: 2; TZP 15 mg: 2).
According to the vignettes provided by the applicant, one of these cases was related to study drug (TZP 10 mg group; 2 SAEs of suicide attempt on days 360 and 370; patient was *"feeling dissatisfied with her body due to weight reduction"*).

AS2C:

A total of 72 (1.14%) TZP-treated participants reported major depressive disorder or suicidal ideation or behavior events. Of these, 42 were from SURMOUNT-1.

- For Depression SMQ (excluding suicide and self-injury) – incremental increase visible with TZP dose: TZP 5 mg: 19 (0.90%); TZP 10 mg: 22 (1.05%); TZP 15 mg: 27 (1.27%)
- For Suicide/self-injury (2 participants from SURMOUNT-1) – incremental increase visible with TZP dose:
  TZP 5 mg: 0; TZP 10 mg: 1 (0.05%); TZP 15 mg: 3 (0.14%)

AS4C analysis according to severity/seriousness:
A total of 8 (0.13%) TZP- *vs.* 1 (0.04%) comparator-treated participants reported serious or severe events. 5 of the affected TZP-treated participants were from SURMOUNT-1. Suicide attempt was reported in 3 (0.05%) TZP-treated participants (2 from SURMOUNT-1) *vs.* 1 (0.04%) in the comparator group. Completed suicide (depression suicidal) was reported in 1 TZP-treated participant from the original T2DM application.

Abuse Potential

Initial screening of the CWM Phase 3 studies suggested minimal to no evidence of abuse potential. A search with the narrow terms from the Drug Abuse and Dependence SMQ across the phase 2 and 3 studies revealed 1 TZP-treated participant in SURMOUNT-1 with 1 event (SAE) of the PT substance abuse (found unresponsive and transported to the Emergency Department on study day 315; urine drug screen positive for cocaine and opiates).

Deaths and Serious adverse events (SAEs)

Deaths

As shown in **Table 66**, in the obese/overweight population of the phase 2/3 studies, 72 deaths (comparator: 32 out of 2711 [1.18%]; TZP_ALL: 40 out of 7354 [0.54%] were reported. Over half (61.11%) of the deaths occurred in SURPASS-4, which was conducted in participants with increased CV risk. In SURMOUNT-1, 11 deaths were reported, 7 (0.37%) in TZP-treated patients, and 4 (0.62%) in the placebo group.

All deaths in Phase 2 and 3 studies were submitted for adjudication by an external CEC. Causes of the adjudicated events in the TZP group were primarily CV in nature (mainly sudden cardiac death), undetermined, or infection.

In TZP-treated participants, 12 deaths (3 from SURMOUNT-1; 1 from SURMOUNT-4) were associated with COVID-19 occurred and were adjudicated as infection (n=7), undetermined (n=2), COVID-19 infection (n=1), pulmonary death (n=1), and sudden cardiac death (n=1).

Table 66: Cause of death as adjudicated by CEC; safety population participants with overweight/obesity in phase 2 and 3 studies

Cause of death as adjudicated by CEC	n								
	TZP 5 mg (N=2159)	TZP 10 mg (N=2141)	TZP 15 mg (N=2207)	TZP MTD 10/15 mg (N=782)	Insulin Degludec (N=316)	Insulin Glargine (N=957)	Sema 1 mg (N=422)	Dula 0.75 + 1.5 mg (N=133)	Placebo (N=900)
Total	20	9	10	1	1	26	1	0	4
Sudden cardiac death	4	3	2	0	0	4	0	0	0
Undetermined	7	3	3	0	0	9	0	0	1
Infection	6	1	3	0	1	6	0	0	0
Malignancy	0	1	0	0	0	1	0	0	1
Pulmonary	0	0	1	0	0	2	1	0	0
Suicide	0	0	1[a]	0	0	0	0	0	0
Other: Massive PE	1	0	0	0	0	0	0	0	0
Acute MI	0	0	0	0	0	1	0	0	0
CV procedure	0	0	0	0	0	1	0	0	0
Non-CV procedure or surgery	0	0	0	0	0	1	0	0	0
Trauma	1	1	0	0	0	1	0	0	0
Hepatobiliary	1	0	0	0	0	0	0	0	0
Stroke	0	0	0	0	0	0	0	0	1
COVID-19	0	0	0	1	0	0	0	0	0
PE	0	0	0	0	0	0	0	0	1

Abbreviations: CEC = clinical endpoint committee; CV = cardiovascular; Dula = dulaglutide; MI = myocardial infarction; MTD = maximum tolerated dose; N = number of participants in treatment group; n = number of participants; PE = pulmonary embolism; Sema = semaglutide; TZP = tirzepatide.

[a]from SURPASS-3.

Note 1: This table should not be used to compare treatment groups. Different treatment groups are included across the studies with different populations.

Note 2: The randomization ratio for SURPASS-4 was 1:1:1:3 (TZP 5 mg: TZP 10 mg: TZP 15 mg: insulin glargine), while other Phase 3 studies with a comparator arm were 1:1:1:1 (TZP 5 mg: TZP 10 mg: TZP 15 mg: comparator).

Other SAEs

AS1C: The number of patients with ≥1 SAE was similar across treatment groups (TZP 5 mg: 51 [6.13%]; 10 mg: 57 [6.87%]; 15 mg: 41 [4.95%] and placebo: 53 [6.41%]). The most common SAEs (≥0.2% in TZP_ALL) were in the following SOCs:

- Infections and infestations (mainly COVID-19-related, and appendicitis):
  TZP_ALL: 51 (2.05%) *vs.* placebo: 15 (1.81%)
- Hepatobiliary disorders (mainly cholelithiasis):
  TZP_ALL: 10 (0.40%) *vs.* placebo: 3 (0.36%)
- Neoplasms benign, malignant and unspecified (incl cysts and polyps):
  TZP_ALL: 16 (0.64%) *vs.* placebo: 10 (1.21%)
- Cardiac disorders:
  TZP_ALL: 12 (0.48%) *vs.* placebo: 5 (0.60%)

- Respiratory, thoracic, and mediastinal disorders
  TZP_ALL: 12 (0.48%) *vs.* placebo: 4 (0.48%)
- Renal and urinary disorders
  TZP_ALL: 8 (0.32%) *vs.* placebo: 2 (0.24%)
- Vascular disorders
  TZP_ALL: 7 (0.28) vs. placebo: 4 (0.48)
- Psychiatric disorders
  TZP_ALL: 6 (0.24) vs. placebo: 0

In AS4C, fewer participants treated with TZP than with all comparators reported SAEs (TZP_ALL: 450 [7.1%]; comparator: 262 [9.7%]). An analysis according to SOCs is shown in **Table 67**. Numerical imbalances disfavouring TZP were observed for the SOCs *"Gastrointestinal disorders"*, *"Hepatobiliary disorders"*, and *"Psychiatric disorders"*.

Table 67: SAEs occurring in more than 1 subject, according to SOC; safety population; phase 2/3 comparator-controlled analysis set (AS4C) in participants with baseline BMI ≥27 kg/m^2

SOC	TZP_ALL (N=6372)	Comparator (N=2711)
Infections and infestations	125 (2.0)	78 (2.9)
Cardiac disorders	78 (1.2)	65 (2.4)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	50 (0.8)	27 (1.0)
Gastrointestinal disorders	49 (0.8)	13 (0.5)
Nervous system disorders	45 (0.7)	29 (1.1)
Hepatobiliary disorders	36 (0.6)	10 (0.4)
Injury, poisoning and procedural complications	31 (0.5)	14 (0.5)
Renal and urinary disorders	26 (0.4)	14 (0.5)
Respiratory, thoracic and mediastinal disorders	26 (0.4)	22 (0.8)
General disorders and administration site conditions	19 (0.3)	7 (0.3)
Vascular disorders	18 (0.3)	15 (0.6)
Metabolism and nutrition disorders	13 (0.2)	17 (0.6)
Musculoskeletal and connective tissue disorders	12 (0.2)	11 (0.4)
Psychiatric disorders	10 (0.2)	2 (0.1)
Investigations	7 (0.1)	4 (0.1)
Surgical and medical procedures	5 (0.1)	2 (0.1)
Eye disorders	4 (0.1)	4 (0.1)
Reproductive system and breast disorders	4 (0.1)	3 (0.1)
Blood and lymphatic system disorders	3 (0.0)	5 (0.2)
Ear and labyrinth disorders	3 (0.0)	2 (0.1)
Pregnancy, puerperium and perinatal conditions	3 (0.0)	0
Endocrine disorders	2 (0.0)	0

Laboratory findings

Clinical laboratory measurements were performed for haematology, chemistry, urinalysis, and special analytes at time points specified in each protocol within the TZP phase 2 and 3 studies. For laboratory results associated with special safety topics (renal safety, hepatobiliary safety, exocrine pancreas safety, thyroid safety), please see corresponding sections above.

Haemoglobin
More TZP- than placebo-treated participants shifted from normal/high to low haemoglobin in AS1C (placebo: 7.4%; TZP 5 mg: 13.8%; TZP 10 mg: 13.0%; TZP 15 mg: 14.7%; TZP_ALL: 13.8%). The incidence in TZP-treated patients was confirmed in AS2C, but without dose/effect relationship (5 mg: 13.02%; 10 mg: 13.38%; 15 mg: 13.15%). For TZP-treated participants shifting to low haemoglobin

levels in AS1C, the mean drop in haemoglobin was 1.91 g/dL and the mean and median post-baseline haemoglobin levels were 11.17 g/dL and 11.20 g/dL respectively.

Anaemia

AS1C: Anaemia (cluster) was reported by 43 (1.73%; 33 patients from SURMOUNT-1) TZP- and 7 (0.85%) placebo-treated participants. For 40 of these participants, the decrease in haemoglobin from baseline ranged from -0.1 to -6.2 g/dL. In 2 of these participants, there was no drop in haemoglobin from baseline.

The SURMOUNT-1 participant, diagnosed with adenocarcinoma and receiving chemotherapy, reported a decrease of 7.1 g/dL (from 14.5 g/dL at baseline).

One participant from study GPGI (a T2DM study) experienced a severe event of anaemia (drop in haemoglobin from 13.7 g/dL at baseline to 11.4 g/dL on day 169), but comorbidities and concurrent medications (enoxaparin, clopidogrel) may have acted as confounders.

AS2C, AS4C: There was no dose effect of TZP on anaemia-related TEAEs (TZP 5 mg: 6 [0.3%]; TZP 10 mg: 11 [0.5%]; TZP 15 mg: 10 [0.5%]). The comparator-controlled AS4C dataset shows a similar incidence rate for TZP_ALL and comparator (TZP_ALL: 100 [1.57%]; comparators: 42 [1.55%]).

Safety in special populations

Intrinsic factors

AS1C: Subgroup-by-treatment interactions for TEAEs occurring in ≥5% of patients were analysed in the following subgroups: age (<65 years; ≥65 years), sex (male/female), race (Asian, Black/African American, White, Other), baseline BMI (<30; ≥30 to <35; ≥35 to <40; ≥35 kg/m^2), baseline eGRF (<60; ≥60 mL/min/1.73 m^2) and ethnicity (Hispanic or Latino; not Hispanic or Latino, not reported).

The strongest interactions (p<0.10) in AS1C are as follows:

Sex x

- *Eructation:* significant treatment effect (p<0.05) *vs.* placebo for all three TZP doses in females, but only for TZP 10 mg and 15 mg in males.

Ethnicity x

- *Eructation:* significant treatment effect (p<0.05) *vs.* placebo for all three TZP doses in "Not Hispanic or Latino" patients, but only for TZP 10 mg and 15 mg in those reporting being "Hispanic or Latino".

Age x

- *Diarrhoea:* significant treatment effect (p<0.05) *vs.* placebo in patients <65 years. Lack of this effect in patients ≥65 years may be due to diarrhoea reported in a higher-than-expected percentage of placebo-treated participants but in a lower-than-expected percentage of TZP-treated patients in this age group.
- *Injection site reaction:* significant treatment effect (p<0.05) vs. placebo in patients <65 years. Lack of this effect in patients ≥65 years may be due to injection site reactions reported by a higher-than-expected percentage of placebo-treated participants but a lower-than-expected percentage of TZP 5mg and 10 mg-treated patients in this age group.

eGFR x

- *Diarrhoea:* significant treatment effect (p<0.05) vs. placebo in patients with eGFR ≥60 mL/min/1.73 m^2, but not for patients with eGFR <60 mL/min/1.73 m^2.

Lack of this effect in patients with eGFR <60 mL/min/1.73 m^2 may be due to diarrhoea reported by a higher-than-expected percentage of placebo-treated participants, but in a lower-than-expected percentage of TZP 5 mg and 10 mg-treated patients in this eGFR category.

No subgroup-by-treatment interaction analysis was presented for the AS4C.

TEAEs by age group

The applicant presented an overview of AE categories by age group for AS3C (phase 2/3 program). Increases in % patients with increased age were shown for SAEs, AEs leading to study drug discontinuation, accidents and injuries, cardiac disorders, vascular disorders, central nervous system vascular disorders as well as hypotension, falls and fractures (**Table 68**).

Table 68: Overview of AEs by age category – TZ-treated participants with overweight/obesity in AS3C (TZP_ALL)

Event Category	n (%)			
	<65 (N=5909)	**65-74 (N=1281)**	**75-84 (N=160)**	**≥85 (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
CNS 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: N = number of participants in specified age group; n = number of participants with at least one specified event; PT = preferred term; SAE = serious adverse event; SMQ = Standardised MedDRA Query; SOC = System Organ Class; TEAE = treatment emergent adverse event

[a]Fractures includes 6 high-level terms: 'Fractures and dislocations not elsewhere classified,' '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]Lilly customized query, includes the 6 high-level terms for fractures, 'Decreased and nonspecific blood pressure disorders and shock' high level group term, and 'Fall' PT.

Extrinsic factors

In general, the percentages of frequently reported TEAEs in TZP-treated participants was comparable among regions. In dataset AS4C, Asian patients (excl. Japan) were more affected by diarrhoea as compared to patients from other regions (TZP_ALL: 33.8% in Asia *vs.* 11.5 - 19.4% in other regions). Asian patients (excl. Japan) also reported more events of decreased appetite (TZP_ALL: 24.3% in Asia *vs.* 7.3 - 11.2% in other regions). Nasopharyngitis occurred more frequently in patients from Japan as compared to other regions (TZP_ALL: 14.7% *vs.* 1.9 - 5.7% in other regions).

Renal or hepatic insufficiency

Few patients with moderate (n=44) and no patients with severe renal impairment have been included in SURMOUNT-1. The wording in section 4.2 of the SmPC applicable to the T2DM indication is limited to severe renal impairment and no change is proposed with this variation. Regarding patients with hepatic impairment, no new data were provided that would lead to a change of the information in the SmPC.

Safety related to drug-drug interactions and other interactions

Similar to established GLP1 receptor agonists, TZP delays gastric emptying and intestinal transit time. This may result in altered absorption of other orally administered concomitant medications, potentially altering PK parameters like C_{max} and T_{max}. The influence of TZP on gastrointestinal function was addressed with acetaminophen as a probe to assess gastric emptying in the phase 1 study GBGA (healthy participants and T2DM patients) and in study GPHU (participants with obesity or overweight with or without T2DM).

In Study GPGA, a delay in gastric emptying was indicated by a decrease of acetaminophen C_{max} and T_{max}) without altering the extent (total drug amount) absorbed. In Study GPHU, acetaminophen PK was impacted in a similar manner, and the effect tachyphylaxed faster in participants with obesity and without T2DM compared to participants with obesity and T2DM.

In addition, the drug-drug interaction study GPGR was conducted to evaluate the interaction of TZP with combination oral contraceptives in healthy female subjects. No clinically relevant impact was found.

Discontinuation due to adverse events

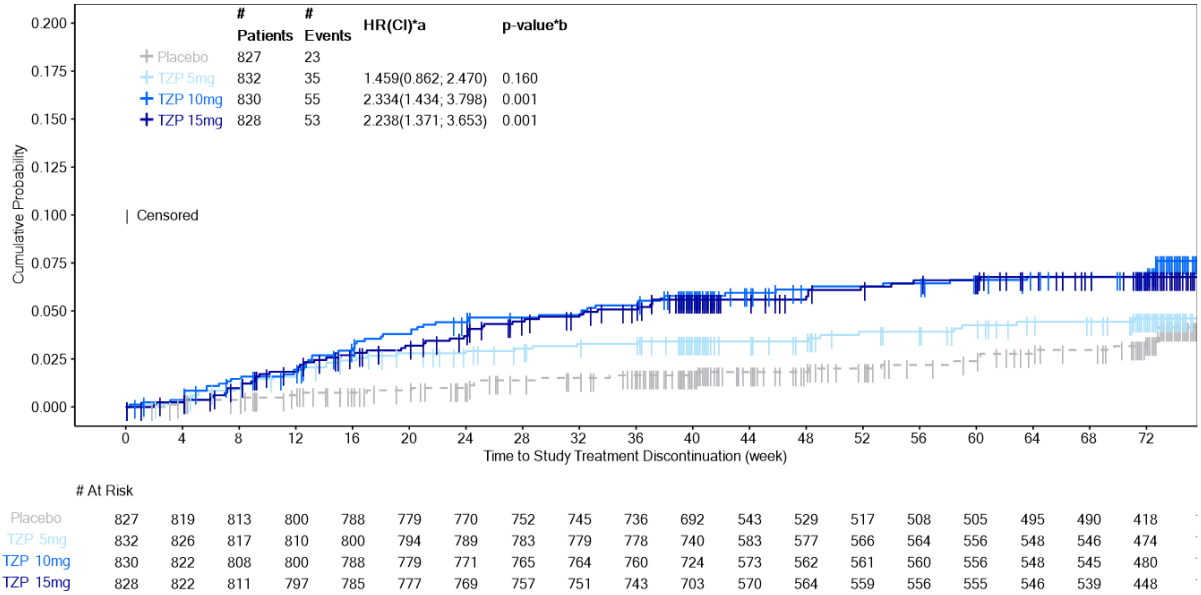
SURMOUNT-1
Permanent discontinuation from study drug due to an AE occurred in 137 (5.4%) participants (placebo: 21 [3.3%]; TZP 5 mg: 30 [4.8%]; TZP 10 mg: 46 [7.2%]; TZP 15 mg: 40 [6.3%]). AEs in the Gastrointestinal disorders SOC were the most common reasons for study drug discontinuation (placebo: 3 [0.5%]; TZP 5 mg: 12 [1.9%]; TZP 10 mg: 28 [4.4%]; TZP 15 mg: 26 [4.1%].

AS1C
In AS1C, a higher percentage of TZP-treated than placebo-treated patients permanently discontinued study drug due to an AE (placebo: 26 [3.14]; TZP 5 mg: 38 [4.57%]; 10 mg: 56 [6.75%]; 15 mg: 54 [6.52%]).

This difference was mostly driven by AEs from the SOC *gastrointestinal disorders* (placebo: 4 [0.48]; TZP 5 mg: 17 [2.04%]; 10 mg: 37 [4.46%]; 15 mg: 36 [4.35%]). The percentage of participants discontinuing TZP due to GI AEs (TZP_ALL: 3.61%) was lower than in the placebo-controlled analysis set of the original T2DM application (5.0%). However, the percentage in the placebo groups was similar (0.48% in CWM application vs. 0.4% in T2DM application). The most common GI TEAEs leading to discontinuation were nausea, diarrhoea and vomiting.

Figure 29 shows an incremental increase with regard to "Time to premature study treatment discontinuation due to AEs" from placebo to TZP 10 mg; however, there is practically no difference any more between TZP 10 mg and 15 mg. About half of the participants discontinued study drug due to AEs that occurred during dose escalation.

Figure 29: Kaplan-Meier plot of time to premature study treatment discontinuation due to AEs in participants with overweight/obesity (placebo-controlled dataset **AS1C**)



AS4C and AS2C

In AS4C, 436 (6.8%) of TZP-treated participants (TZP_ALL) and 102 (3.8%) of comparator-treated participants discontinued treatment due to an AE. The difference between the two groups was mainly driven by the difference in the SOC "Gastrointestinal Disorders" (TZP_ALL: 229 [3.6%]; comparator: 24 [0.9%]) and "Investigations" (TZP_ALL: 35 (0.5%); comparator: 6 [0.2%]). In the SOC "Investigations", discontinuations in the TZP-treated patients were mostly due to changes in calcitonin, pancreatic and hepatic enzymes or excessive weight loss.

In the following, other SOCs are listed with more discontinuations in the TZP arm as compared to comparator and with the most important AEs responsible for discontinuation in the TZP-treated patients:

- *General disorders and administration site conditions:* TZP_ALL: 25 (0.4); comparator: 7 (0.3)
  In TZP group mainly fatigue (n=5), asthenia (n=4), injection site reaction (n=4), malaise (n=3)
- *Metabolism and nutrition disorders:* TZP_ALL: 24 (0.4); comparator: 1 (0.0)
  In TZP group mainly decreased appetite (n=21)
- *Injury, poisoning and procedural complications:* TZP_ALL: 5 (0.1); comparator: 1 (0.0)
  In TZP group (n=1 each): Fall, Multiple injuries, procedural headache, road traffic accident and spinal column injury
- *Hepatobiliary disorders:* TZP_ALL: 4 (0.2); comparator: 1 (0.0)
  In TZP group (n=1 each): cholelithiasis, cholestasis, hepatic cirrhosis, hepatic failure
- *Musculoskeletal and connective tissue disorders*: TZP_ALL: 3 (0.0); comparator: 1 (0.0)
  In TZP group (n=1 each): muscular weakness, musculoskeletal pain, myalgia
- *Psychiatric disorders:* TZP_ALL: 3 (0.0); comparator: 2 (0.1)
  In TZP group (n=1 each): depression, mania, suicide attempt
- *Renal and urinary disorders:* TZP_ALL: 3 (0.0); comparator: 1 (0.0)
  In TZP group (n=1 each): chronic kidney disease, end stage renal disease, renal mass
- *Vascular disorders:* TZP_ALL: 3 (0.0); comparator: 0
  In TZP group: orthostatic hypotension (n=2), deep vein thrombosis (n=1)

- *Ear and labyrinth disorders:* TZP_ALL: 2 (0.0); comparator: 0
  In TZP group: vertigo (n=2)

For AS4C, no Kaplan-Meier Plot was presented for discontinuations. However, the plot for the phase 3 dose effect analysis set AS2C basically confirms what was already shown above for the AS1C dataset.

In AS2C, a higher percentage of TZP-treated than placebo-treated patients permanently discontinued study drug due to an AE with an incremental increase visible across TZP doses (TZP 5 mg: 116 [5.50%]; 10 mg: 150 [7.16%]; 15 mg: 156 [7.35%]). Again, the differences were mostly driven by AEs from the SOC *gastrointestinal disorders* (TZP 5 mg: 48 [2.28%]; 10 mg: 80 [3.82%]; 15 mg: 89 [4.19%]).

60.5% (89 out of the 147) of TZP-treated participants in AS2C who discontinued the study drug due to nausea, vomiting, or diarrhoea did so prior to reaching their maintenance dose.

2.5.1. Discussion on clinical safety

10 065 overweight/obese participants (6744 with T2DM) received study drug in 12 phase 2/3 studies (TZP: n=7354). The exposure meets the recommendations in the "Note for Guidance on Population Exposure" (CPMP/ICH/375/95), and the safety analysis sets are largely acceptable.

In general, the safety profile of TZP for weight management appears similar to the effect seen in subjects with T2DM in the original TZP application. The percentage of patients with TEAEs and discontinuations of study treatment due to an AE (most commonly GI events) increased dose-dependently with TZP compared to placebo.

While treatment discontinuations occurred at a comparable frequency with the 10 mg and the 15 mg TZP dose, fewer patients on TZP 5 mg discontinued treatment. This suggests that the 5 mg dose is an important treatment option for obese/overweight patients who do not tolerate higher dose levels. Slightly fewer deaths occurred in TZP- as compared to placebo-treated patients. The frequency of SAEs in the SOCs "gastrointestinal disorders" and "hepatobiliary disorders" was higher for TZP than for comparator, which is consistent with the known safety profile of GLP-1 receptor agonists. Slightly more AEs occurred with TZP in the SOC "Psychiatric disorders", which may be relevant for the discussion of depression/suicide-related risk (see below).

As in the previous T2DM procedure, the most common TEAEs with higher incidence in TZP-treated patients were gastrointestinal events (specifically nausea, vomiting, diarrhoea and constipation). GI-related TEAEs mostly occurred during dose escalation and decreased in the maintenance phase. The incidence of gastrointestinal AEs in the CWM population was considerably larger (TZP: 51-56% vs placebo: 29%) than in previous studies in the T2DM population (TZP: 37-44% vs placebo: 20%). In contrast to previous studies, a secondary peak in prevalence of GI AEs (nausea, vomiting, and diarrhoea) was seen after week 52 in AS2C, driven by SURMOUNT-1 (WM population). However, discontinuations due to GI AEs were not higher in the CWM population compared to the original T2DM population. Constipation was added to the paragraph "Summary of safety profile" in the SmPC, which is considered justified.

The AEs of alopecia, hypotension and dizziness were added to SmPC section 4.8.

Slightly more renal TEAEs and a trend towards a higher percentage of patients shifting to lower eGFR categories were observed for TZP as compared to placebo. However, a direct detrimental effect of TZP on kidney function is unlikely, specifically as UACR was reduced with TZP as compared to placebo. Loss of fluid, e.g. due to GI AEs, and other confounding factors may have contributed to the renal events. The data on patients with renal impairment are only limited. Thus, the applicant has provided an additional analysis of AEs by renal function for both the AS2C and the AS4C dataset. It is acknowledged

that the total number of participants in the eGFR category ≥30 to <60 mL/min/1.73 m^2 is considerably lower than in the higher eGFR categories. Moreover, the absolute number of cases within each event is relatively low and the 17 PTs, for which the OR increased with decreasing kidney function, do not seem to be interrelated. Moreover, it is difficult to establish a plausible causal relationship with tirzepatide treatment. Based on these considerations, the applicant concluded that the observed increase in OR with decreasing kidney function may rather be a chance finding without clinical relevance. The applicant has further discussed the SOCs of "Investigations" and "General disorders and administration site conditions" that show the most prominent increase of OR with decreasing renal function in the AS4C dataset in participants with baseline BMI ≥27 kg/m^2. The applicant noted that among the very heterogeneous PTs making up these SOCs, the PT of fatigue is mainly driving the General disorders and administration site conditions SOC, which typically occurs with anti-obesity medications and is at the same time increased in patients with CKD and during weight loss. Similarly, the applicant points out that the PTs of lipase increased or blood creatinine increased are increased in later CKD stages due to reduced renal elimination, and lipase increased is additionally a typical AE of tirzepatide.

The applicant's explanation is acknowledged. However, it should be pointed out that an increase of OR with decreasing renal function suggests that participants with later CKD stages are more susceptible for these AEs. This is independent of whether these AEs are typical AEs for tirzepatide and/or due to reduced kidney function.

An increased susceptibility of patients with reduced kidney function to AEs (including those typically caused by tirzepatide) is also supported by the analysis of the relative risk in the 15 mg vs. the 5 mg treatment group in the different kidney function categories of dataset AS2C.

Most prominently, the relative risk for Injury, poisoning and procedural complications is increased from 1.08 at eGFR ≥90 mL/min/1.73 m^2 to 5.62 at eGFR ≥30 to <60 mL/min/1.73 m^2. However, this effect is not driven by one specific PT, but by an imbalance of 1-2 events vs. 0 events (15 mg vs. 5 mg) in PTs like fall, ankle fracture, muscle strain, rib fracture, contusion, head injury, hip fracture, injury, joint dislocation, ligament sprain, limb injury or lower limb fracture. This may indicate that patients with advanced CKD may be more prone to falls and associated injuries, possibly due to fatigue and other AEs reducing general wellbeing and interfering with muscle strength, motor coordination or the ability to concentrate. However, it also cannot be excluded that the above-mentioned injuries partly belong to the same subject, which would considerably reduce the impact of the observed increase in OR in this SOC category.

In summary, it seems that patients with advanced CKD are more susceptible to some AEs as compared to patients in higher eGFR categories, but due to the low number of cases and due to the fact that, in clinical practice, tirzepatide treatment is likely adjusted to individual tolerability, it is not warranted to include an extra warning in the SmPC. The current information in the SmPC *("Experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with tirzepatide"*) is considered sufficient. A widening of the wording to moderate renal impairment is currently not required.

However, the applicant is requested to further analyse the safety data of tirzepatide across eGFR categories, when more data become available in clinical studies submitted in the future.

As already known from other GLP-1 agonists and from the TZP T2DM programme, TZP leads to an elevation of the pancreatic enzymes lipase and p-amylase, but there was no clear indication that TZP increases the risk of pancreatitis. The percentage of patients with serum lipase shifts from ≤1 x ULN to >1 x ULN was considerably lower in the current dataset as compared to the preceding T2DM procedure, while no such difference was visible for p-amylase. The applicant was requested to compare the mean increases of lipase and p-amylase in the comparator-controlled datasets of the previous T2DM application and of the current weight reduction application. The applicant has provided the requested comparison.

There is no clinically relevant difference detectable between the increase of pancreatic enzymes in the T2DM- and the CWM population with BMI ≥ 27.

An analysis of hepatobiliary events showed that 9 of 12 "potentially clinically important" cases with ≥10 x ALT/AST (including three patients in Hy's law range) were from SURMOUNT-1. However, 7 of these cases could be medically explained by cholelithiasis (4 cases), hepatitis B (1 case) and vigorous physical exercise (2 cases). Thus, it is unlikely that TZP induces direct hepatic damage, specifically, as the hepatic enzymes tend to decrease over time to a higher extent in TZP- as compared to placebo-treated patients. The observed enzyme increases are probably due to gallbladder disease (mainly cholelithiasis and cholecystitis), the risk of which increases proportionally to weight reduction. While cholelithiasis is already labelled in section 4.8 of the SmPC, the AE of cholecystitis was also added with the frequency "uncommon" .

The TZP-induced increases of blood calcitonin were reversible and mostly not of acute clinical concern, but the consequences of a long-term stimulation of calcitonin release are unclear. The current short-term data do not report medullary thyroid carcinoma (MTC) or C cell hyperplasia. However, spontaneous reporting of AEs and measurement of blood calcitonin may not be adequate to reliably detect C-cell hyperplasias. It is noted that 5 cases of papillary thyroid cancer occurred (4 in TZP groups). The evidence for a causal relationship between tirzepatide (and GLP-1 RA in general) and various forms of thyroid cancer is rather weak and currently does not allow a conclusion. Nevertheless, an effect of tirzepatide cannot be fully excluded. The applicant's plan to further evaluate the risk of MTC in 2 post-marketing studies (active surveillance program in the US and analysis of real-world data) is therefore appreciated. However, it is recommended to focus not only on MTC, but also on other forms of thyroid cancer.

Hypersensitivity and injection site reactions occurred more frequently than in the T2DM application, and were reported more often with TZP than with placebo. However, no serious hypersensitivity reaction was reported, and most injection site reactions were mild to moderate in severity. Upon request, the applicant provided the underlying pooled analysis of immediate and non-immediate hypersensitivity reactions that resulted in the frequencies mentioned in section 4.8 of the SmPC. TZP induced a prominent increase in ADA (new data added to SmPC section 4.8), which did not appear to influence TZP PK and efficacy. More hypersensitivity and injection site reactions occurred in TE ADA^+- as compared to TE ADA^- patients. The percentage difference between TE ADA^+ and TE ADA^- patients with injection site reactions was larger than in the T2DM application.

An excessive TZP-associated CV risk had been excluded in the previous T2DM application (hazard ratio [HR]: 0.80 [95% CI, 0.57 to 1.11]). This was confirmed by the new MACE data for obese/overweight patients. However, the MACE used for the new CV safety analysis contained more than four components, and no meta-analysis to calculate hazard ratio and 95% CI for conventional 3-point MACE was provided for the comparator-controlled AS4C dataset; due to the 10-15 year younger study population in SURMOUNT-1 a low number of events is expected. The results from the meta-analysis for MACE-3 in dataset AS4C also supported the notion that CV risk is not increased in tirzepatide-treated patients. The TZP-induced decreases in SBP and DBP were more pronounced, and hypotension was reported more frequently than in the previous T2DM procedure. An abnormally high mean nighttime DBP was observed in the TZP 15-mg group in the SURMOUNT-1 ABPM. However, the clinical significance of the isolated finding of increased nighttime DBP with tirzepatide 15 mg is unknown. On the one hand, increased nighttime DBP is known to be associated with an increased risk for CV events. On the other hand, tirzepatide causes numerous other, rather beneficial effects like body weight reduction, lower mean 24-hour SBP, reduced daytime SBP, reduced nighttime SBP, and lower HbA1c, and improved other key cardiometabolic risk factors, including waist circumference and lipid profile. The CV meta-analysis does not suggest an increased CV risk associated with tirzepatide. Further CV data are awaited from the phase 3 study SURMOUNT-MMO (completion projected for 2027) and the ongoing CV outcome study SURPASS-CVOT in T2DM patients (completion projected for 2024).

The T2DM-specific AEs of hypoglycaemia and diabetic retinopathy were also analysed in the new weight management dataset. The applicant has clarified that the hypoglycaemias of the category *"BG <54 mg/dL or severe hypoglycaemia*" are not related to the use of glucose-lowering medications in addition to tirzepatide. The data on worsening diabetic retinopathy are currently inconclusive (phase 3 programme: TZP: 0.36% *vs.* comparator: 0.25 %). The results of the ongoing dedicated addendum study to SURPASS-CVOT are needed for a more reliable estimation of the TZP-associated retinopathy risk.

The general malignancy risk does not seem to be increased with TZP. However, the applicant was requested to provide Forest Plots summarizing all data on the occurrence of various kinds of tumours in the TZP- and comparator groups. Across all analysed datasets, tumours affecting breast, gastrointestinal system, kidneys and skin were observed with an OR>1.00, i.e, they showed a tendency to be increased in the tirzepatide-treated patients. The most prominent increase in risk was observed for skin tumours in the analyses regarding the AS4C dataset. When only the phase 2/3 T2DM studies of the original T2DM application were analysed, the most prominent increases in risk were observed for tumours of the gastrointestinal system and of the kidneys. However, it is also noted that the 95% CI are very wide and in none of the tumour types with OR>1.00, the lower limit of the CI was >1.00. More data have to be collected to allow a final decision on whether the risk for certain tumours may be increased by tirzepatide. Thus, the Forest Plots should be amended, whenever new data become available.

Massive weight loss may be associated with negative emotional effects. On the one hand, there was a suicide attempt in a patient which was considered related to TZP-induced weight reduction, and more TZP- than comparator–treated patients reported severe or serious TEAEs of major depression or suicidal ideation. On the other hand, patient-reported outcomes (C-SSRS, PHQ-9) from SURMOUNT-1 suggest a trend towards emotional improvement with TZP. However, SURMOUNT-1 and -4 did not enroll participants with significant active or unstable depression, a PHQ-9 score ≥15 or a lifetime history of suicide attempt, and this pre-selection may have influenced the C-SSRS- and PHQ-9 data. Thus, these studies probably do not represent clinical reality, where active depression may be more common in obese/overweight patients. The applicant submitted an analysis for the AS4C dataset to obtain information on the incidence of all depression-related events in the pooled comparator groups (Depression SMQ, excluding suicide and self-injury and events of suicide/self-injury) and discussed the potential relationship to TZP. The available data suggest no difference in the percentage of participants reporting major depressive disorder or suicidal ideation in AS4C (TZP_ALL: 1.15%; comp.: 1.44%). Similarly, no difference was visible for individual SMQs of Depression (excl. suicide and self-injury) (TZP_ALL: 1.08%; comp.: 1.40%), or suicide/self-injury (TZP_ALL: 0.06%; comp.: 0.07%). Thus, the current results do not suggest an increased risk of depression and suicidality. The applicant states that all 4 cases under the suicide/self-injury SMQ reported with tirzepatide were confounded by pre-existing mental health issues. However, from the viewpoint of the CHMP, subjects with pre-existing mental health issues may even be more susceptible for potential negative effects of tirzepatide. Moreover, it is reminded that 8 (0.13%) TZP- vs. 1 (0.04%) comparator-treated participants reported at least 1 serious or severe AE of major depressive disorder/suicidal ideation or behaviour in the Phase 2 and 3 comparator-controlled studies. Thus, although no need for action as regards the product information is currently seen, the risk for depressive disorders is going to be further evaluated, when new study results with tirzepatide in the CWM indication are submitted post-marketing.

2.5.2. Conclusions on clinical safety

The safety profile in the new non-diabetic obese/overweight population confirms the profile from the previous T2DM application. The new population seems to be more susceptible to certain AEs (e.g., GI TEAEs). Four new AEs (alopecia, dizziness, cholecystitis and hypotension) were added to section 4.8 of

the SmPC. In addition, the AE of cholecystitis and the slight imbalance in level 2/3 hypoglycaemia for TZP vs. placebo has also been adequately reflected in the SmPC.
Some AEs may be related to weight reduction (e.g., gallbladder disease or alopecia). The question, whether TZP may increase the risk for depression and suicidality or of certain malignancies requires additional data analyses. Finally, data from ongoing studies have to be awaited to arrive at reliable conclusions regarding the risks for worsening of diabetic retinopathy and CV events.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 2.1 with this application. The (main) proposed RMP changes were the following:

- A proposed new indication of chronic weight management (CWM) is included along with relevant information on incidence, prevalence, demography, main existing treatment options, natural history of the indicated condition, and important comorbidities.
- Updated overall cumulative exposure in Tirzepatide clinical trial program and exposure in special populations.
- Updated information on important potential risks considering the proposed new indication of CWM.
- Minor editorial changes have been made.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:
The safety concerns, PhV plan and risk minimisation measures already in place for Mounjaro (Tirzepatide) have not changed in the updated RMP, which is considered acceptable at this point.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

As the introduced changes are considered to not significantly alter the structure of the Package Leaflet and the population who performed the user testing of the SmPC prior to introduction of the CWM related changes is similar to the new target population, it is agreed not to perform a new readability testing.

3. Benefit-Risk Balance

3.1. Therapeutic Context

With this type II variation the following indication is proposed to be added:

"…Weight management

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

- *≥ 30 kg/m² (obesity) or*
- *≥ 27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus)."*

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist which is administered subcutaneously once-weekly.

3.1.1. Disease or condition

Overweight/obesity is defined as abnormal or excessive fat accumulation that impairs health (WHO 2021). It is a chronic progressive disease caused by disruptions in the normal mechanisms that control energy balance.

In 2016, the World Health Organization reported that more than 1.9 billion adults aged 18 years and older (39% of adult population) were living with obesity or overweight based on BMI criteria. Of these, over 650 million adults had obesity (WHO 2021).

Obesity is a risk factor for long-term health consequences, many of which represent the top causes of mortality globally (WHO 2020). More than 200 health complications have been associated with obesity, including cardiometabolic, inflammatory, degenerative, mechano-physical, neoplastic, and psychological conditions (Wilding and Jacob 2021). Obesity significantly impacts patients' daily activities and quality of life (Poon et al. 2022). Obesity is also associated with depression, anxiety, and increased suicidality (Luppino et al. 2010; Dutton et al. 2013; Wagner et al. 2013). Recently, studies indicated that individuals with obesity were more likely to be hospitalized, require mechanical ventilation, and die from COVID-19 than those without obesity (Foo et al. 2021; Gao et al. 2021; Smati et al. 2021).

In 2015, excess body weight accounted for approximately 4 million deaths and 120 million disability-adjusted life years worldwide (GBD 2015 Obesity Collaborators 2017). Secondary to the emergence of multisystem comorbid disease, obesity shortens life expectancy, with Class 3 obesity decreasing life expectancy by up to 20 years (OECD 2019; Müller et al. 2022).

3.1.2. Available therapies and unmet medical need

Patients with obesity or overweight often do not achieve sustainable weight loss with lifestyle therapies alone. Lifestyle-based treatment achieves a 10% weight reduction at one year in only some individuals (Wing and Hill 2001), and most regain the weight over longer periods of time (Knowler et al. 2009). In addition, larger effect sizes of weight loss are often needed for the resolution of obesity-related co-morbidities (sleep apnoea, osteoarthritis) and reduction of CV mortality (Wing et al. 2011).

Bariatric surgery is an effective option for substantial and durable weight reduction. However, the risk of perioperative and postoperative complications, limited access, and apprehension regarding the invasive and permanent nature of the procedure, results in less than 1% of the eligible population (based on BMI) receiving bariatric surgery as a treatment for obesity (ASMBS 2021).

Until recently, anti-obesity medication used in conjunction with behaviour modifications demonstrated single digit average percentage body weight reductions. The GLP-1 receptor agonist class has demonstrated greater body weight reductions than previous AOMs, with some GLP-1 receptor agonists achieving a 12.4% change in baseline body weight compared with placebo (Wilding et al. 2021).

Tirzepatide addresses an unmet medical need, at least in the subpopulation of obese patients without T2DM, as the demonstrated effect size of weight loss approaches that achievable with bariatric surgery while being less invasive and risky.

3.1.3. Main clinical studies

The pivotal phase 3 study mainly supporting this application is the SURMOUNT-1 study. This is a placebo-controlled, double-blinded study of the safety and efficacy of tirzepatide 5, 10, and 15 mg QW, compared with placebo, when used in conjunction with a reduced-calorie diet and increased physical activity for weight management. Participants did not have diabetes and had obesity (BMI ≥30 kg/m2), or overweight (BMI ≥27 kg/m2), the latter with at least one weight-related comorbid condition, for example, hypertension, dyslipidaemia, CVD, or obstructive sleep apnoea.

SURMOUNT-4 is currently ongoing and data from the open-label lead-in period were submitted, which are considered to support efficacy. The SURPASS 1-5 studies had been conducted for the T2DM indication; subgroup analyses in patients with BMI >27kg/m^2 support use in patients with T2DM.

Key design elements of the studies supporting the CWM indication are summarised in the following table:

Table 5. Global Phase 3 Clinical Studies Contributing to the Tirzepatide CWM Application

Design Elements	I8F-MC-GPHK SURMOUNT-1	I8F-MC-GPHN SURMOUNT-4	I8F-MC-GPGK SURPASS-1	I8F-MC-GPGL SURPASS-2	I8F-MC-GPGH SURPASS-3	I8F-MC-GPGM SURPASS-4	I8F-MC-GPGI SURPASS-5
	Conducted under the tirzepatide CWM development program		Conducted under the tirzepatide T2DM development program				
Participant Population	Participants without diabetes, with obesity, or overweight with at least 1 weight-related	Participants without diabetes, with obesity, or overweight with at least 1 weight-related	Participants with T2DM with inadequate glycaemic control with diet and exercise	Participants with T2DM with inadequate glycaemic control on metformin alone	Participants with T2DM with inadequate glycaemic control on metformin with or	Participants with T2DM and increased CV risk with inadequate glycaemic	Participants with T2DM with inadequate glycaemic control on insulin

Design Elements	I8F-MC-GPHK SURMOUNT-1	I8F-MC-GPHN SURMOUNT-4	I8F-MC-GPGK SURPASS-1	I8F-MC-GPGL SURPASS-2	I8F-MC-GPGH SURPASS-3	I8F-MC-GPGM SURPASS-4	I8F-MC-GPGI SURPASS-5
	comorbid condition	comorbid condition	alone, naive to diabetes injectable therapies, and have not been treated with any OAM		without SGLT-2i and naive to insulin treatment	control on at least 1 and no more than 3 OAMs, which may include metformin, SGLT-2i, and/or SU	glargine (U100) QD with or without metformin
Comparator	Placebo	None[b]	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo
Randomisation (TZP 5 mg: TZP 10 mg: TZP 15 mg: comparator)	1:1:1:1	N/A[b]	1:1:1:1	1:1:1:1	1:1:1:1	1:1:1:3	1:1:1:1
Treatment Duration	72 weeks[a]	36 weeks[b]	40 weeks	40 weeks	52 weeks	Up to 104 weeks[c]	40 weeks
Primary Endpoint	• Mean percent change in body weight • Proportion of participants who achieved ≥5% body weight reduction	Mean percent change in body weight[b]	Mean change in HbA1c[d]				

Blinding	Double blind	Open label[b]	Double blind	Open label	Open label	Open label	Double blind
Trial Size (N)	2539[a]	782[b]	478	1878	1437	1995	475
Number of Participants with Obesity or Overweight, n (%)	2539 (100)	782 (100)	371 (77.6)	1670 (88.9)	1255 (87.3)	1689 (84.7)	407 (85.7)
Number Of Participants with Obesity or Overweight from	-	-	-	69 (4.1)	677 (53.9)	490(29.0)	322(79.1)

EU/UK, n (%)							
Countries that Enrolled Participants	Argentina, Brazil, China, India, Japan, Mexico, Russian Federation, Taiwan, and United States	Argentina, Brazil, Taiwan, and United States	India, Japan, Mexico, and United States	Argentina, Australia, Brazil, Canada, Israel, Mexico, United Kingdom, and United States	Argentina, Austria, Greece, Hungary, Italy, Poland, Romania, South Korea, Spain, Taiwan, Ukraine, and United States	Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania, Russian Federation, Slovakia, Spain, Taiwan, and United States	Czech Republic, Germany, Japan, Poland, Slovakia, Spain, and United States

Abbreviations: BMI = body mass index; CV = cardiovascular; CWM = chronic weight management; HbA1c = haemoglobin A1c; n = number of participants with BMI ≥27 kg/m^2 at baseline; N = number of participants in category; N/A = not applicable; OAM = oral antihyperglycaemic medication; QD = once daily; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

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

b Information in this table for SURMOUNT-4 is for the completed 36-week tirzepatide open-label lead-in period, except for primary endpoint, which will be assessed at Week 88.

c For SURPASS-4, the primary endpoint is 52 weeks with a variable treatment duration of up to 104 weeks.

d Mean change from baseline in body weight was a key secondary endpoint controlled for type 1 error.

Note: EU/UK includes Austria, Czech Republic, Germany, Greece, Hungary, Italy, Poland, Romania, Slovakia, Spain, and United Kingdom.

3.2. Favourable effects

Results are given for the treatment-regimen estimand.

SURMOUNT-1

Tirzepatide treatment led to statistically significant weight reductions across doses. The mean percent weight reduction for tirzepatide 5, 10, and 15 mg from baseline to 72 weeks (first component of the co-primary endpoint) was 15%, 19.5%, and 20.8%. Weight reduction for placebo was 3.1%. The percent change difference in body weight from placebo at 72 weeks were 11.9%, 16.4% and 17.8% for tirzepatide 5 mg, 10 mg and 15 mg, respectively.

Percent patients with a weight reduction of ≥5% body weight at week 72 (second component of the co-primary primary endpoint for the 10 mg and 15 mg tirzepatide doses) showed superiority to placebo; 85.1% on tirzepatide 5 mg, 88.9% on tirzepatide 10 mg, and 90.9% on tirzepatide 15 mg, compared to 34.5% on placebo.

Significantly higher percentages of participants treated with tirzepatide 5, 10, or 15 mg compared with placebo achieved the secondary endpoints of ≥10%, ≥15%, and ≥20% body weight reductions at 72 weeks (percentage of participants with weight reduction ≥10%: tirzepatide 5 mg 68.5%, tirzepatide 10 mg 78.1%, tirzepatide 15 mg 83.5%, placebo 18.8%; percentage of participants with weight reduction ≥15%: tirzepatide 5 mg 48.0%, tirzepatide 10 mg 66.6%, tirzepatide 15 mg 70.4%, placebo 8.8%; percentage of participants with weight reduction ≥20%: tirzepatide 5 mg 30.0%, tirzepatide 10 mg 50.1%, tirzepatide 15 mg 56.7%, placebo 3.1%).

Results from the DXA addendum demonstrated that mean percent reduction from baseline in total body fat mass was significantly greater for pooled tirzepatide 5, 10, and 15 mg (-33.9%) compared with placebo (8.2%).

Tirzepatide 5mg, 10mg and 15mg each achieved superiority compared with placebo for mean change (reduction) in waist circumference at 72 weeks (tirzepatide 5 mg -14.0cm, tirzepatide 10mg -17.7cm, tirzepatide 15mg -18.5cm, placebo -4.0cm).

Pooled tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo on the key secondary endpoints of mean change in triglycerides (reduction), mean change in non-HDL-C (reduction), and mean change in HDL-C (increase) at 72 weeks. Pooled tirzepatide 5, 10, and 15 mg also significantly reduced VLDL-C, LDL-C, total cholesterol, and FFA from baseline compared with placebo at 72 weeks. Pooled tirzepatide 5, 10, and 15 mg achieved superiority on the key secondary endpoint of mean change in SBP (reduction) compared with placebo at 72 weeks. Pooled tirzepatide 5, 10, and 15 mg significantly reduced DBP from baseline compared with placebo at 72 weeks. Pooled tirzepatide 5, 10, and 15 mg achieved superiority compared with placebo on the key secondary endpoint of mean change (reduction) in fasting insulin at 72 weeks (pooled tirzepatide -5.1 mIU/L, placebo -0.8mIU/L). Tirzepatide 5, 10, and 15 mg significantly reduced HbA1c from baseline compared with placebo at 72 weeks (tirzepatide 5 mg -0.4%, tirzepatide 10 mg -0.4%, tirzepatide -0.4%, placebo -0.1%). Of 1032 participants with prediabetes at baseline, 893 participants had reverted to normoglycemia at Week 72 as assessed by FSG, HbA1c, and oral glucose tolerance test, using American Diabetes Association guideline criteria (ADA 2019):

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

Pooled tirzepatide 10 and 15 mg achieved superiority on the change from baseline (increase) in the generic mean SF-36v2 acute form Physical Functioning domain compared with placebo at 72 weeks (pooled tirzepatide increase in score by 3.6; placebo increase in score by 1.7 from baseline values of 49.5 and 49.6, respectively). For the PRO instrument specific for overweight/obesity, the IWQOL-Lite-CT, all tirzepatide doses showed numerically greater improvements compared with placebo in IWQOL-Lite-CT Physical Function composite, Physical composite, Psychosocial composite, and total scores.

SURMOUNT-4

At the completion of the 36-week open-label tirzepatide lead-in period of SURMOUNT-4, participants treated with tirzepatide reduced body weight from baseline by 20.9%. In addition, the percentages of participants achieving body weight reduction targets were: ≥5% (98.2%), ≥10% (93.1%), ≥15% (78.7%), or ≥20% (57.0%) by the end of the 36 week tirzepatide lead-in period.

Subgroup analysis of SURPASS 1-5

All tirzepatide doses led to reductions in body weight. The mean percent change in body weight for tirzepatide-treated participants ranged from -5.8% to -12.2%.

Tirzepatide demonstrated body weight loss >5% from baseline weight in all studies compared with placebo, semaglutide and basal insulin (insulin degludec and insulin glargine): tirzepatide 5 mg: -5.4 kg (Study GPGI, 40 weeks) to -7.6 kg (Study GPGL, 40 weeks), tirzepatide 10 mg: -7.0 kg (Study GPGK, 40 weeks) to -9.6 kg (Study GPGH, 52 weeks), and tirzepatide 15 mg: -7.8 kg (Study GPGK, 40 weeks) to -11.3 kg (Study GPGH, 52 weeks). All three doses of tirzepatide also had numerically higher percentages of participants achieving the ≥10%, ≥15%, and ≥20% weight reduction targets compared to placebo and T2DM active comparators, with up to 67% of participants achieving ≥10% weight reduction, 40% of participants achieving ≥15% weight reduction, 20% of participants achieving ≥20%

weight reduction. Reductions in body weight were observed regardless of concomitant therapy with SU or insulin. A reduction of the volume of visceral adipose tissue, and the volume of abdominal subcutaneous adipose tissue, as demonstrated in the MRI sub-study, showed that weight loss was related to loss of fat mass. Likewise, other cardiometabolic measures (waist circumference, lipid parameters, blood pressure, hepatic fat content) improved with tirzepatide. Tirzepatide led to greater improvement in PRO scores compared to placebo or active comparator.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties with respect to the weight loss benefit in the intended target population.

Sustainability of action needs to be further substantiated upon availability of the randomised withdrawal period and the safety follow-up in SURMOUNT-4 and the safety follow-up in SURMOUNT-1. The Applicant has committed to submit these data post-marketing as part of a type II variation.

3.4. Unfavourable effects

The safety profile in the new obese/overweight population largely confirms the safety data from the previous T2DM application. The most prominent unfavourable effects are gastrointestinal TEAEs (more commonly occurring than in the previous T2DM application) that also represent the most common causes for treatment discontinuation. TZP appears to increase the risk of gallbladder events like cholelithiasis or cholecystitis (both included in the SmPC with a frequency of "uncommon"), which is probably due to the strong weight reduction rather than a direct effect of TZP.

Consistent with the previous T2DM data, TZP induced a reversible increase of blood calcitonin, but no events of C cell hyperplasia or medullary thyroid carcinoma were reported. The current data do not suggest an increased risk for pancreatitis. However, as already known from the T2DM application and from other GLP-1 agonists, pancreatic enzymes (p-amylase, lipase) are increased by TZP.

An abnormally high mean nighttime DBP was observed in the TZP 15-mg group of SURMOUNT-1 ABPM. However, the current results do not indicate an increased risk of CV events with TZP, which confirms the previous analysis in the T2DM dataset.

New TEAEs (alopecia, hypotension, cholecystitis and dizziness) were identified in the obese/overweight population and were added to the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

For clarification of the influence of TZP on the risk of worsening of diabetic retinopathy and of CV events future data are awaited (retinopathy: ongoing dedicated addendum study to SURPASS-CVOT; CV risk: studies SURMOUNT-MMO and SURPASS-CVOT).

Currently, the general malignancy risk does not seem to be increased with TZP. The applicant has provided Forest Plots summarizing all data on the occurrence of various kinds of tumours in the TZP- and comparator groups. The long-term consequences of the TZP-induced increase of blood calcitonin remain unclear. The methodology used by the applicant to detect C-cell hyperplasia (spontaneous AE reporting and blood calcitonin measurements) can probably not reliably identify C cell hyperplasias. MTC and pancreatic cancer are followed as important potential risks in the RMP.

As SURMOUNT-1 and -4 did not enroll participants with depression- and suicide-related problems, the patient-reported outcomes (CSSR-S, PHQ-9) may be skewed towards emotionally favorable effects of TZP. However, currently, there are no clear indications that TZP treatment may be associated with a

higher risk of depression or suicide. The risk will be re-assessed, when more data become available in the future.

3.6. Effects Table

Results for the treatment-regimen estimand

Effect	Short Description	Control	TZP 5 mg	TZP 10 mg	TZP 15 mg	Study or Analysis Set	Strengths/Limitations/Uncertainties
Favorable Effects							
Body Weight Percent Change	**Participants without T2DM**						**Strengths of evidence related to benefits** • The CWM development program included a target population that represents the intended patient population for CWM with tirzepatide • Across studies, 86% to 96% of participants completed the primary study period, leading to limited missing data at the primary endpoint visit and allowing for robust assessment of the study objectives. • All tirzepatide doses reduced body weight, associated with an improvement in body composition. • In SURMOUNT-1, approximately half of participants in the 10- and 15-mg dose groups achieved at least 20% reduction in body weight. The effect size of weight reduction was large. • The data from the 36-week open-label treatment period of SURMOUNT-4 are consistent with those of SURMOUNT-1 showed favorable effects of tirzepatide on body weight (mean %body weight reduction 20.9% at 36 weeks). • cardiometabolic parameter improved consistently. **Limitations and uncertainties related to benefits** • none
	LS Mean CFB at 72 wks (%)	-3.1 (PBO)	-15.0	-19.5	-20.9	SURMOUNT-1	
	Participants with T2DM						
	LS Mean CFB at 40 wks (%)	-1.3 (PBO)	-7.3	-8.6	-9.3	SURPASS-1	
		1.6 (PBO)	-5.8	-8.1	-9.4	SURPASS-5	
		-6.1 (Sema 1 mg)	-8.2	-10.2	-12.0	SURPASS-2	
	LS Mean CFB at 52 wks (%)	2.1 (IDeg)	-7.7	-10.5	-12.0	SURPASS-3	
		1.7 (IGlar)	-7.3	-10.0	-12.2	SURPASS-4	
Weight Reduction Target of ≥5%	**Participants without T2DM**						
	Proportion of participants at 72 wks (%)	34.5 (PBO)	85.1	88.9	90.9	SURMOUNT-1	
	Participants with T2DM						
	Proportion of participants at 40 wks (%)	14.0 (PBO)	62.6	70.3	61.2	SURPASS-1	
		6.1 (PBO)	48.0	58.6	70.6	SURPASS-5	
		53.4 (Sema)	64.3	75.7	79.5	SURPASS-2	
	Proportion of participants at 52 wks (%)	8.8 (IDeg)	61.0	74.8	78.9	SURPASS-3	
		9.5 (IGlar)	58.3	72.9	78.9	SURPASS-4	
Weight Reduction Target of ≥20%	**Participants without T2DM**						
	Proportion of participants at 72 wks (%)	3.1 (PBO)	30.0	50.1	56.7	SURMOUNT-1	
	Participants with T2DM						
	Proportion of	0.0 (PBO)	2.1	6.4	16.0	SURPASS-1	

Effect	Short Description	Control	TZP 5 mg	TZP 10 mg	TZP 15 mg	Study or Analysis Set	Strengths/Limitations/Uncertainties
	participants at 40 wks (%)	0.0 (PBO)	3.8	3.0	9.9	SURPASS-5	
		1.5 (Sema)	6.8	8.7	16.8	SURPASS-2	
	Proportion of participants at 52 wks (%)	0.5 (IDeg)	5.2	12.4	17.8	SURPASS-3	
		0.3 (IGlar)	2.9	9.8	19.0	SURPASS-4	
Waist Circumference Change	**Participants without T2DM**						
	LS Mean CFB at 72 wks (cm)	-4.0 (PBO)	-14.0	-17.7	-18.5	SURMOUNT-1	
	Participants with T2DM						
	LS Mean CFB at 40 wks (cm)	-1.9 (PBO)	-5.3	-6.8	-6.3	SURPASS-1	
		1.3 (PBO)	-2.9	-7.1	-7.6	SURPASS-5	
		-5.5 (Sema)	-7.0	-8.9	-9.2	SURPASS-2	
	LS Mean CFB at 52 wks (cm)	0.9 (IDeg)	-6.9	-8.6	-9.5	SURPASS-3	
		0.6 (IGlar)	-7.2	-7.6	-9.3	SURPASS-4	
Serum non-HDL Percent Change	**Participants without T2DM**						
	LS Mean CFB at 72 wks (%)	-2.3 (PBO)	-8.0	-9.4	-11.7	SURMOUNT-1	
	Participants with T2DM						
	LS Mean CFB at 40 wks (%)	-2.0 (PBO)	-7.8	-8.2	-12.2	SURPASS-1	
		0.8 (PBO)	-11.8	-13.0	-14.2	SURPASS-5	
		-7.7 (Sema)	-10.1	-8.7	-9.3	SURPASS-2	
	LS Mean CFB at 52 wks (%)	-2.8 (IDeg)	-5.9	-9.9	-9.6	SURPASS-3	
		-0.7 (IGlar)	-8.5	-10.6	-9.3	SURPASS-4	
SBP Change	**Participants without T2DM**						
	LS Mean CFB at 72 wks (mmHg)	-1.0 (PBO)	-6.6	-7.7	-7.4	SURMOUNT-1	
	Participants with T2DM						
	LS Mean CFB at 40 wks (mmHg)	-1.9 (PBO)	-4.0	-5.6	-4.6	SURPASS-1	
		-1.6 (PBO)	-5.8	-7.8	-12.4	SURPASS-5	
		-4.0 (Sema)	-4.7	-4.7	-6.6	SURPASS-2	

Effect	Short Description	Control	TZP 5 mg	TZP 10 mg	TZP 15 mg	Study or Analysis Set	Strengths/Limitations/Uncertainties
	LS Mean CFB at 52 wks (mmHg)	0.7 (IDeg)	-4.9	-5.8	-5.0	SURPASS-3	
		0.7 (IGlar)	-2.7	-3.7	-5.0	SURPASS-4	
HbA1c Percent Change	**Participants without T2DM**						
	%CFB; difference to plc	N/A	-0.3	-0.4	-0.4	SURMOUNT-1	
	Participants with T2DM						
	%CFB; difference to plc/comparator	N/A	-1.5	-1.5	-1.6	SURPASS-1	
		N/A	-1.3	-1.6	-1.5	SURPASS-5	
		N/A Vs. Sema	-0.2	-0.4	-0.5	SURPASS-2	
		N/A Vs. Ins degludec	-0.6	-0.8	-0.9	SURPASS-3	
		N/A vs ins glargine	-0.8	-1.0	-1.1	SURPASS-4	
Unfavorable effects							
TEAEs	Number and proportion of participants during the study (n [%])	463 (72.0) (PBO)	510 (81.0)	520 (81.8)	497 (78.9)	SURMOUNT-1	**Strengths of evidence related to risks** • The safety profile of TZP was characterized in 7354 participants with obesity or overweight treated with TZP in the Phase 2/3 studies, representing 7071.3 patient-years of TZP exposure. **Limitations and uncertainties related to risks** • Currently, there are no indications that TZP treatment may be associated with a higher risk of depression or suicide. However, it is noted that SURMOUNT-1 and -4 did not enroll participants with depression- and suicide-related problems. • Currently, the general malignancy risk does not seem to be increased with TZP, but the duration of the clinical studies does not allow identification of long-latency events, such as malignant neoplasms. MTC and pancreatic cancer are followed as important potential risks in the RMP.
		589 (71.22) (PBO	654 (78.61)	648 (78.07)	643 (77.66)	AS1C	
SAEs		44 (6.8) (PBO)	40 (6.3)	44 (6.9)	32 (5.1)	SURMOUNT-1	
		53 (6.41) (PBO)	51 (6.13)	57 (6.87)	41 (4.95)	AS1C	
Alopecia [b]		6 (0.9) (PBO)	32 (5.1)	31 (4.9)	36 (5.7)	SURMOUNT-1	
		6 (0.73) (PBO)	32 (3.85)	31 (3.73)	36 (4.35)	AS1C	
Hypotension [b]		0 (PBO)	4 (0.6)	5 (0.8)	10 (1.6)	SURMOUNT-1	
		1 (0.12) (PBO)	6 (0.72)	5 (0.60)	12 (1.45)	AS1C	

Effect	Short Description	Control	TZP 5 mg	TZP 10 mg	TZP 15 mg	Study or Analysis Set	Strengths/Limitations/Uncertainties
Dizziness [b]		15 (2.3) (PBO)	26 (4.1)	35 (5.5)	26 (4.1)	SUR-MOUNT-1	• For clarification of the influence of TZP on the risk of worsening of diabetic retinopathy and of CV events, future data are awaited (retinopathy: ongoing dedicated addendum study to SURPASS-CVOT; CV risk: SURMOUNT-MMO and SURPASS-CVOT).
		17 (2.06) (PBO)	28 (3.37)	39 (4.70)	32 (3.86)	AS1C	
Gastro-intestinal AEs [c]		236 (28.54) (PBO)	427 (51.32)	458 (55.18)	460 (55.56)	AS1C	

Abbreviations: AS1C = Phase 3 Placebo-Controlled Analysis Set; AS2C = Phase 3 Dose-effect analysis set; AS4C = Phase 2/3 comparator-controlled analysis set; AUC = area under the concentration versus time curve; CFB = change from baseline; C_{max} = maximum observed drug concentration; CWM = chronic weight management; HDL = high-density lipoprotein; IDeg = insulin degludec; IGlar = insulin glargine; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical trials; LS = least squares; n = number of participants with at least 1 event; PBO = placebo; PGIS = Patient Global Impression of status for physical activity; PRO = patient-reported outcome; SAE = serious adverse events; SBP = systolic blood pressure; sema = semaglutide; SF-36v2 = Short Form-36, Version 2; TEAE = treatment-emergent adverse events; T2DM = type 2 diabetes mellitus; TZP = tirzepatide; wks = weeks.

[a] Fasting insulin was not analyzed in SURPASS-3, -4, and -5 because some (SURPASS-3 and -4) or all (SURPASS-5) participants received insulin, which could confound the assessment of endogenous insulin.

[b] New adverse events reported in the overweight/obese population of the chronic weight management procedure.

[c] more frequently in the obese/overweight population as compared to the population of the T2DM procedure

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The most important benefit of tirzepatide is the clinically meaningful weight reduction demonstrated in SURMOUNT-1. The effect size is considered large with considerable proportions of patients achieving a weight reduction target of ≥20% body weight. This magnitude of weight reduction approaches that seen with bariatric surgery. The reduction in fat mass was about three times greater than the reduction in lean mass, resulting in improved body composition.

Other important benefits are clinically meaningful improvements in lipid parameters, blood pressure and measures of glycaemic control. In addition to reductions in HbA1c, the vast majority of patients with prediabetes at baseline treated with tirzepatide reverted to normoglycemia. An additional benefit is a modest improvement in generic and disease-specific PRO measures, most prominent for physical functioning. These key benefits have likewise been shown for patients with T2DM in subgroup analyses of the SURPASS studies.

The evidence of efficacy was considered statistically convincing and there is good concordance among efficacy endpoints and among subgroups, underlining the robustness of the results.

Importance of unfavourable effects

Highest importance:

- Elevated pancreatic enzymes
- Depression: may have serious consequences, e.g. suicidality. Relationship to TZP unclear.
- Cholelithiasis: it is known that rapid weight loss can trigger gallstones for the same reasons as obesity — it alters the balance of cholesterol, lecithin, and bile acids, and prevents the gallbladder from emptying adequately; although mostly not life threatening, it may require cholecystectomy.

Minor importance:

- Gastrointestinal TEAEs: mostly occurring temporarily, and can be controlled by dose adjustment
- Increase in serum calcitonin: reversible and mostly without clinical relevance; however, long-term consequences are unclear.
- TZP-associated increase in nighttime DBP, TZP effects on blood pressure and heart rate: the effect on nighttime DBP was only an isolated finding with TZP 15 mg, and the effect on heart rate is well-known from other GLP1 receptor agonists; both effects are of minor importance, as, in general, no increased risk for CV events was identified to date (meta-analysis for MACE-3 in dataset AS4C).
- Increase in pancreatic enzymes: not associated with pancreatitis in most of the cases and well known from established GLP1 receptor agonists.
- Hypersensitivity- and injection site reactions: mostly not serious or severe, and self-limiting.
- Hypotension, dizziness, alopecia: of minor importance, as long, as these AEs are reversible or can be controlled by dose reduction.

3.7.2. Balance of benefits and risks

The key benefit of TZP is pronounced weight reduction accompanied by improvements in cardiometabolic parameters. The risk profile of TZP in overweight/obese subjects appears overall similar to that in patients with T2DM and therefore is generally acceptable. The benefits of TZP are therefore considered to outweigh its risks.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall B/R of Mounjaro is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of indication to include weight management, including weight loss and weight maintenance, for MOUNJARO, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial body mass index (BMI) of ≥ 30 kg/m2 (obesity), or ≥ 27 kg/m2 to < 30 kg/m2 (overweight) in the presence of at least one weight-related comorbid condition, based on a global, pivotal phase 3 study I8F-MC-GPHK (SURMOUNT-1) and five supportive phase 3 studies (SURPASS-1 to -5) in participants with T2DM and BMI ≥ 27 kg/m2. SURMOUNT-1 is a phase 3, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of tirzepatide once weekly in participants without type 2 diabetes who have obesity or are overweight with weight related comorbidities. As a consequence, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.

Amendments to the marketing authorisation

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies and bariatric surgery (see appendix 1).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘EMEA-H-C-005620-II-0007’