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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mounjaro

International non-proprietary name: Tirzepatide

Procedure No. EMEA/H/C/005620/II/0038

Note

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

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List of abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
ADA	anti-drug antibody
AE	adverse event: Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AF	atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin-II receptor blocker
ARD	absolute risk difference
ARNI	angiotensin Receptor-Neprilysin Inhibitor
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
bpm	beat per minute
CEC	clinical endpoint committee
CI	confidence interval
CKD-EPI	chronic kidney disease-epidemiology
cMRI	cardiac magnetic resonance imaging
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	adherence to all study-related GCP and applicable regulatory requirements
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
cTNT	cardiac troponin T
CV	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	all participants who are assigned to the open-label treatment period
enter	participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERA	environmental risk assessment
FFM	Fat-free mass
GCP	good clinical practice
GI	Gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide

GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin A1c
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fracture
HLT	high level term
HR	heart rate
hsCRP	high-sensitivity C-reactive protein
IC_{50}	inhibitory concentration to reach 50% inhibition
ICF	informed consent form
ICH	The International Council for Harmonisation
IG	immunogenicity
IIV	interindividual variability
Informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.
ITT	intent-to-treat
IV	intravascular
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire – Clinical Summary Scale
KM	Kaplan-Meier
LA	left atrial
LV	left ventricular
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MOF	Model objective function
MMRM	mixed model for repeated measures
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MWPC	meaningful within-patient change
NCO	non-clinical overview
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
ODI	oral diuretics intensification
OSS	overall summary score
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic
PGIS	Patient Global Impression of Status
PI	principal investigator
PK	pharmacokinetic
PK / PD	pharmacokinetics / pharmacodynamics
PRO	patient-reported outcome
PT	preferred term
pcVPC	prediction-corrected Visual Predictive Check
QW	once weekly
RA	receptor agonist

SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
screen	The act of determining whether an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDP	single-dose pen
SGLT2	Sodium glucose co-transporter 2
SMQ	standardized MedDRA queries
SOC	system organ class
T1D	type 1 diabetes
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TSS	total symptom score
UACR	urine albumin creatinine ratio
ULN	upper limit of normal
VAS	visual analog scale
IRB / IEC	Institutional Review Boards / Independent Ethics Committees

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 11 November 2024 an application for a variation.

The following changes were proposed:

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

Extension of indication to include treatment of symptomatic chronic heart failure with preserved ejection fraction (HFpEF) in adults with obesity for MOUNJARO, based on results from the Phase 3 trial I8F-MC-GPID (SUMMIT). SUMMIT was a randomized, multicenter, international, placebo-controlled, double-blind, parallel-arm study in participants with HFpEF and obesity. The study was designed to evaluate the effect of tirzepatide compared with placebo on both clinical and symptomatic or functional outcomes. As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0478/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0478/2023 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.

Scientific advice

The MAH received Scientific advice from the CHMP on 18 October 2018 (EMA/CHMP/SAWP/689326/2018). The Scientific advice pertained to quality, non-clinical and clinical aspects of the dossier.

2. Recommendations

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

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

Update of sections 4.1, 4.8 and 5.1 of the SmPC based on final results from the Phase 3 trial I8F-MC-GPID (SUMMIT). SUMMIT was a randomized, multicenter, international, placebo-controlled, double-blind, parallel-arm study in participants with HFpEF and obesity. The study was designed to evaluate the effect of tirzepatide compared with placebo on both clinical and symptomatic or functional outcomes. The Package Leaflet is updated accordingly. Version 4.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI.

☒is recommended for approval.

Amendments to the marketing authorisation

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

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disorder including different but partially overlapping pathophysiologic phenotypes. HFpEF is defined as HF with an LVEF of 50% or higher at diagnosis (Redfield and Borlaug 2023). Approximately 50% of patients with HF have HFpEF. HFpEF is associated with various comorbidities including hypertension, AF, T2DM, and obesity. Some authors assume that the obesity phenotype (obesity-related HFpEF) displays a distinct phenotype, where increased ectopic adiposity coupled with metabolic derangements and plasma volume expansion play a causal role (Kitzman and Shah 2016; Packer 2018; Borlaug et al. 2022).

HFpEF affects 32 million people worldwide and is known to occur more in females and older patients (Redfield and Borlaug 2023). Its incidence and prevalence continue to rise (Balestrieri et al. 2024). The obesity phenotype is the most common phenotype. Approximately 50% of patients with HFpEF are estimated to have obesity. Patients with the obesity phenotype are about a decade younger than patients without obesity (Borlaug et al. 2022).

HFpEF is associated with high hospitalisation and mortality rates and significant patient burden. Patients with HFpEF present signs and symptoms such as dyspnoea, fatigue, and peripheral oedema, which severely impair patients' daily activities. HFpEF is a progressive condition characterized by variable durations of symptomatic stability often interrupted by decompensation episodes with worsening symptoms, requiring interventions, such as hospitalisation, the use of intravenous drugs in an urgent care setting, or the intensification of oral diuretics. Worsening HF is an important identifier of subsequent demise (Shah et al. 2017; Chatur et al. 2023).

Patients with obesity-related HFpEF have significant degrees of exercise intolerance and a markedly impaired quality of life and health status compared with patients without obesity (Reddy et al. 2020), and abdominal obesity is associated with increased morbidity and mortality (Tsujimoto and Kajio 2017; Chen et al. 2021).

The burden on patients with HFpEF and obesity is multifaceted and extends beyond the symptoms of the disease.

Claimed therapeutic indication

Tirzepatide is currently approved as (1) an adjunct to diet and exercise to improve glycaemic control in adults with T2DM and (2) 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.

The MAH initially requested an extension of indication to include the treatment of Heart failure with preserved ejection fraction. The following indication was initially proposed to be added to section 4.1 of the SmPC:

"Heart failure with preserved ejection fraction

Mounjaro is indicated for the treatment of symptomatic chronic heart failure with preserved ejection fraction (HFpEF) in adults with obesity."

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

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

Weight management

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

- *≥ 30 kg/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).*

For trial results with respect to obstructive sleep apnoea (OSA) ***and heart failure with preserved ejection fraction (HFpEF)****, see section 5.1.*

Management

Current guidelines emphasize the importance of managing comorbidities, such as hypertension, volume control, AF, T2DM, and obesity (Heidenreich et al. 2022; McDonagh et al. 2023). The goal of treatment is to relieve symptoms, improve quality of life, prevent hospitalisations and clinical worsening, and decrease mortality.

Some treatment options are already available that specifically target obesity-related HFpEF. A multidisciplinary approach used for treatment includes weight management, diuretics for fluid management, management of AF, and medications for comorbidities such as hypertension and diabetes (Heidenreich et al. 2022). SGLT2 inhibitors have shown benefits in patients with HF across the broad range of LVEF, whereas the efficacy of sacubitril-valsartan was more evident in patients with HFpEF whose LVEF is less than 57% (Solomon et al. 2019). Recently, finerenone was shown to reduce the risk of HF worsening in patients with heart failure with mildly reduced ejection fraction (HFmrEF) and HFpEF (Solomon et al. 2024). Semaglutide also showed some benefits in HFpEF both in heart failure symptoms and physical function.

3.1.2. About the product

Tirzepatide (TZP) is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. TZP includes a 39-amino acid peptide sequence and a C20 fatty acid moiety that is covalently linked to Lys20 via a linker with 3 additional amino acids (a γ-Glu and two 8-amino-3,6-dioxaoctanoic acids) for a total of 42 amino acids. The C20 fatty diacid moiety enables albumin binding and prolongs the half-life. TZP selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1. The molecular weight of TZP is 4.8 kDa.

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

The following study provides primary evidence for this application:

SUMMIT (Study I8F-MC-GPID)

A Phase 3, randomized, multicenter, international, placebo-controlled, double-blind, parallel-arm study in participants with HFpEF and BMI of at least 30 kg/m^2. The study was designed to evaluate the effect of tirzepatide QW MTD up to 15 mg on both clinical and symptomatic or functional outcomes. To determine whether tirzepatide's benefit could be associated with effects on cardiac structure, geometry, and function, a cMRI substudy was conducted.

3.1.4. General comments on compliance with GLP, GCP

GCP:

The applicant confirms that the clinical trial that supports this application was conducted in accordance with

(1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects
(2) the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6], and
(3) applicable laws and regulations of the country or countries where a study is conducted.

The applicant declares that the clinical trial was conducted outside the European Union, met the ethical requirements of Directive 2001/20/EC, and is listed as follows:

- Study I8F-MC-GPID: Argentina, Brazil, China, India, Israel, Mexico, the Russian Federation, Taiwan, and the United States.

The clinical study in this application was GCP-inspected by US FDA. Moreover, an internal audit has been conducted on Study I8F-MC-GPID.

3.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

However, the MAH has provided a new calculation of the exposure margins (animal exposure in the toxicology studies versus human therapeutic exposure) based on the human exposure in the HFpEF population from the SUMMIT study.

3.2.1. Introduction

The present application is for the use of tirzepatide to reduce the risk of worsening heart failure and to improve clinical symptoms and functional capacity in adults with heart failure with preserved ejection fraction (HFpEF) and obesity. The newly submitted addendum to the Non-Clinical Overview (NCO) supplements the previously submitted NCO for T2DM and weight management with revised exposure multiples based on the population pharmacokinetics (PK) data from the HFpEF clinical trial.

3.2.2. Pharmacology

Not applicable

3.2.3. Pharmacokinetics

Not applicable

3.2.4. Toxicology

Toxicokinetic data

The table below provides revised exposure multiples based on the population PK data from the HFpEF clinical trial, I8F-MC-GPID (SUMMIT) (Population PK Report). Since the population PK data from SUMMIT were comparable to the data from the T2DM and weight management clinical trials (AUC0-τ, steady-state = 250000 and 266000 ng*hr/mL, respectively), the exposure multiples are generally similar across all three indications. Exposure multiples were derived from repeat-dose toxicology studies using the highest proposed clinical dose of 15 mg/week.

Table 1. Exposure Multiples for Subcutaneous Administration of Tirzepatide in Pivotal Toxicology Studies

Species Dose	$AUC_{0-\tau}$, steady-state (ng*hr/mL)	Exposure Multiple
Human		
15 mg/week	268800[a]	–
Repeat-Dose Toxicology		
6-Month Rat (Study 8337876)[a, c]		
3 mg/kg/twice weekly[b]	279500	1.82
6-Month Monkey (Study 8336517)[d, e]		
0.5 mg/kg/weekly[b]	336500	1.25
Reproductive and Developmental Toxicology		
Rat Embryo/Foetal Development (Study WIL-353354)[f, g]		
0.5 mg/kg/twice weekly	35800	0.23
Rabbit Embryo/Foetal Development (Study WIL-353355)[h]		
0.1 mg/kg/weekly	56400	0.21

Abbreviations: AUC_{0-T} = 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 EM is calculated as (AUC_{0-T}/τ in animals)/(AUC_{0-T}/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 AUC_{0-T} values are the average of male and female values when studies include both male and female rodents.

b NOAEL for target organ toxicity.

c Plasma AUC determined on Day 176.

d EM is calculated as (AUC_{0-T}/τ in animals)/(AUC_{0-T}/τ in humans). τ is 168 hours in monkeys and humans. Therefore, EM in monkey = (monkey AUC/168)/(human AUC/168). Monkey steady state AUC_{0-T} values are the average of male and female values.

e Plasma AUC determined on Day 176.

f EM is calculated as (AUC_{0-T}/τ in animals)/(AUC_{0-T}/τ in humans). τ is 96 hours in maternal rats and 168 hours in humans.

g Plasma AUC determined on GD 17.

h EM is calculated as (AUC_{0-T}/τ in animals)/(AUC_{0-T}/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.

3.2.5. Ecotoxicity/environmental risk assessment (ERA)

The ERA provided is considered complete and acceptable. Tirzepatide is administered in parenteral form and has been described to be not excreted in unchanged form (m1.6, m2.5, m5.3). Tirzepatide includes a 39-amino acid peptide sequence and a 1,20-eicosanedioc acid moiety that is covalently linked to Lys20 via a linker with 3 additional amino acids (a γ-Glu and two 8-amino-3,6-dioxaoctanoic acids) for a total of 42 amino acids. The 1,20-eicosanedioic acid moiety is identical to naturally occurring substances. The fate of the linker is unknown. The MAH has provided evidence that tirzepatide is readily biodegradable.

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

3.2.6. Discussion on non-clinical aspects

The CHMP agreed that the existing non-clinical toxicology data also support the HFpEF indication; no relevant changes in exposure margins result from the clinical exposure data in the HFpEF population of the new SUMMIT study.

ERA: The active substance is a protein covalently linked with a 20-carbon fatty acid, excretion of the intact molecule from humans does not occur. Therefore, tirzepatide is not expected to pose a risk to the environment. There are no open issues left in the ERA. The ERA provided is considered complete and acceptable. No ERA studies are required with respect to the chemical nature of the molecule.

3.3. Clinical aspects

3.3.1. Introduction

GCP

See section 4.1.4.

3.3.2. Pharmacokinetics

Since the prior submissions (T2DM, weight management), no additional Phase 1 studies have been completed.

3.3.3. Pharmacodynamics

Mechanism of action

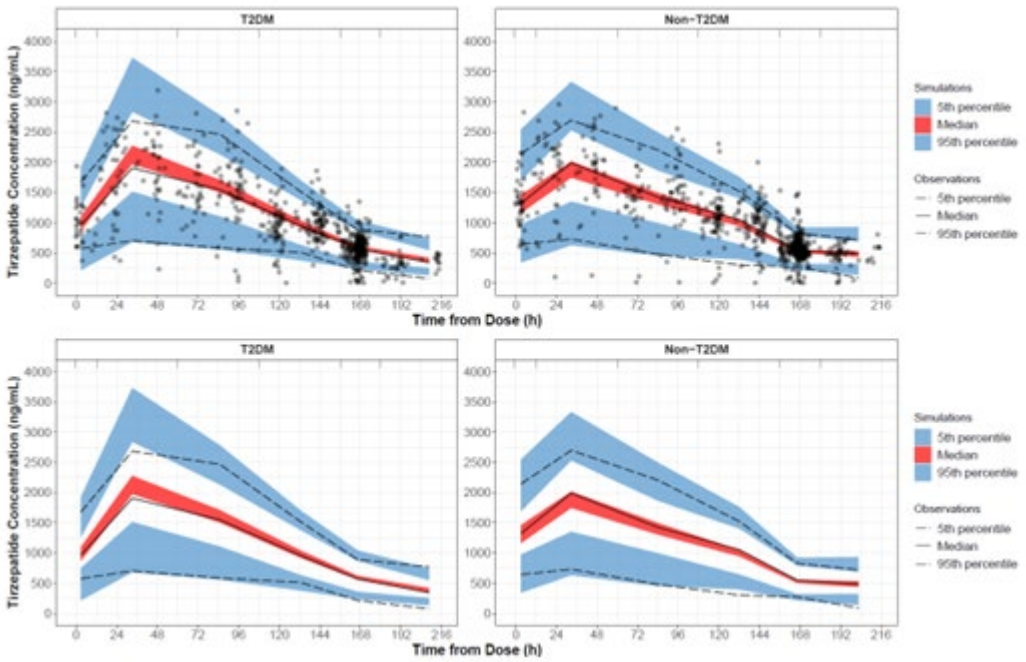
Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

Population pharmacokinetics

The popPK analysis dataset contained data from Study GPID. In this study, tirzepatide doses were escalated to the MTD (5, 10, or 15 mg QW) or placebo was used, via SC route of administration (solution formulation in autoinjector) for at least 52 weeks. Sparse blood samples collection for PK assessment were collected. Sampling occurred prior to tirzepatide dose administration and at the same time as the planned immunogenicity samples at visits at Weeks 0, 4, 12, 24, and 52, and follow-up per the protocol. Different response endpoints were evaluated. KCCQ-CSS was assessed at baseline and weeks 24 and 52. 6MWD was measured at baseline and weeks 24 and 52. Body weight was measured during the study period at weeks 0, 4, 8, 12, 16, 20, 24, 40, and 52, and follow-up. hsCRP was measured at baseline and weeks 12, 24, and 52. Adverse events of special interest, such as nausea, vomiting, and diarrhoea, were reported at each study visit. PK, immunogenicity, KCCQ-CSS, 6MWD, body weight, and hsCRP data were collected at early discontinuation visits. The primary dataset for population PK analysis contained 2140 observations from 364 participants. The final dataset for exposure-response analysis included 13,945 (86.8%) observations from 725 (99.2%) participants.

The observed tirzepatide concentrations from participants with HFpEF and obesity in Study GPID were adequately described by the same model structure and parameter estimates from the population PK model previously developed from studies of tirzepatide for treatment of T2DM and weight management. Estimation of parameters with or without priors was evaluated as well. However, these attempts did not lead to any significant improvements in diagnostic plots and thus were not further pursued. The final model used for the analysis of Study GPID tirzepatide concentrations has 2 compartments, with first-order absorption and IIV on ka, CL, Vc, and proportional residual error. Parameters were fixed to values estimated from SURMOUNT-1.

No factors other than body weight were included in the final population PK models for T2DM and weight management. The baseline body weight and BMI distribution in Study GPID were similar to SURMOUNT-1 and the T2DM populations. The relationship between FFM and fat mass and CL and Vd was incorporated into the model using published equations developed in individuals with body weights similar to the tirzepatide treated population. The potential impact of immunogenicity and ADA on tirzepatide PK was investigated. No overt pattern or trend was evident in the graphical comparison of tirzepatide concentrations in participants with ADA compared with participants without ADA. The range of observed tirzepatide concentrations was comparable in participants with and without ADA and there were no obvious time-dependent trends. No statistically significant difference was observed in tirzepatide CL/F across the range of observed ADA titre values. A pcVPC stratified by T2DM status is shown below.



Abbreviations: T2DM = type 2 diabetes mellitus; pcVPC=prediction-corrected visual predictive check; PK=pharmacokinetics.
Note: Solid circles denote individual values, shaded areas denote the 95% confidence interval of simulation percentiles, and the dashed lines denote the observation percentiles.

Figure 1. pcVPC of the final population PK model stratified by T2DM status with (top) and without (bottom) overlaid observed data after tirzepatide dose

3.3.4. PK/PD modelling

Several exposure-response models were investigated, for efficacy response parameters body weight reduction, KCCQ-CSS, six-minute walk distance, high sensitive C-reactive protein, and for adverse events nausea, vomiting and diarrhoea.

Body Weight: The model developed from participants with obesity or overweight (SURMOUNT-1) was used to evaluate data from participants with HFpEF and obesity in Study GPID. Only the post hoc PK parameters, baseline FFM, baseline fat mass, placebo effects, and first-order elimination rate constant for FFM and fat were estimated from the Study GPID data, as these parameters were expected to be population- and study-specific. IIV of the estimated parameters and residual error were also estimated. Participants in Study GPID showed trends consistent with SURMOUNT-1 and with previously published studies with other incretin-based therapies, such that participants with obesity or overweight with T2DM had less weight reduction compared with those without T2DM. T2DM status as a covariate effect on FFM and fat mass drug concentration that produces 50% of maximum inhibitory effects (IC50s) was incorporated to account for the lower extent of weight loss observed in participants who had HFpEF and obesity with T2DM. All other parameters in the model, including the parameters that describe the relationship between tirzepatide exposure and weight reduction, were fixed to the estimates from the SURMOUNT-1 analysis.

Table 2. Parameter Estimates of Tirzepatide Weight Reduction Model

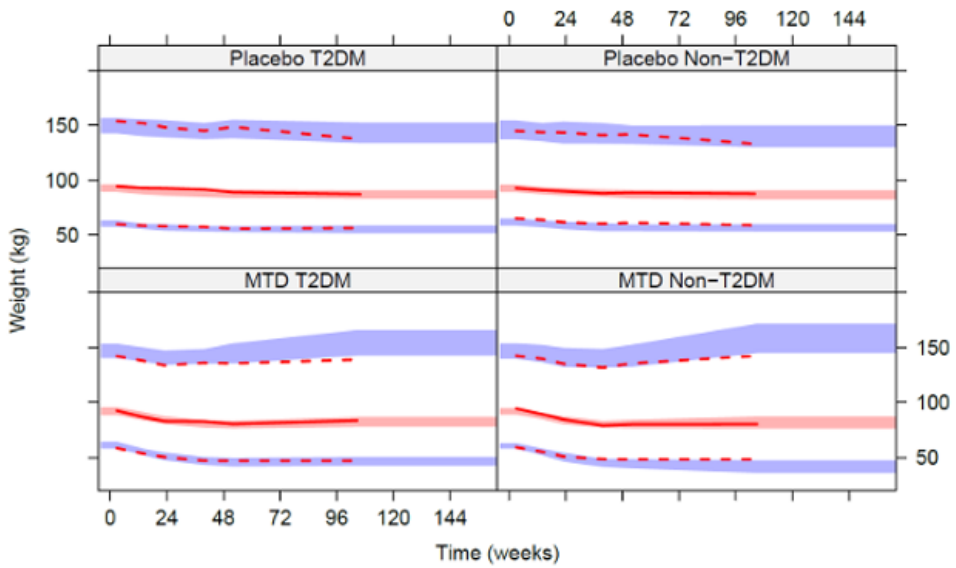
Population Parameter	SURMOUNT-1 Estimate (95% CI)[a]	Study GPID Estimate (95% CI)[a]
Baseline fat-free mass (kg)	73.5 (72.6, 74.3)	70.6 (70, 71.2)
Baseline fat mass (kg)	45.0 (43.4, 46.3)	43.5 (42.6, 44.5)
First-order elimination rate constant, Kout ($week^{-1}$)	0.0314 (0.0295, 0.0348)	0.0162 (0.0125, 0.0208)
Maximum effect for drug-inhibiting formation of fat-free mass	0.144 (0.119, 0.176)	Fixed
Maximum effect for drug-inhibiting formation of fat mass	0.319 (0.266, 0.385)	Fixed
IC50 for drug-inhibiting formation of fat-free mass (ng/mL)	1760 (1490, 2030)	Fixed
IC50 for drug-inhibiting formation of fat mass (ng/mL)	518 (390, 678)	Fixed
Placebo fractional reduction in fat-free mass Kin	0.0658 (0.0594, 0.0698)	0.0409 (0.0352, 0.0473)
Placebo fractional reduction in fat mass Kin	0.213 (0.192, 0.228)	0.133 (0.115, 0.153)
Half-life of waning placebo effect (weeks)	40.3 (34.6, 54.4)	164 (136, 397)[b]
Covariate effects		
Fractional change in baseline fat-free mass in females	-0.312 (-0.322, -0.302)	Fixed
Fractional change in fat mass in females	0.0539 (0.0170, 0.0994)	Fixed
Fractional change in drug maximum effect for fat-free mass in females	1.78 (1.37, 2.33)	Fixed
Fractional change in drug maximum effect for fat mass in females	0.809 (0.528, 1.12)	Fixed
Fractional change in drug IC50 effect for fat-free mass in females	1.14 (0.836, 1.55)	Fixed
Fractional change in drug IC50 effect for fat mass in females	2.05 (1.31, 3.19)	Fixed
Fractional change in baseline fat-free mass in Asians	-0.110 (-0.128, -0.0905)	Fixed
Fractional change in baseline fat mass in Asians	-0.254 (-0.291, -0.214)	Fixed
Fractional change in drug IC50 effect for fat-free mass in T2DM subpopulation	N/A	0.483 (0.463, 0.753)
Fractional change in drug IC50 effect for fat mass in T2DM subpopulation	N/A	0.477 (0.438, 0.964)
Interindividual variability (CV%)		
Baseline fat-free mass	11.0 (10.5, 11.5)	12.4 (11.7, 13)
Baseline fat mass	29.3 (28.1, 30.4)	30.3 (28.8, 31.9)
Correlation between the random effects for baseline fat and fat-free mass	0.851 (0.835, 0.864)	0.849 (0.758, 0.944)
Correlation between the random effects for baseline fat-free mass and Kout	-0.140 (-0.212, -0.0667)	-0.171 (-0.27, -0.0781)
Correlation between the random effects for baseline fat mass and Kout	-0.172 (-0.246, -0.0936)	-0.232 (-0.333, -0.134)
First-order elimination rate constant, Kout	124 (110, 140)	263 (197, 368)
Maximum drug effect on fat-free mass	84.5 (68.4, 102)	Fixed
Maximum drug effect on fat mass	69.6 (54.4, 85.1)	Fixed

Population Parameter	SURMOUNT-1 Estimate (95% CI)[a]	Study GPID Estimate (95% CI)[a]
Correlation between the random effects for maximum effect (IMAX)	0.993 (0.988, 0.994)	Fixed
IC50 for drug-inhibiting formation of fat-free mass	25.7 (19.4, 34.7)	Fixed
IC50 for drug-inhibiting formation of fat mass	47.4 (35.3, 66.1)	Fixed
Correlation between the random effects for IC50	0.9994 (0.9986, 0.9998)	Fixed
Placebo effect for fat-free mass	96.6 (87.5, 107)	106 (86.1, 133)
Placebo effect on fat mass	94.7 (86.3, 106)	104 (84.7, 128)
Correlation between the random effects for placebo	0.977 (0.972, 0.985)	0.977 (0.63, 1.49)
Residual error		
Proportional for fat-free mass (%)	0.985 (0.910, 1.04)	1.17 (1.06, 1.34)
Proportional for fat mass (%)	3.35 (3.08, 3.54)	4.39 (3.94, 5.04)
Correlation between residual error (%)	98.4 (98.4, 98.6)	99.0 (81, 132)

Abbreviations: CI = confidence interval; CV = coefficient of variation; IC50 = drug concentration that produces 50% of maximum inhibitory effect; Kin = formation rate; Kout = first-order elimination rate constant.

[a] Confidence interval obtained from a bootstrap analysis.

[b] Estimated for the placebo arm only.



Note: The upper dotted line represents the 95th percentile of the observed data. The middle continuous line represents the 50th percentile of the observed data. The lower dotted line represents the 5th percentile of the observed data. The shaded areas represent the model-predicted 95% confidence interval of the corresponding percentiles. Due to their high density, the observed data points have been removed from the plot to increase the clarity of the percentiles.

Figure 2. Visual predictive check for final model of weight reduction model stratified by status – total body weight

KCCQ-CSS: KCCQ-CSS data collected from participants who received placebo or tirzepatide treatment at baseline, Week 24, and Week 52 of the treatment period were pooled together. The relationship between tirzepatide treatment and the improvement of KCCQ-CSS over time was well described by including both an effect of tirzepatide concentration and an effect of percent body weight reduction. The relationships of tirzepatide concentration and percent change in body weight with KCCQ CSS were first evaluated separately. The model with tirzepatide concentration alone had a lower MOF compared with a model with percent change in body weight alone. A model with both an effect of tirzepatide concentration and an effect of percent change in body weight had the lowest MOF. A lag time in the relationship

between tirzepatide concentration and KCCQ-CSS was included based on a drop in the model objective function. The lag time was parameterized with transit compartments. The model estimated mean transit time for the lag between tirzepatide concentration and KCCQ-CSS was approximately 1 week. A time-independent additive placebo effect was included in the final model. Additive IIV on baseline KCCQ-CSS and the placebo effect were associated with a significant decrease in MOF and were included in the final model. A correlation between baseline BMI and baseline KCCQ-CSS was detected and was incorporated into the final model. At baseline, the KCCQ-CSS was inversely related to BMI such that participants with higher BMI had a lower KCCQ-CSS. Parameter estimates for the final model are summarized in Table 3.

Table 3. Parameter Estimates of Tirzepatide KCCQ-CSS Model for Study GPID

Population Parameter	Estimate (95% CI)[a]
Baseline KCCQ-CSS (score/100)	55.7 (54.1, 57.5)
Placebo effect	12.5 (10.3, 14.4)
Lag time (week)	1.12 (0.666, 3.12)
Effect of tirzepatide concentration[b]	0.236 (0.110, 0.290)
Effect of percent change in body weight[c]	0.244 (0.0835, 0.495)
Covariate effects	
Baseline BMI on baseline KCCQ-CSS[d]	-0.0248 (-0.0326, -0.0182)
Interindividual variability (CV%)	
Baseline KCCQ-CSS	211% (174, 244)
Placebo effect	72.3% (60.6, 84.2)
Residual error	
Tau	10.7 (9.39, 12.2)

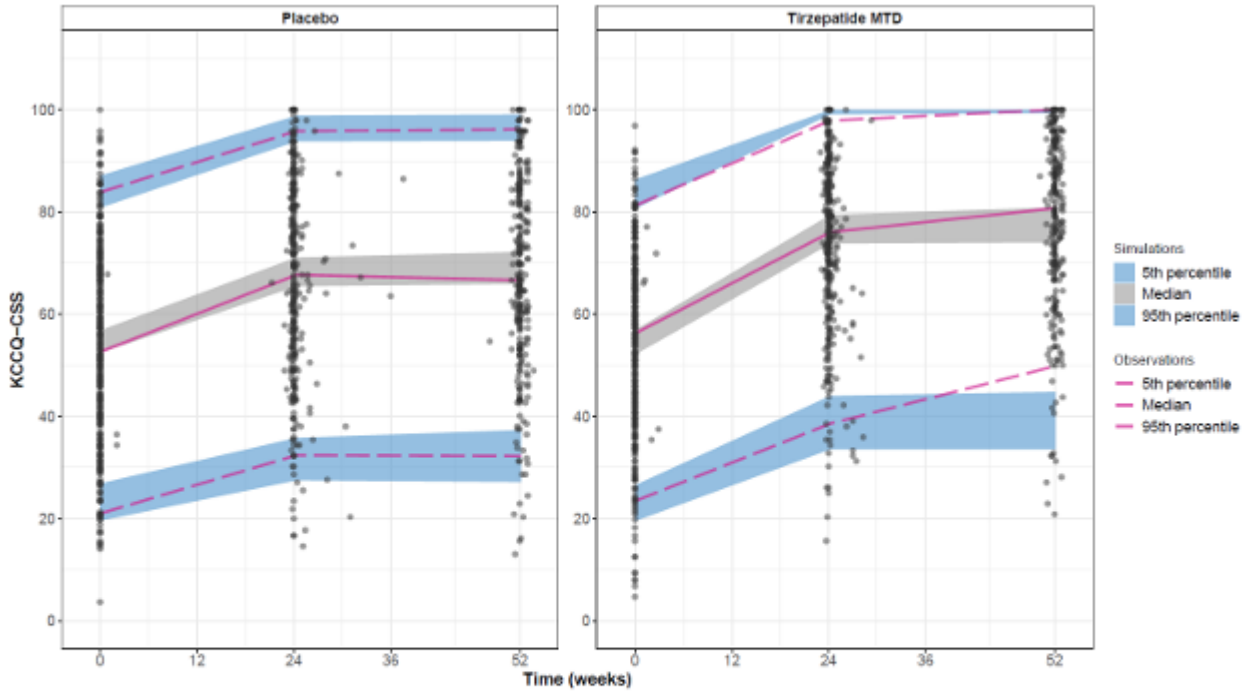
Abbreviations: BMI = body mass index (kg/m^2); CI = confidence interval; CV = coefficient of variation; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; Tau = scale parameter for the beta distribution for residual error.

a Confidence interval obtained from a bootstrap analysis (Section 8.4.3).

b Conc ^TH(4), where Conc is tirzepatide plasma concentration and TH(4) is an estimated power exponent.

c PCWT × TH(5), where PCWT is percent change in body weight and TH(5) is an estimated slope parameter.

d (BMIB-36) × TH(7), where BMIB is baseline BMI centered on the population median baseline BMI (Table 7.4) and TH(7) is an estimated slope parameter.



Abbreviations: KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; MTD = maximum tolerated dose.
Note: The upper dotted line represents the 95th percentile of the observed data. The middle continuous line represents the 50th percentile of the observed data. The lower dotted line represents the 5th percentile of the observed data. The shaded areas around each line represent the model-predicted 95% confidence interval of the corresponding percentiles.

Figure 3. Visual predictive check for final tirzepatide KCCQ-CSS model stratified by treatment – absolute value KCCQ-CSS

Additionally, exploratory correlations were done with hsCRP and 6MWD.

Nausea, Vomiting, and Diarrhoea: For the evaluation of nausea, vomiting, and diarrhoea events in Study GPID, the models developed for the SURMOUNT-1 analysis were used as the reference final models. The SURMOUNT-1 models were used to simulate nausea, vomiting, and diarrhoea prevalence (the proportion of participants with events) to compare with the observed nausea, vomiting, and diarrhoea prevalence in Study GPID. Parameters describing the relationship between tirzepatide exposure and probabilities of nausea, vomiting, and diarrhoea state and tolerance rate constant were fixed to the estimates from SURMOUNT-1 analysis. The influence of population characteristics on PK and PD was taken into consideration by randomly sampling with replacement from the sets of baseline demographics from participants in Study GPID to preserve the correlation of demographics in the simulations. The exposure-response relationship and observed nausea, vomiting, and diarrhoea events from Study GPID were most comparable to the model predictions for tirzepatide 5 mg QW even though most participants in Study GPID reached tirzepatide 15 mg QW. Of the participants in the treatment arm of Study GPID, 77.2% took 15 mg of tirzepatide as the highest dose. For the simulation, the covariates of females and Caucasians that were associated with higher probability of nausea were removed from the model predictions. The prevalence of nausea in Study GPID corresponded to the lower range of model predictions while the prevalence of vomiting and diarrhoea are shown to be comparable with model predictions. The results from Study GPID confirmed the stepwise dose-escalation scheme, starting at 2.5-mg dose for 4 weeks, followed by increases in doses by 2.5-mg increments every 4 weeks to attain

maintenance dose levels of 10 and 15 mg, have mitigated GI adverse events in participants with HFpEF and obesity.

3.3.5. Discussion on clinical pharmacology

PKPD models for Weight reduction, KCCQ-CSS and nausea, vomiting and diarrhoea were conducted. Post hoc values of the population PK analysis were taken as input for the PKPD models. PKPD models for Weight reduction, KCCQ-CSS and nausea, vomiting and diarrhoea were conducted. Post hoc values of the population PK analysis were taken as input for the PKPD models. All parameters were fixed to the values of the previous popPK analysis of SURMOUNT-1 data. This is considered acceptable since estimation of all PK parameters (without fixing parameters to previously estimated values from SURMOUNT-1) led to unreliable estimation of the ka and interindividual variability of ka and yielded an instable model.

3.3.6. Conclusions on clinical pharmacology

Population PK and PKPD results for different efficacy endpoints and safety parameters have been presented. The models are considered acceptable.

3.4. Clinical efficacy

3.4.1. Dose response study

No dedicated dose-response study was submitted with this application.

3.4.2. Main study

SUMMIT-study

Study Number 18-F-MC-GPID

Title of study

A Phase 3, randomized, multicenter, international, placebo-controlled, double-blind, parallel-arm study in participants with HFpEF and BMI of at least 30 kg/m^2.

Methods

Study I8F-MC-GPID (GPID, SUMMIT) was a randomized, outpatient, multicenter, international, placebo-controlled, double-blinded, parallel-arm, Phase 3 study. The study was designed to evaluate the efficacy and safety of SC QW tirzepatide, MTD up to 15 mg, compared with placebo, in participants with HFpEF and obesity.

Two intervention groups were studied as follows:

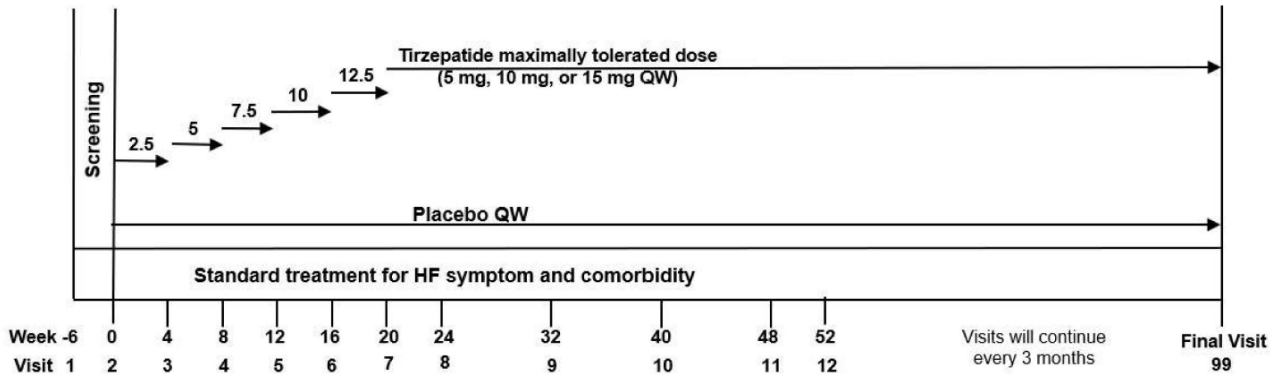
- tirzepatide MTD up to 15 mg SC QW, and
- placebo.

The study included 2 periods:

- Period 1: screening period, lasting no more than 12 weeks, and

- Period 2: treatment period, with a 20-week escalation, followed by at least a 32-week maintenance period.

The study continued until approximately 52 weeks after the last study participant was randomly assigned. The maximum duration of an individual's participation was estimated to be 120 weeks and was dependent on the duration of study enrollment. Study completion was defined as the completion of the final visit (Visit 99) in the study. The final study visit occurred no later than 02 July 2024 (approximately 52 weeks after the last participant was randomly assigned) – see **Figure 4** and **Table 4** below:



Abbreviation: HF = heart failure; QW = once weekly.

Figure 4. Design of the SUMMIT study (Study I8F-MC-GPID)

In addition, a cardiac magnetic resonance imaging (cMRI) addendum was completed in a subset of 106 participants. MRI measurements were taken at baseline and at week 52.

Table 4 summarises the global phase 3 clinical study contributing to the tirzepatide HFpEF application.

Table 4. Study Design Features for SUMMIT study

	SUMMIT
Number of randomly assigned participants	731
Patient population	Patients with chronic HF (NYHA Class II-IV), LVEF ≥50%, and BMI ≥30.0 kg/m^2
Total treatment duration	52 weeks after the last participant is randomly assigned, with a maximum duration of up to 160.3 weeks
Randomization ratio	1:1
Number of participants receiving at least 1 dose	Tirzepatide: 364 Placebo: 367
Study design	Multicenter, international, randomized, parallel-arm, double-blind, placebo-controlled, Phase 3 study
cMRI substudy	
Analysis population	Participants who have MRI measurements at both baseline and Week 52
Number of randomly assigned participants	175 (subset of participants)
Number of participants receiving at least 1 dose	Tirzepatide: 80 Placebo: 95
Number of participants with both baseline and Week 52 measurements	Tirzepatide: 50 Placebo: 56
Objective	Evaluation of cardiac function and structure by cMRI

Abbreviations: BMI = body mass index; cMRI = cardiac magnetic resonance imaging; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NYHA = New York Heart Association.

Study participants

Main inclusion criteria

Participants with or without T2DM, chronic HF diagnosis (NYHA Classes II to IV) for at least 3 months, an LVEF of ≥50% at Visit 1 or within 6 months, a BMI of ≥30.0 kg/m², aged 40 or above, and on stable doses of concomitant HF medications for ≥4 weeks were included in the study.

For the HFpEF diagnosis, one of the following was required:

- elevated NT-proBNP (>200 pg/mL for participants without AF or flutter or >600 pg/mL for participants with AF)
- left atrial enlargement on echocardiogram within 6 months or at Visit 1, or
- evidence of increased filling pressure or E/e' by echocardiogram.

To analyse the effect of tirzepatide on functional capacity and to minimize within-subject variability, participants were included if they had a 6MWD between ≥100 m and ≤425 m at Visit 2 and change from the preceding qualifying 6MWD was <20% and <40 m. Additionally, participants were included if they had a KCCQ-CSS ≤80 at Visit 1.

To enrich the study population with participants at a higher risk of HF events, the participants were required to have either eGFR <70 mL/min/1.73 m^2 or HF decompensation within the past 12 months.

Main exclusion criteria (selection)

To minimize the confounding effects, the following patients were excluded from the study:

- patients with recent CV events or HF decompensation
- Participation in a structured exercise training program in the 1 month prior to Visit 1 or planning to start a program during the study.
- patients who had a past record of LVEF <40% within 2 years of Visit 1
- patients with cardiac amyloidosis, cardiac accumulation disease, cardiomyopathy, including hypertrophic cardiomyopathy

- patients with moderate-to-severe valvular diseases requiring surgery
- patients with noncardiac cause of exercise impairment or symptoms
  - patients with pulmonary arterial hypertension or severe lung diseases such as chronic obstructive pulmonary disease, and
  - patients with orthopaedic conditions that limit the ability to walk
- patients with type 1 diabetes
- patients with uncontrolled type 2 diabetes or history of severe hypoglycaemia within 6 months prior to Visit 1
- patients with proliferative diabetic retinopathy or diabetic maculopathy, and
- patients who had impaired renal function defined as eGFR <15 mL/min/1.73 m^2
- patients with NYHA class I HF at either visit 1 or 2
- completed prior surgical treatment for obesity or undergone liposuction or abdominoplasty within 1 year prior to visit 1
- undergone treatment with any incretin or GLP-1 RA in the 3 months prior to Visit 1.
- Current use of medication associated with weight gain or weight loss, except when on stable dose for at least 3 months prior to Visit 1, and expected to be stable during the study period.

Treatments

Tirzepatide MTD (5 mg, 10 mg, 15 mg), or matched placebo was administered subcutaneously once weekly via single-dose pen. The dose-escalation scheme used in the SUMMIT study started at a dose of 2.5 mg QW, with subsequent dose escalations every 4 weeks until the participants achieved the MTD of 15 mg QW or the highest maintenance dose tolerated by the participant (5 or 10 mg QW). The highest dose of tirzepatide at any time during the study ranged from 2.5 to 15 mg.

For the management of tolerability issues including in cases of excessive weight reduction, temporary dose interruption (at any time) is the preferred method, but de-escalation is also possible. After a temporary dose interruption, participants may resume study drug at the same dose, re-escalate to the prior dose level (if re-escalation is desired or required), or resume at a lower MTD dose level, as tolerated.

After the dose escalation period and at the investigator's discretion, when excessive weight reduction is not warranted due to safety concerns, the investigator may choose to adjust the study drug dose without first attempting a temporary dose interruption. The participant's study drug dose will be permanently reduced to 5 mg, in a blinded fashion for the remainder of the study and the dose cannot be re-escalated.

For participants receiving the 5 mg maintenance dose, only dose interruption (but no dose de-escalation) is permitted to manage tolerability issues.

Background therapy

No lifestyle modifications were enforced. By contrast, participation in a structured exercise training program was even defined as an exclusion criterion (see above).

The following HF medications were permitted according to the inclusion criteria: renin-angiotensin system (and neprilysin) inhibitors, diuretics, beta blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors.

Other therapies permitted during the study were e.g. anti-emetic or antidiarrhoeal medications to control gastrointestinal adverse events, anti-hypertensive drugs, lipid-lowering and anti-hyperglycemic agents. As defined in the exclusion criteria (see above), medications associated with weight gain or weight loss were only allowed, when on stable dose for ≥3 months prior to Visit 1, and when expected to be stable during the study period.

Objectives and Outcomes/endpoints

The objectives/endpoints of the SUMMIT study are listed in **Table 5**.

Table 5. Objectives and endpoints of the SUMMIT phase 3 study

Objectives	Endpoints
Primary	
▪ To demonstrate that a maximally tolerated tirzepatide dose up to 15 mg administered SC QW is superior to placebo to improve patient-reported symptoms and physical limitations in participants with HFpEF and obesity ▪ To demonstrate that a maximally tolerated tirzepatide dose up to 15 mg administered SC QW is superior to placebo based on the composite HF outcome endpoint in participants with HFpEF and obesity	• Change from baseline to Week 52 in the KCCQ-CSS • Occurrence of the composite endpoint of CV death and/or HF events over time
Key Secondary (multiplicity controlled)	
Exercise capacity	Change from baseline to Week 52 in 6MWD
Long-term weight loss	Percent change from baseline to Week 52 in body weight
Evaluation of change in inflammation	Change from baseline to Week 52 in hsCRP
Other secondary	
Hierarchical composite assessed by win ratio	A hierarchical composite of the following: 1. Time to all-cause mortality through the end of the study 2. Occurrence of HF events through the end of the study • number of HF events • time to first HF events 3. Change from baseline in KCCQ-CSS category at Week 52 4. Change from baseline in the 6MWD category at Week 52 Categories for change from baseline in the KCCQ-CSS: 1. ≥10-point worsening 2. ≥5- but <10-point worsening 3. No change (<5-point change) 4. ≥5- but <10-point improvement 5. ≥10- but <15-point improvement, and 6. ≥15-point improvement. Categories for change from baseline in the 6MWD: 1. ≥30% worsening 2. ≥20% and <30% worsening 3. ≥10% and <20% worsening 4. No change (<10% change) 5. ≥10% and <20% improvement 6. ≥20% and <30% improvement, and 7. ≥30% improvement.

Objectives	Endpoints
Clinical outcome events of HF	• Time to all-cause death • Time to first occurrence of HF events or all-cause death • Time to recurrent events of HF events and all-cause death • Time to first occurrence of HF events • Time to recurrent events of HF events
NYHA class	Proportion of participants with NYHA class change at Week 52
Exercise capacity	Change from baseline to Week 24 in 6MWD
Patient-reported symptoms and physical limitations	• Change from baseline to Week 24 in KCCQ-CSS Limitations • Proportion of participants attaining KCCQ-CSS meaningful within-patient change (MWPC) threshold at Week 52
Exploratory	
Waist circumference	Change from baseline (centimetres)
Patient-reported health-related quality of life	Change from baseline in KCCQ: • Total Symptom Score (TSS) • Overall Summary Score (OSS)
Patient-reported health status	Change from baseline in EQ-5D-5L: • Index score • VAS score
Patient-reported global health status	Proportion of participants with improvements in global health status from baseline as assessed by the POIS-Overall
Patient-reported global impression of physical function	Proportion of participants with improvements in physical function from baseline as assessed by the POIS-Physical Function
Patient-reported global symptom severity	Proportion of participants with improvements in symptom severity from baseline as assessed by the POIS-Symptom Severity
Evaluation of prespecified biomarkers	• NT-proBNP • Cardiac Troponin T
Waist to height ratio	Change from baseline to Week 52 in waist-to-height ratio
Kidney function	eGFR slope

Abbreviations: 6MWD = 6-minute walk distance; CV = cardiovascular; eOFR = estimated glomerular filtration rate; EQ-5D-5L = 5-level version ofEQ-5D; hsCRP = high-sensitivity C-reactive protein; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; NT-proBNP = N-terminal prob-type natriuretic peptide; NYHA = New York Heart Association; POIS = Patient Global Impression of Status; QW = once weekly; SC = subcutaneous; VAS = visual analog scale.

Patient-reported outcomes (only those used in primary and secondary endpoints)

KCCQ-CSS

The KCCQ is a 23-item, participant self-administered questionnaire that assesses impacts of HF "over the past 2 weeks" in 7 domains: physical limitation, symptom stability, symptom frequency, symptom burden, self-efficacy, quality of life, and social limitation. Domain scores are obtained by averaging the associated individual items and transforming the score to a 0 to 100 range. Higher scores indicate better health status. The mean of the Total Symptom Score (Symptom Frequency, Symptom Burden) and Physical Limitation Score are combined to obtain the KCCQ-CSS.

Sample size

Approximately 700 participants were planned to be randomized to either tirzepatide or placebo in a 1:1 ratio (i.e., approximately 350 participants per treatment arm).

According to the study protocol, the statistical powers were evaluated for each of the 2 primary efficacy endpoints at a 2-sided significance level of 0.01 to ensure that the sample size and power are sufficient for registration purposes.

This sample size will provide

- ~85% power or higher to demonstrate superiority of tirzepatide MTD to placebo for the hierarchical composite endpoint using Finkelstein-Schoenfeld method (Finkelstein and Schoenfeld 1999)
- ~95% power for the change from baseline in 6MWD using Wilcoxon rank sum test, and
- >95% power to demonstrate superiority for at least one of above.

According to the study protocol, the sample size and power were estimated through simulations under the assumptions shown in **Table 6**.

Table 6. Assumptions underlying sample size and power estimation

Variable	Placebo	Tirzepatide MTD	Treatment Difference
All-cause mortality (n per 100 yr)	5	5 or 4.75	0 or -0.25 (0 or 5% RRR)
First HF events (n per 100 yr)	10	8 or 7	-2 or -3 (20% or 30% RRR)
6MWD – change from baseline (mean±SD)	0±75	30±85	30
KCCQ-CSS – change from baseline (mean±SD)	5±19	10±19	5

Randomisation

The study compared treatment with tirzepatide and with placebo. Assignment to tirzepatide or placebo groups was randomly allocated in a 1:1 ratio. Randomization was stratified according to

- **HF decompensation** (hospitalisation for HF requiring IV diuretic treatment or urgent HF visit requiring IV diuretic treatment) within 12 months of screening (Y/N)
- **baseline diagnoses T2D** (Y/N), and
- **BMI** ≥35 kg/m^2 (Y/N).

Blinding (masking)

Blinding

This study was double blind. The study was set up with a double-blind design. Sponsor, investigators, site staff, clinical monitors, and participants were blinded throughout the study. It is noted that there was an instance of accidental unblinding for the sponsor in the study that occurred after the last patient visit; however, there was no known impact as a result of this unblinding.

The identity of tirzepatide and placebo was masked because both the study drugs were provided in SDP with the same appearance.

Independent adjudication

The independent adjudication committees performed adjudication of

- HF events and death (CV, non-CV, and undetermined)
- major adverse cardiovascular events, and
- suspected pancreatitis.

All independent adjudication committees were blinded to the study drug assignment.

Statistical methods

Populations for Analyses

Randomized / intent-to-treat (ITT) population: All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.

Safety population: All participants in the ITT population who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment group to which they were assigned.

Efficacy Analyses

The primary estimand for primary endpoints and key secondary endpoints is to assess the treatment difference between tirzepatide and placebo relative to the efficacy measures for all randomized participants. The treatment policy strategy will be used to handle intercurrent events (ICEs), meaning all the observed values for the variable of interest are used regardless of whether or not the ICE occurs.

An on-treatment period efficacy analysis is conducted for selected endpoints without confounding the treatment effect from the data collected after treatment discontinuation. The analysis utilizes a hypothetical strategy to represent efficacy if all the patients remained on randomized treatment for the entire planned treatment duration.

Analyses of Dual Primary Endpoints

Change from baseline in KCCQ-CSS at Week 52

Main Analytical Approach:

A stratified Wilcoxon test (van Elteren 1960) will be used as the main analysis method, controlling for the stratification factors of HF decompensation within 12 months of screening (Y/N), diagnosed T2DM (Y/N), and baseline BMI (<35, ≥35 kg/m^2). The Hodges-Lehmann estimate for the median difference and 2-sided 99% and 95% CIs will be reported.

The missing measurement for KCCQ-CSS at 52 weeks for the primary estimand will be imputed through multiple imputation based on the reason for missingness.

- For missing measurements due to death, multiple imputation will be performed using the worst 15% observed data at 52 weeks from the same treatment group.
- For missing data due to all other ICEs or without ICE, retrieved dropout imputation will be applied, which will utilize observed data from participants in the same treatment group who had outcome measures at Week 52 after early discontinuation of study drug to impute the missing value. In case there are not enough retrieved dropouts to provide a reliable imputation model, reference to the placebo imputation will be used.

The complete datasets generated through multiple imputation will be analyzed and a Van Elteren test will be conducted for treatment comparison. The final statistical inference over multiple imputation will be guided by the method proposed by Rubin (1987).

Sensitivity Analyses:

A mixed-effects model repeated measures (MMRM) analysis will be conducted to analyse the change from baseline in KCCQ-CSS. The analysis will be guided by the treatment policy strategy. All values of the collected KCCQ-CSS data at baseline, 24 weeks, and 52 weeks will be used in the MMRM analysis. The primary endpoint assessment will be the contrast between tirzepatide and placebo at Week 52. The MMRM analysis will be repeated using data during the on-treatment period, which is considered as up to the last dose date plus 7 days.

The MMRM model will IIe treatment, time (Weeks 24 and 52), treatment-by-time interaction, stratification factors as fixed effects, and baseline value of the KCCQ-CSS as a covariate. Restricted maximum likelihood (REML) will be used to obtain model parameter estimates and the Kenward-Roger option will be used to estimate the denominator degrees of freedom. An unstructured covariance structure will be used to model the within-patient errors. If the analysis fails to converge, the following variance-covariance matrices will be used until convergence is achieved: heterogeneous Toeplitz, heterogeneous first order autoregressive, heterogeneous compound symmetry, Toeplitz, first order autoregressive, and compound symmetry.

The change from baseline in KCCQ-CSS will also be analyzed using an ANCOVA model. The ANCOVA model will include the categorical effect of treatment, stratification factors, and the continuous covariate of baseline KCCQ-CSS value. Missing KCCQ-CSS measurements at Week 52 will be imputed through multiple imputations as specified for the primary analysis.

Time to first occurrence of Cardiovascular Death or Heart Failure Event

The primary analysis will be a Cox proportional hazards model with treatment as a fixed effect adjusting for diagnosed T2DM (Y/N), baseline probability of HFpEF (<0.8, ≥0.8), and baseline N-terminal pro b-type natriuretic peptide (NTproBNP) (<200, ≥200 ng/L). The probability of HFpEF is derived from the HFpEF-ABA model (Reddy et al 2024). Participants who did not have an adjudicated primary endpoint event on or prior to the end of follow-up will be censored at the date of participant's end of follow-up. The missing data due to censoring will be implicitly handled by the Cox regression model, assuming censoring is independent of the outcome. The hazard ratio, with its CI and p-value, will be provided through the primary analysis model.

The analysis will be repeated using the investigator's reported events.

Analyses of Key Secondary Endpoints (multiplicity controlled)

Main Analytical Approach:

For the change from baseline in 6MWD at Week 52, the same nonparametric approach and the same missing data imputation as described for the primary endpoint KCCQ-CSS will be utilized.

The percent change from baseline in body weight at Week 52 will be analyzed using an analysis of covariance (ANCOVA). The ANCOVA model will include the categorical effect of treatment, stratification factors excluding baseline BMI group (<35, ≥35 kg/m^2), and the continuous covariate of baseline body weight value. Missing body weight data at the scheduled postbaseline visits will be imputed using the retrieved dropout approach through multiple imputation.

The change from baseline in hsCRP at Week 52 will be analyzed using an ANCOVA model. The ANCOVA model will include the categorical effect of treatment, stratification factors, and the continuous covariate of baseline hsCRP value. The ANCOVA model will be based on the log-transformed values of hsCRP. Missing hsCRP at the scheduled postbaseline visits will be imputed using the retrieved dropout approach through multiple imputation.

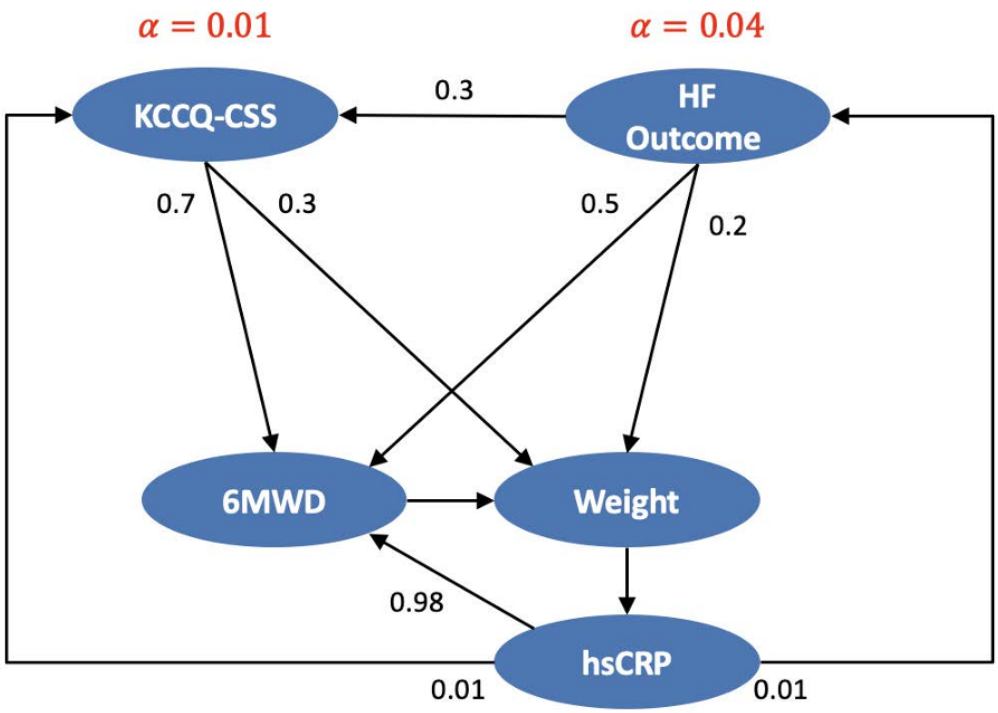
Sensitivity Analyses:

For the change from baseline in 6MWD, percent change from baseline in body weight and the change from baseline in hsCRP, a similar MMRM analysis as described for the change from baseline in KCCQ-CSS will be conducted using data during the on-treatment period.

The change from baseline in 6MWD will also be analyzed using an ANCOVA model. The ANCOVA model will include the categorical effect of treatment, stratification factors, and the continuous covariate of the baseline 6MWD value. Missing 6MWD measurements at Week 52 will be imputed through multiple imputation as specified for the primary endpoint KCCQ-CSS.

Type I Error Rate Control Strategy for Primary and Key Secondary Efficacy Analyses

All primary and key secondary hypotheses will be tested with the overall family-wise type I error rate at a 2-sided alpha level of 0.05 through the multiplicity control approach based on the graphical multiple testing procedure. For the primary hypotheses, the HF outcome will be tested at a 2-sided alpha level of 0.04 and change in KCCQ-CSS will be tested at a 2-sided alpha level of 0.01 in parallel for statistical significance. If significant, the respective alpha of the primary endpoints will be propagated to test the key secondary endpoints. If any of the primary endpoints is not significant, then the appropriate alpha after the key secondary endpoints testing will be recycled to that primary endpoint.



Abbreviations: 6MWD = 6-minute walk distance; HF = heart failure ; hsCRP = high-sensitivity C-reactive protein; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score.

Results

Participant flow

Figure 5 presents participant disposition for the study from screening to the end of study. Overall, 731 participants underwent randomization and received at least 1 dose of tirzepatide (364 participants) or placebo (367 participants).

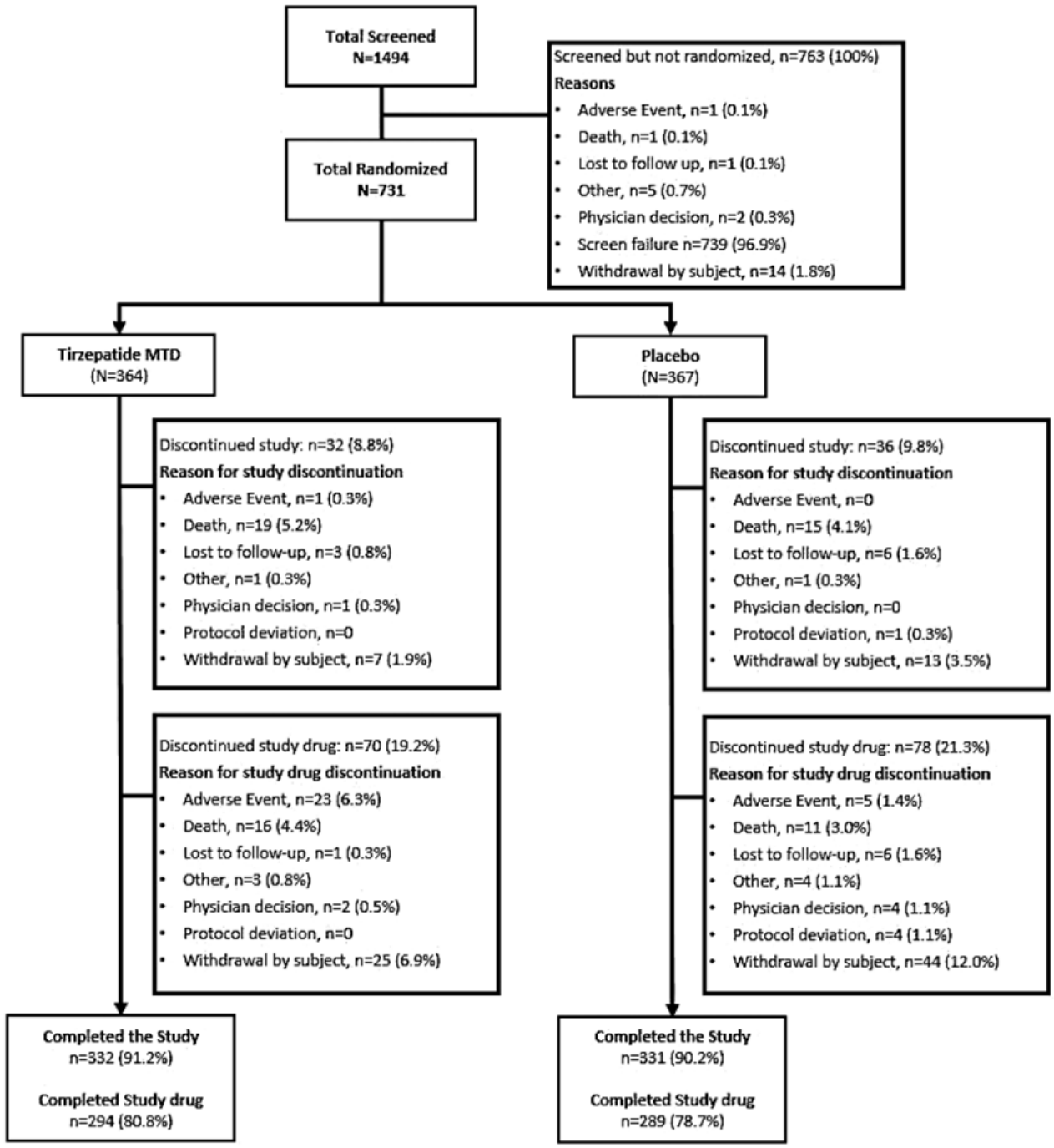
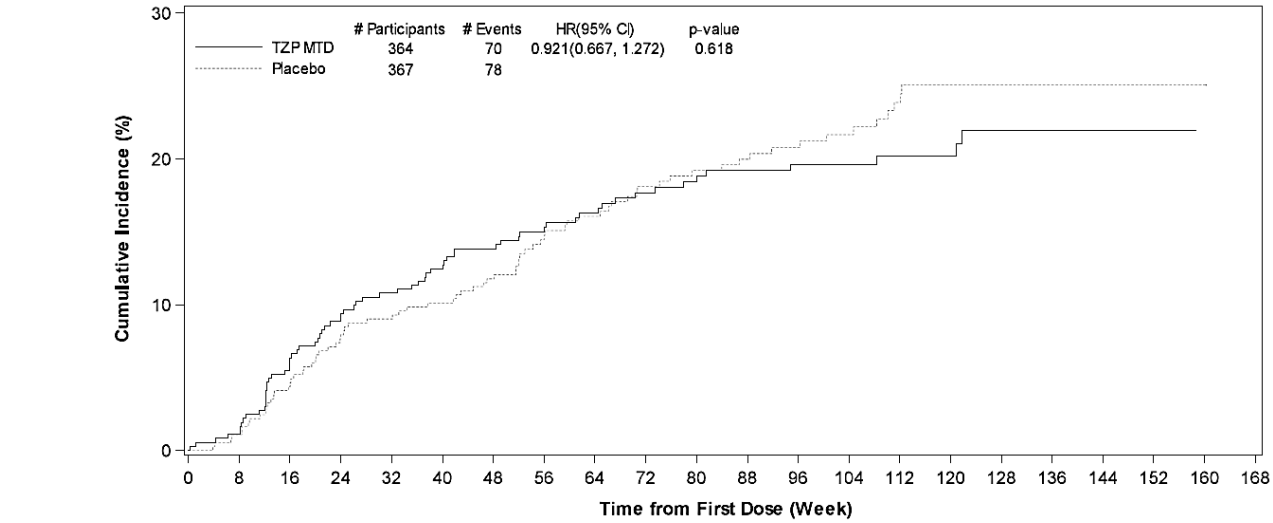


Figure 5. Participant flow in the SUMMIT study

Reason for premature discontinuation from study and study drug

For those participants who discontinued the study drug or study participation early, **Figure 5** summarizes the reasons for study and study treatment discontinuation for each treatment group. The most common reason for study discontinuation was death (5.2% in TZP MTD arm *vs.* 4.1% in placebo arm. The most common reason for study drug discontinuation was withdrawal by subject (6.9% in TZP MTD arm *vs.* 12.0% in placebo arm).

The Kaplan-Meier representation (**Figure 6**) illustrates that the probability of treatment discontinuation in the placebo group was higher than that in the tirzepatide group over time.



# Participants at Risk																						
TZP MTD	364	358	341	328	321	315	308	264	252	231	209	200	178	152	133	95	77	42	11	5	0	0
Placebo	367	362	349	337	332	327	319	266	256	234	214	208	183	151	128	81	67	39	11	5	1	0
Cumulative # Participants with Events																						
TZP MTD	0	4	23	34	39	45	50	55	58	62	65	66	67	67	68	68	70	70	70	70	70	70
Placebo	0	4	17	29	33	37	43	53	57	63	66	68	70	72	76	78	78	78	78	78	78	78

Abbreviations: CI = confidence interval; HR = hazard ratio; MTD = maximum tolerated dose; TZP = tirzepatide

Figure 6. Kaplan-Meier plot of time from first dose to premature study discontinuation

Recruitment

This study was conducted at 129 centres that randomly assigned 731 participants in Argentina, Brazil, China, India, Israel, Mexico, the Russian Federation, Taiwan, and the United States.

First participant first visit: 20 April 2021
Last participant last visit: 02 July 2024

The analyses presented in this report are based on database lock dates of 24 July 2024 for primary outcome and 09 August 2024 for PK, immunogenicity, and cardiac MRI.

Conduct of the study

Protocol amendments

The following three amendments were implemented:

(1) Amendment a (approved 15 December 2021)

The purpose of this protocol amendment is to clarify dosing information to allow for more participant retention and clarity on the dosing regimen, add additional unscheduled visits, and make inclusion/exclusion criteria updates.

In addition to numerous clarifications, there was also the following change in endpoints:

- Added Other Secondary title & moved Incidence HF events and CV Death from Exploratory
- Added timing to first occurrence and recurrent events for HF events and CV death
- The Endpoint wording for the exploratory Objective Atrial fibrillation is updated

(2) Amendment b (approved 21 January 2022)

The purpose of this protocol amendment is to incorporate feedback received from the FDA on exclusion criterion and concomitant therapy (mainly clarification of inclusion criterion #7, of exclusion criterion #13 and of concomitant therapy).

(3) Amendment c (approved 14 February 2024): **Substantial amendment**

The amendment is considered to substantial because of the change in design and methodology, and revision to the primary endpoints, which impacts the scientific value of the study.

Overall Rationale for the Amendment:

The purpose of this protocol amendment is to revise the dual primary endpoints. Given the significant weight loss, and associated cardiometabolic improvements, achieved with tirzepatide, assessment of CV death and HF events, in addition to KCCQ score as a primary endpoint, offers the unique opportunity to evaluate tirzepatide for the benefit of patients with HFpEF and obesity. The dual primary endpoints described in GPID Protocol Amendment (b) may not be able to capture the full potential benefit offered by tirzepatide in this patient population.

In the following, the difference between previous protocol version (left; hierarchical composite) and new dual primary endpoint defined in amendment c (right) is shown:

Previous version (hierarchical composite):	Amendment c (dual):
A hierarchical composite of the following: 1. Time to all-cause mortality through the end of the treatment period 2. Occurrence of heart failure (HF) events through end of the treatment period, where HF events include HF hospitalization OR urgent HF visit (adjudicated) o number of HF events o time to first HF event 3. Change from baseline in the 6-minute walk test distance (6MWD) category at Week 52 4. Change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) category at Week 52	Change from baseline to Week 52 in the KCCQ-CSS Occurrence of the composite endpoint of CV death and/or HF events over time

Additionally, this amendment broadens the heart failure endpoint definition based on growing evidence that supports outpatient intensification of oral diuretics indicating worsening of HF.
This change results in a new definition of HF event, defined as worsening symptoms or signs of HF, which are treated either as an inpatient (by hospitalisation, treated by oral or IV diuretic intensification) or as an outpatient (by IV or oral diuretic intensification).

Further addenda:

Milestone	Approval date	Rationale for Amendments / Addenda
Protocol GPID (1)	26 Jan 2021	The purpose of this addendum to the main protocol of Study GPID was to perform cardiac MRI in a subset of participants enrolled. This addendum applies to participants enrolled at selected sites that have the technical capability to conduct cardiac MRI.
Protocol GPID (2)	04 Feb 2021	This addendum to the main protocol of Study GPID described the changes to be followed specifically at all investigative sites in the People's Republic of China (PRC). It was to be applied in addition to all procedures required by Protocol GPID or any subsequent amendments to that protocol.

Protocol GPID (3)	26 Jan 2021	The purpose of this addendum was to provide trial-related mitigations that could be put into place based on exceptional circumstances.
Protocol GPID (4) Addenda	05 Feb 2021	The purpose of this addendum was to ensure investigator sites' compliance with the regulatory requirements of Brazil.
Protocol GPID (5)	05 Feb 2021	The purpose of this addendum was to comply with local laws and regulatory requirements in Taiwan.
Protocol GPID (1.1)	17 Dec 2021	The purpose of the revision to the addendum was to provide more flexibility in the consenting process for Addendum 1 participants, modify the Exclusion Criterion (46), and provide guidance for conducting study procedures after a delay in coordinating the MRI scan occurs.
Protocol GPID (2.1)	08 Mar 2023	The purpose of this revision to Addenda (2) was to amend schedule of activities to meet China local authority requirement.
Protocol GPID (3.1)	25 Jan 2022	The purpose of this revision to Addenda (3) was to remove reference to screening period guidance listed under Provisions for Changes in Study Conduct During Exceptional Circumstances.
Protocol GPID (6)	17 Nov 2022	The purpose of this addendum to the main protocol of Study I8F-MC-GPID (GPID or SUMMIT) is to comply with local laws and regulatory requirements in India.
Last participant last visit	02 July 2024	N/A
Abbreviations: 6MWD = 6-minute walk distance; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; MRI = magnetic resonance imaging; N/A = not applicable.		

Protocol deviations

Important protocol deviations

Important protocol deviations were defined as any deviation from the protocol that could potentially impact the study assessment, participant rights, and study integrity. A summary is provided in **Table 4**. A total of 271 participants (37.1 %) had at least 1 important protocol deviation. Overall, the percentages of important protocol deviations were similar across the treatment groups (36.5% in placebo and 37.6% in tirzepatide group).

The most common important protocol deviations were related to

- study procedure compliance (15.0%)
- investigational medicinal product and/or investigational device (11.1 %), and
- informed consent (9.8%)

A total of 34 (4.7%) participants had an important protocol deviation related to eligibility.

When the sponsor or investigator identified a participant who did not meet enrolment criteria and was inadvertently enrolled, the participant remained in the study and safety follow-up was performed as outlined in the protocol. Study drug was continued if the investigator and the sponsor agreed that it was medically appropriate after the approval of Sponsor's Chief Medical Officer. These participants were included in the analyses. At Visit 15, a participant from placebo treatment group, mistakenly received a single dose of tirzepatide 10 mg due to an incorrect IMP dispensing by the site personnel.

Table 7. Summary of Important Protocol Deviations Randomized Population Study I8F-MC-GPID

Protocol Deviation Category Study Specific Deviation Term	**TZP MTD (N=364) n (%)**	**Placebo (N=367) n (%)**	**Total (N=731) n (%)**
Subjects with >=1 Important Protocol Deviation	133 (36.5)	138 (37.6)	271 (37.1)
Protocol Deviation	133 (36.5)	138 (37.6)	271 (37.1)
Study Procedure Compliance	53 (14.6)	57 (15.5)	110 (15.0)
Investigational Medicinal Product and/or Investigational Device	40 (11.0)	41 (11.2)	81 (11.1)
Informed Consent	35 (9.6)	37 (10.1)	72 (9.8)
Treatment Assignment/Randomization	24 (6.6)	25 (6.8)	49 (6.7)
Eligibility Criteria	13 (3.6)	21 (5.7)	34 (4.7)
Safety Reporting	7 (1.9)	2 (0.5)	9 (1.2)
Concomitant Medication	1 (0.3)	2 (0.5)	3 (0.4)

Discontinuation Criteria	0	1 (0.3)	1 (0.1)
Persistent GCP Non-compliance	0	1 (0.3)	1 (0.1)
Visit Schedule Criteria	0	1 (0.3)	1 (0.1)
Abbreviations: N = number of subjects in the analysis population; n = number of subjects in the specified category; TZP MTD = tirzepatide maximum tolerated dose; Percentages are based on the treatment column denominator, N.			

Due to the COVID-19 pandemic, wearing masks was mandatory in some regions. Thus, the protocol instructed investigators to conduct the 6MWT while wearing a mask for all 6MWTs if the participant wore a mask during baseline and/or Visit 2. This regulation was violated by ≤1.2% of participants.

Additionally, due to the COVID-19 pandemic, an extenuating circumstance addendum was created to permit additional visit windows and/or changes in the type of visit (remote).

Baseline data

Demographics and baseline disease characteristics

Table 8 summarizes baseline demographics and clinical characteristics. It is noted that no European subjects were included in the study.

Table 8. Summary of selected baseline demographic characteristics; all randomized population

Attribute	TZP MTD (N=364)	Placebo (N=367)	Total (N=731)
Age (years), mean ± SD	65.5±10.5	65.0±10.9	65.2±10.7
Age Category, n (%)			
<65	158 (43.4)	166 (45.2)	324 (44.3)
65-74	130 (35.7)	124 (33.8)	254 (34.7)
75-84	72 (19.8)	71 (19.3)	143 (19.6)
≥85	4 (1.1)	6 (1.6)	10 (1.4)
Sex, n (%)			
Female	200 (54.9)	193 (52.6)	393 (53.8)
Male	164 (45.1)	174 (47.4)	338 (46.2)
Country, Region n (%)			
Argentina	101 (27.7)	103 (28.1)	204 (27.9)
Brazil	51 (14.0)	54 (14.7)	105 (14.4)
China	25 (6.9)	30 (8.2)	55 (7.5)
India	9 (2.5)	11 (3.0)	20 (2.7)
Israel	17 (4.7)	21 (5.7)	38 (5.2)
Mexico	41 (11.3)	40 (10.9)	81 (11.1)
Russian Federation	13 (3.6)	8 (2.2)	21 (2.9)
Taiwan	24 (6.6)	32 (8.7)	56 (7.7)
United States	83 (22.8)	68 (18.5)	151 (20.7)
Region, n (%)			
US	83 (22.8)	68 (18.5)	151 (20.7)
Central/South America	193 (53.0)	197 (53.7)	390 (53.4)
Asia	58 (15.9)	73 (19.9)	131 (17.9)
Other	30 (8.2)	29 (7.9)	59 (8.1)
Race, n (%)			
American Indian or Alaska Native	24 (6.6)	23 (6.3)	47 (6.4)
Asian	58 (15.9)	73 (19.9)	131 (17.9)
Black or African American	22 (6.0)	14 (3.8)	36 (4.9)
Multiple	2 (0.5)	0	2 (0.3)
Native Hawaiian or Other Pacific Islander	2 (0.5)	1 (0.3)	3 (0.4)
White	256 (70.3)	256 (69.8)	512 (70.0)
Ethnicity, n (%)			
Hispanic or Latino	195 (53.6)	205 (55.9)	400 (54.7)
Not Hispanic or Latino	164 (45.1)	159 (43.3)	323 (44.2)
Not reported	5 (1.4)	3 (0.8)	8 (1.1)
Abbreviations: N = number of participants in the analysis population; n = number of participants in the specified category; SD = standard deviation; TZP = tirzepatide.			

Baseline disease-related characteristics

As shown in **Table 9**, the mean body weight and BMI were 103.0 kg and 38.2 kg/m^2, respectively, and about 33% of participants had a BMI of ≥40 kg/m^2. Almost half (48.2%) of the participants randomized had T2D. The NYHA class was II in 72.5% and III in 27 .4% and IV in 0.1 % participants. Overall, 186 (25.4%) participants had atrial fibrillation at baseline. The median baseline eGFR was 62 mL/min/1.73 m^2 and 343 (46.9%) of participants had a history of HF decompensation requiring IV diuretic treatment within a year prior to Visit 1. The baseline median NT-ProBNP was 175 ng/L.

Table 9. Summary of Selected Baseline Clinical Characteristics; All Randomized Population

Attribute	TZP MTD (N=364)	Placebo (N=367)	Total (N=731)
Weight (kg), mean ± SD	102.9±21.7	103.1±22.7	103.0±22.2
Waist circumference (cm), mean ± SD	119.7±15.5	119.7±14.4	119.7±14.9
Waist to height ration (cm), mean ± SD	0.7±0.1	0.7±0.1	0.7±0.1
BMI (kg/m^2), mean ± SD	38.3±6.4	38.2±7.0	38.2±6.7
BMI category, n (%)			
<35	147 (40.4)	148 (40.3)	295 (40.4)
≥35 to <40	92 (25.3)	105 (28.6)	197 (26.9)
≥40	125 (34.3)	114 (31.1)	239 (32.7)
6MWD (meters), median (Q1, Q3)	315.0 (245.0, 371.5)	315.0 (234.0, 370.0)	315.0 (240.0, 371.0)
HF decompensation within 12 months of V1, n(%)			
No	193 (53.0)	195 (53.1)	388 (53.1)
Yes	171 (47.0)	172(46.9)	343 (46.9)
Hypertension, n(%)	320 (87.9)	315 (85.8)	635 (86.9)
Atrial fibrillation[a], n(%)			
No	269 (73.9)	276 (75.2)	545 (74.6)
Yes	95 (26.1)	91 (24.8)	186 (25.4)
Type 2 Diabetes, n(%)			
No	190 (52.2)	189 (51.5)	379 (51.8)
Yes	174 (47.8)	178(48.5)	352 (48.2)
Coronary artery disease			
No	248 (69.1)	258 (70.9)	506 (70.0)
Yes	111 (30.9)	106 (29.1)	217 (30.0)
LVEF (%), mean ± SD	61.0 ± 6.5	60.7 ± 6.2	60.8 ± 6.3
NYHA class, n (%)			
NYHA class II	262 (72.0)	268 (73.0)	530 (72.5)
NYHA class III	102 (28.0)	98 (26.7)	200 (27.4)
NYHA class IV	0	1 (0.3)	1 (0.1)
NT-proBNP (ng/L), median (Q1, Q3)	196.0 (55.9, 488.0)	169.0 (64.0, 476.0)	175.0 (60.0, 485.0)
Cardiac Troponin T (mcg/L), mean ± SD	0.015 (0.015)	0.015 (0.013)	0.015 (0.014)
KCCQ-CSS score (points), median (Q1, Q3)	55.7 (40.9, 66.9)	52.1 (39.6, 67.7)	54.4 (40.1, 67.7)
hsCRP (mg/L), mean (SD)	5.8 (8.6)	5.8 (8.4)	5.8 (8.4)
eGFR (ml/min/1.73 m^2), median (Q1, Q3)	62.0 (46.0, 84.0)	62.0 (47.0, 83.0)	62.0 (47.0, 83.0)
eGFR Category, n (%)			
<60	167 (45.9)	168 (45.8)	335 (45.8)
≥60	197 (54.1)	199 (54.2)	396 (54.2)
Probability of HFpEF, mean[b] (SD)	0.821 (0.160)	0.807 (0.168)	0.814 (0.164)
Systolic BP (mmHg), mean ± SD	127.9 ± 13.2	128.2 ± 13.7	128.0 ± 13.4
Diastolic BP (mmHg), mean ±SD	75.7 ± 9.7	77.0 ± 10.0	76.3 ± 9.8
Heart Rate (beats/min), mean ±SD	71.0 ± 11.2	71.2 ± 10.7	71.1 ± 10.9
Use of concomitant medications			
RAS inhibitors[c]	293 (80.5)	295 (80.4)	588 (80.4)
Diuretics	267 (73.4)	271 (73.8)	538 (73.6)
Beta blockers	245 (67.3)	263 (71.7)	508 (69.5)
MRAs	131 (36.0)	125 (34.1)	256 (35.0)
SGLT2 inhibitors	69 (19.0)	57 (15.5)	126 (17.2)

Abbreviations: 6MWD = 6-minute walk distance; ACE = angiotensin converting enzyme; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; hsCRP = high-sensitivity C-reactive protein; IQR = interquartile range; KCCQ-CSS = ; L VEF = left ventricular ejection fraction; MRA = Mineralocorticoid Receptor

Attribute	TZP MTD (N=364)	Placebo (N=367)	Total (N=731)
Antagonists; n = number of participants in the specified category; N = number of participants in the analysis population; NT-proBNP = N-terminal prob-type natriuretic peptide; NYHA = New York Heart Association; Q = quarter; RAS = renin-angiotensin system; SD = standard deviation; SGL T2 = Sodium-glucose Co-transporter 2; V = visit.			
[a] Atrial fibrillation was diagnosed using ECG at baseline. [b] Probability ofHFpEF was derived from the HFpEF-ABA model (Reddy et al. 2024).			

Concomitant medications at baseline

Heart failure (HA) medications

711 (97.3%) participants were treated with ≥1 HF concomitant medication at baseline. The use of HF medications at baseline was balanced between the two treatment groups. The most commonly used HF medications at baseline were RAS inhibitors (80.4%; incl. ACE inhibitors, angiotensin II receptor blockers, and angiotensin receptor-neprilysin inhibitor), followed by diuretics (73.6%), beta blockers (69.5%), mineralocorticoid receptor antagonists (MRA; 35.0%), and SGLT2 inhibitors (17.2%) – see **Table 10**.

Table 10. Concomitant medications at baseline in the SUMMIT study

Attribute	TZP MTD (N=364)	Placebo (N=367)	Total (N=731)
RAS inhibitors	293 (80.5)	295 (80.4)	588 (80.4)
ACE inhibitors	70 (19.2)	63 (17.2)	133 (18.2)
Angiotensin II receptor blockers	225 (61.8)	232 (63.2)	457 (62.5)
Angiotensin receptor-neprilysin inhibitor	10 (2.7)	24 (6.5)	34 (4.7)
Diuretics	267 (73.4)	271 (73.8)	538 (73.6)
Beta blockers	245 (67.3)	263 (71.7)	508 (69.5)
MRAs	131 (36.0)	125 (34.1)	256 (35.0)
SGLT2 inhibitors	69 (19.0)	57 (15.5)	126 (17.2)

Antihypertensive therapy other than HF medications

A total of 285 (39.0%) participants were treated with ≥1 antihypertensive therapy other than HF medications at baseline (balanced between treatment groups). The most common medications were dihydropyridine calcium channel blockers (TZP: 27.7%; placebo: 31.1%; total: 29.4%), followed by diltiazem (TZP: 3.0%; placebo: 4.1%; total: 3.6%).

Antihyperglycaemic Medications

Almost half (48.2%) of the randomly assigned participants had T2D. A total of 375 (51.3%) participants were being treated with ≥1 antihyperglycemic therapy at baseline (balanced between treatment groups). The most common antihyperglycaemic medication was metformin (TZP: 32.7%; placebo: 35.4%; total: 34.1%), followed by SGLT2 inhibitors (TZP: 17.6%; placebo: 13.9%; total: 15.7%) and sulfonylureas (TZP: 7.1%; placebo: 6.8%; total: 7.0%).

Lipid-Lowering Therapy

A total of 517 (70. 7%) participants were being treated with ≥1 lipid-lowering therapy at baseline (balanced between treatment groups). The most common lipid-lowering medications were statins (TZP: 62.1%; placebo: 66.2%; total: 64.2%), followed by ezetimibe (TZP: 6.0%; placebo: 7.9%; total: 7.0%).

Change in concomitant medications used during study (baseline to post-baseline)

Heart failure (HA) medications

Dose reduction: 17.6% in the tirzepatide group *vs.* 11.2% in the placebo arm

Dose increase: 13.7% in the tirzepatide group *vs.* 17.2% in the placebo arm

Antihypertensive therapy other than HF medications (mainly consisting of calcium channel blockers)
Dose reduction: 2.2% in the tirzepatide group *vs.* 1.6% in the placebo arm
Dose increase: 1.1% in the tirzepatide group *vs.* 3.0% in the placebo arm

Antihyperglycaemic Medications
Dose reduction: 5.2% in both tirzepatide and placebo group
Dose increase: 2.5% in the tirzepatide group *vs.* 7.4% in the placebo arm

Lipid-Lowering Therapy
Dose reduction: 0.5% in the tirzepatide group *vs.* 0.8% in the placebo arm
Dose increase: 0.8% in the tirzepatide group *vs.* 3.0% in the placebo arm

Compliance with study drug and achieved final doses

Treatment compliance was defined as taking at least 75% and not >125% of the required doses of the study drug. A total of 662 (90.6%) participants were study drug compliant in the safety population (similar across treatment groups: TZP: 90.7%; placebo: 90.5%).

Per protocol, any participant who missed a dose was required to take it as soon as possible unless it was within 72 hours of the next dose, in which case that dose was skipped and the next dose was taken at the appropriate time. Overall, 24.5% of the participants (TZP: 29.4% *vs.* placebo: 19.6%) missed ≥3 consecutive doses of the study drug. Dose de-escalation was required in 77 (21.2%) participants in the tirzepatide group compared to 21 (5.7%) in the placebo group. Dose interruptions occurred in 31.6% of tirzepatide-treated patients and in 19.9% of participants in the placebo arm.

77.2% of the participants took 15 mg of tirzepatide as the highest dose.

The final doses were distributed among the 364 participants of the TZP MTD arm as follows:

TZP 2.5 mg: 4 (1.1%)
TZP 5.0 mg: 74 (20.3%)
TZP 7.5 mg: 12 (3.3%)
TZP 10.0 mg: 26 (7.1%)
TZP 12.5 mg: 10 (2.7%)
TZP 15.0 mg: 238 (65.4%)

Numbers analysed

Number of Participants (planned and analyzed):
- Number planned: 700
- Number randomly assigned: 731
- Number completed on study intervention: 583
- Number completed study: 663
- Number of deaths: 34

Outcomes and estimation

Dual primary endpoints

The **dual primary endpoints** were
(1) Occurrence of the composite endpoint of CV death and/or HF events over time
(2) Change from baseline to Week 52 in the KCCQ-CSS

Treatment with tirzepatide achieved superiority compared with placebo for reduction in the risk of HF

outcomes assessed as composite endpoint of CV/undetermined death and HF events (HR: 0.62, 95% CI: 0.41 to 0.95, p-value: 0.026) and improvement in KCCQ-CSS at week 52 (estimated median difference: 6.9 points; 95% CI: 3.3 to 10.6, p-value: <0.001). Both endpoints met the pre-specified p-value thresholds.

In the following, the results are presented in detail for both dual primary endpoints:

(1) Occurrence of the composite endpoint of CV death and/or HF events over time

Unwitnessed deaths and deaths for which there is no information at all were also considered CV deaths. A HF event was defined as worsening clinical symptoms or signs related to HF, which are meaningful to the participant and require intensification of treatment characterized by 1 or more of the following:

- hospitalisation for heart failure regardless of duration or treatment received
- use of intravenous drug, usually an intravenous diuretic, but may include intravenous vasodilators or positive inotropic drugs, or
- augmentation or increase in oral diuretic therapy.

Regarding the composite endpoint of CV/undetermined death and HF events, tirzepatide was superior to placebo (HR: 0.62, 95% CI: 0.41 to 0.95, p-value: 0.026). The primary composite of CV/undetermined death or HF event occurred in a lower proportion of participants in the tirzepatide group (n = 36, 9.9%) compared with the placebo group (n = 56; 15.3%).

As shown in **Table 11** below, the risk reduction was mainly driven by HF events (% participants with HF events with TZP = 8.0% and with placebo = 14.2%) and by the corresponding subcomponents (hospitalisation for HF; urgent visits for HF; required oral diuretic intensification for HF). By contrast, CV/undetermined death occurred in 10 (2.7%) participants receiving tirzepatide and in 5 (1.4%) participants receiving placebo, showing no significant difference.

Table 11. Summary and analysis of first HF outcomes confirmed by clinical endpoint committee (includes CV/undetermined death and HF events); randomized population

Endpoint **Component** ***Subcomponent***	**Tirzepatide (N = 364) n (%), n/100 Patient Years**	**Placebo (N = 367) n (%), n/100 Patient Years**	**HR (95% CI)[a]**	**p-Value[a]**
HF outcomes	36 (9.9), 5.53	56 (15.3), 8.80	0.62 (0.41, 0.95)	0.026
CV / undetermined death	10 (2.7), 1.45	5 (1.4), 0.73	1.99 (0.68, 5.81)	0.211
HF events	29 (8.0), 4.46	52 (14.2), 8.17	0.54 (0.34, 0.85)	0.008
Hospitalization for HF	12 (3.3), 1.78	26 (7.1), 3.94	0.44 (0.22, 0.87)	0.018
Urgent visit for HF	5 (1.4), 0.73	12 (3.3), 1.79	0.41 (0.14, 1.16)	0.093
Oral diuretics intensification for HF	17 (4.7), 2.55	21 (5.7), 3.15	0.80 (0.42, 1.52)	0.492

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; n = number of participants in the specified category; N = number of participants in the analysis population; NTproBNP = N-terminal prohormone of brain natriuretic peptide; T2D = type 2 diabetes mellitus.
Note 1: Subjects may be counted in more than one category.
Note 2: Heart Failure Outcome is the composite endpoint of cardiovascular death and heart failure events.
[a]derived from a Cox proportional-hazards model with treatment (tirzepatide versus placebo) as a fixed effect, adjusting for T2D status, baseline probability of HFpEF (<0.8, ≥0.8), and baseline NTproBNP (<200, ≥200 ng/L). p-Value is from Wald test.
When the total number of outcomes is <10, survival analysis is not performed.

Figure 7 shows the Kaplan-Meier plot depicting time to first occurrence of adjudicated HF outcomes. The tirzepatide and placebo curves separate around week 24 and continue to diverge throughout the follow up period.

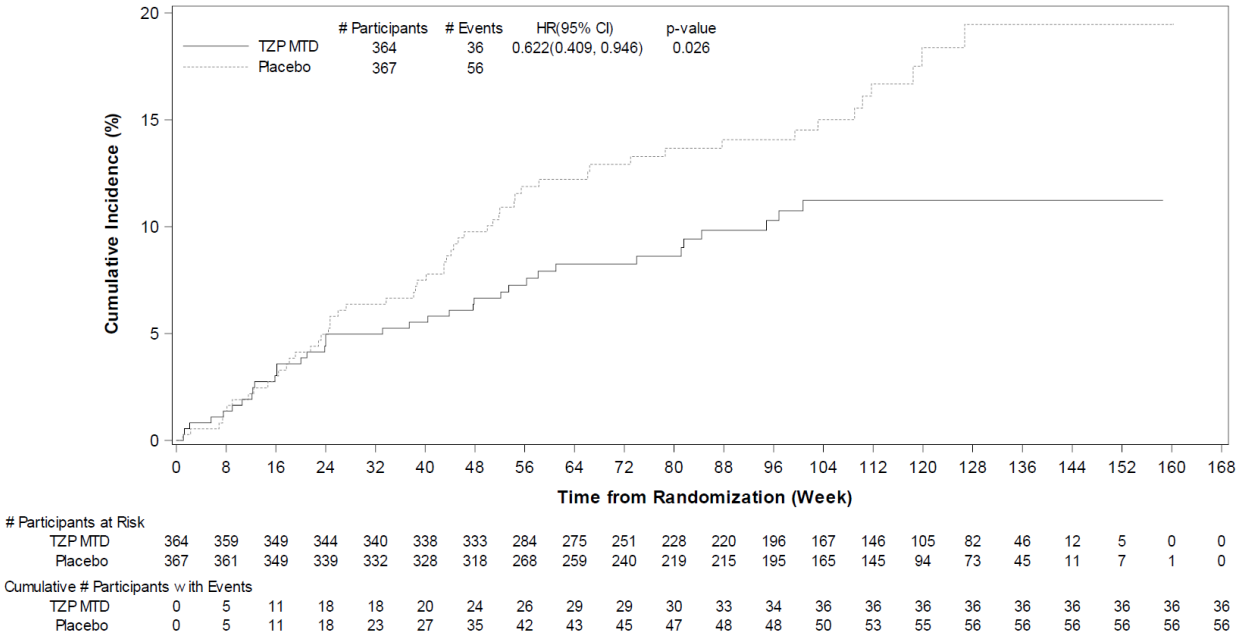


Figure 7. Kaplan-Meier plot for time to first occurrence of adjudication confirmed heart failure outcome; randomized population

The applicant has provided an additional analysis based on **investigator-reported outcomes** (not shown in this AR), which largely confirms the results from the CEC adjudication-confirmed outcomes. There were major differences in the subcomponent "*oral diuretics intensification for HF*" (investigator-reported: HR = 0.39, 95% CI: 0.17, 0.89, p-value: 0.025 *vs.* CEC-adjudicated: HR = 0.80, 95% CI: 0.42, 1.52, p-value: 0.492), which the applicant attributes to revisions in HF event definitions (amendment c to add "oral diuretic intensification" as an HF event).
However, the applicant has re-analysed the first HF outcomes confirmed by CEC after excluding oral intensification of diuretics, and the result (HR = 0.57, 95% CI: 0.34 to 0.95, p-value: 0.030) was consistent with the primary analysis of HF outcomes.

In addition to the above-discussed analysis of first HF outcomes, the applicant has also presented a discussion of **total** (i.e., first and recurrent) CEC-confirmed HF outcomes. The summary is provided in **Table 12**.

Table 12. Summary and analysis of total (first and recurrent) HF events and CV/undetermined death confirmed by clinical endpoint committee, randomized population

Endpoint **Component** ***Subcomponent***	**Tirzepatide (N = 364) n (Total Number of Events), n/100 Patient Years**	**Placebo (N = 367) n (Total Number of Events), n/100 Patient Years**	**Rate ratio (95% CI)[a]**	**p-Value[a]**
Total HF outcomes	36 (53), 8.06	56 (73), 11.32	0.70 (0.43, 1.15)	0.156
CV / undetermined death	10 (10), 1.46	5 (5), 0.73	1.99 (0.67, 5.85)	0.214
HF events	29 (44), 6.70	52 (68), 10.55	0.62 (0.37, 1.05)	0.077
Hospitalization for HF	12 (17), 2.52	26 (36), 5.41	0.45 (0.21, 0.98)	0.043
Urgent visit for HF	5 (7), 1.03	12 (13), 1.94	0.53 (0.16, 1.70)	0.283
Oral diuretics intensification for HF	17 (22), 3.29	21 (21), 3.15	1.02 (0.53, 1.98)	0.954

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; LWYY = Lin–Wei–Yang–Ying; N = number of participants in the analysis population; n = number of participants in the specified category; NTproBNP = N-terminal pro b-type natriuretic peptide; ODI = oral diuretic intensification; T2D = type 2 diabetes mellitus.

Note 1: Total events include first and recurrent events. A 30-day spacing rule is applied when consider recurrent events

[a]Derived from LWYY model with treatment (tirzepatide versus placebo) as a fixed effect, adjusting for T2D Status, baseline probability of HFpEF (<0.8, ≥0.8), and baseline NTproBNP (<200, ≥200 ng/L).

(2) Change from baseline to Week 52 in the KCCQ-CSS

The results summarized in **Table 13** show that tirzepatide was superior to placebo at improving total symptoms and physical limitation as assessed by median difference in term of KCCQ-CSS change from baseline to week 52. The observed median change in KCCQ-CSS at week 52 was 20.8 points in the tirzepatide group compared with 12.0 points in the placebo group (estimated median difference: 6.9 points; 95% CI: 3.3 to 10.6, p<0.001).

Table 13. Summary and analysis of change from baseline to 52 weeks in KCCQ-CSS non-parametric analysis with multiple imputation for missing data at 52 weeks; Randomized population

Change from Baseline (Observed)			TZP MTD vs. Placebo			
Treatment	**Mean (SD)**	**Median (Q1, Q3)**	**Estimated Median Difference*a**	**(95% CI)*a**	**(99% CI)*a**	**p-value*b**
TZP MTD (N=301)	22.4 (21.45)	20.8 (9.3, 35.4)	6.9	(3.3, 10.6)	(2.1, 11.8)	<0.001
Placebo (N=313)	14.4 (19.70)	12.0 (1.6, 27.1)				

Abbreviations: BMI = body mass index; CI = confidence interval; HF = heart failure; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; N = total number of participants in specified treatment arm; Q1 = 1st quartile; Q3 = 3rd quartile; SD = standard deviation; TZP MTD = tirzepatide maximum tolerated dose.

Note 1: TZP MTD is tirzepatide up to 15 mg once weekly.
Note 2: Only participants with non-missing baseline value were included in analysis.
Note 3: Missing post-baseline values were imputed based on the worst 15% observed data in the same treatment arm if data is missing due to death through multiple imputation method; or missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data is not missing at Week 52 if data is missing due to other reasons through retrieved dropout imputation method.
Note 4: Missing data was imputed 100 times.
Note 5: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

*a - Hodges-Lehmann estimate of location shift and corresponding CI.
*b - Van Elteren test stratified by HF decompensation within 12 months of screening, type 2 diabetes status, and baseline BMI group (<35, >=35 kg/m^2).

Cumulative distribution of change in KCCQ-CSS

The empirical cumulative distribution function of change from baseline 52 weeks in KCCQ-CSS (**Figure 8**) shows that the tirzepatide curve is separated from the placebo curve and is shifted towards higher improvement in KCCQ-CSS from baseline to Week 52. The vertical lines in **Figure 8** represent the proportions of participants achieving ≥5, ≥10, ≥15 and ≥20 points (meaningful within-patient change [MWPC] threshold for KCCQ-CSS improvement) improvement in KCCQ-CSS from baseline to Week 52.

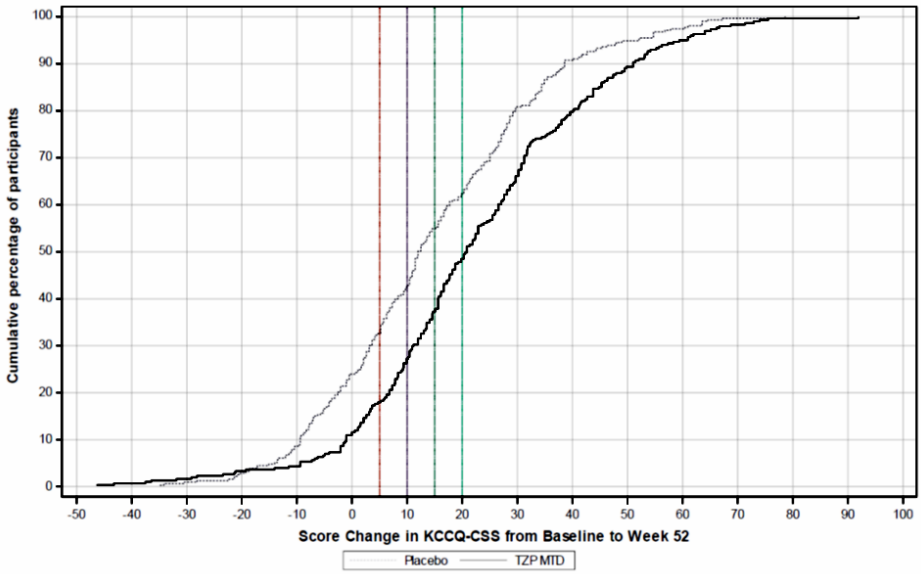


Figure 8: Empirical cumulative distribution of change from baseline to 52 weeks in KCCQ-CSS Randomized population.

The applicant has presented the following additional analyses for change in KCCQ-CSS:

(1) Summary of Change from Baseline in KCCQ-CSS by MMRM
(2) Summary of Change from Baseline in KCCQ-CSS by ANCOVA
(3) Categorical Change in KCCQ-CSS

All additional analyses confirmed the primary analysis and therefore support the robustness of the conclusions based on the KCCQ-CSS score.

The histogram generated in the categorical change analysis reveals higher improvements in KCCQ-CSS from baseline to week 52 for tirzepatide compared with placebo group, especially for improvements ≥10 points. The incidence of worsening KCCQ-CSS from baseline to week 52 was higher in the placebo group than in the tirzepatide group.

Multiplicity-Controlled Secondary Efficacy Endpoints

Change in 6MWD (Meters) from baseline to week 52

Exercise capacity was assessed with the 6MWT, and the distance covered (6MWD) was determined in meters. The observed median change in 6MWD at week 52 was 31.0 meters in the tirzepatide group compared with 5.5 meters in the placebo group (estimated difference: 18.3; 95% CI: 9.9, 26.7, p<0.001). See **Table 14**.

Table 14. Summary and analysis of change from baseline to 52 weeks in 6MWD (meters); nonparametric analysis with multiple imputation for missing data at 52 weeks; randomized population

Change from Baseline (Observed)			TZP MTD (up to 15 mg weekly) vs. Placebo		
Treatment	**Mean (SD)**	**Median (Q1, Q3)**	**Estimated Median Difference*a**	**(95% CI)*a**	**p-value*b**
TZP MTD (N=326)	33.2 (60.40)	31.0 (4.0, 63.0)	18.3	(9.9, 26.7)	<0.001
Placebo (N=314)	9.3 (64.82)	5.5 (-19.0, 35.0)			
Note 1: Only participants with non-missing baseline value were included in analysis.					

Note 2: Missing post-baseline values were imputed based on the worst 15% observed data in the same treatment arm if data is missing due to death through multiple imputation method; or missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data is not missing at Week 52 if data is missing due to other reasons through retrieved dropout imputation method.
Note 3: Missing data was imputed 100 times.
Note 4: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

*a - Hodges-Lehmann estimate of location shift and corresponding CI. *b - Van Elteren test stratified by HF decompensation within 12 months of screening, type 2 diabetes status, and baseline BMI group (<35, >=35 kg/m^2).

Cumulative distribution of change in 6MWD

The empirical cumulative distribution function of change from baseline 52 weeks in 6MWD (**Figure 9**) shows that the tirzepatide curve is separated from the placebo curve and is shifted towards higher improvement in 6MWD from baseline to week 52. The vertical lines in **Figure 9** represent the proportions of participants achieving ≥10, ≥20, ≥25 (MWPC threshold for 6MWD improvement) and ≥30 meters improvement in 6MWD from baseline to week 52.

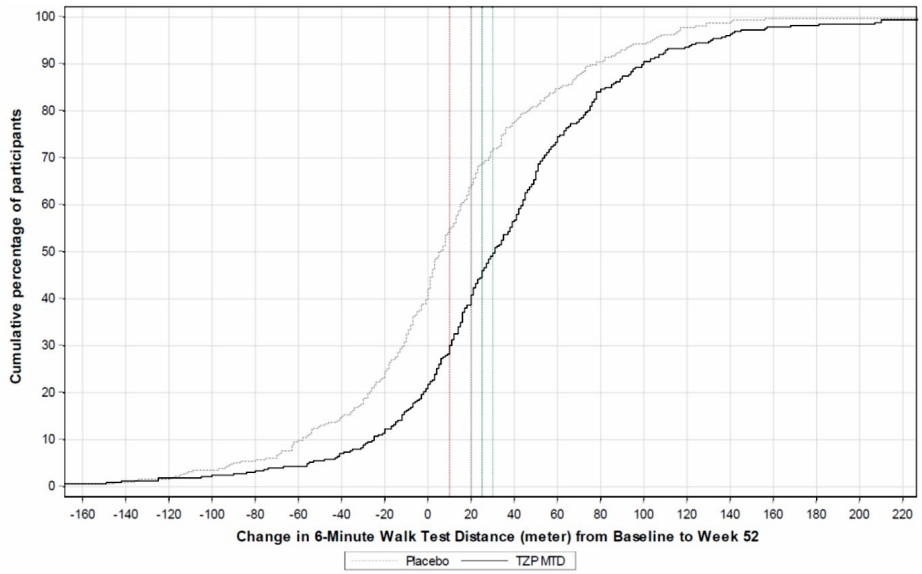


Figure 9. Empirical cumulative distribution function of change from baseline to 52 weeks in 6MWD (meters); randomized population.

Plot of estimated mean for change in 6MWD by treatment and visit

The results of change in 6MWD from baseline to week 52 (on-treatment period) calculated using MMRM are depicted in the plot below (**Figure 10**). The difference between tirzepatide and placebo arm is already significant by week 24.

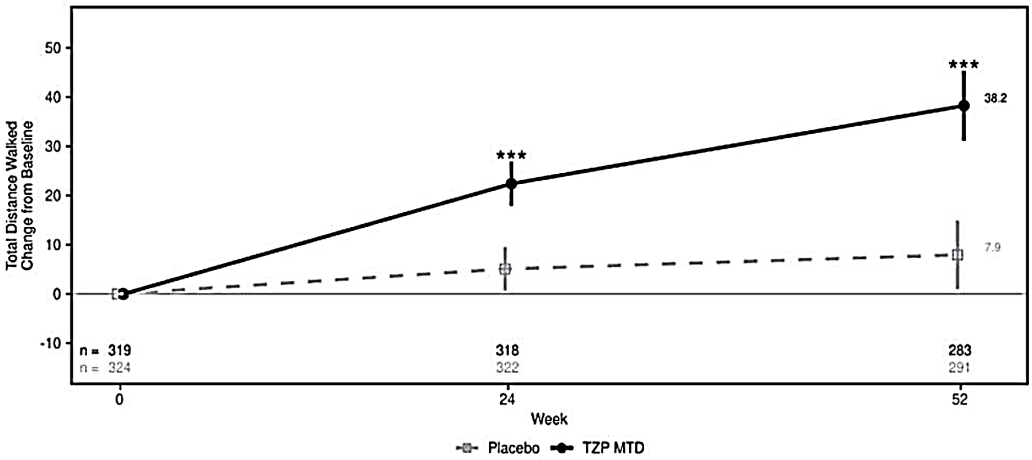


Figure 10. Plot of estimated mean for change from baseline in 6MWD (meters), on-treatment period, MMRM by treatment and visit from baseline to Week 52, randomized population.

The applicant has presented an additional analysis for change from baseline in in 6MWD using the ANCOVA method, which confirmed the primary analysis.

Percent Change in Body Weight from Baseline to Week 52

The LS mean percent change in body weight at week 52 was -13.9% in the tirzepatide group and -2.2% in the placebo group (estimated difference: -11.6; 95% CI: -12.9, -10.4, p<0.001). See **Table 15**.

Table 15. Summary and analysis of percent change from baseline to 52 weeks in body weight (%); ANCOVA with multiple imputation for missing data at 52 weeks; randomized population

Body weight at week 52 (kg)				% change from baseline at week 52		
Treatment	**Mean (SD)**	**Median (Min, Max)**	**Estimate (SE) *a*b**	**Mean (SD)**	**Median (Min, Max)**	**Estimate (SE) *a*b**
TZP MTD (N=331)	87.2 (19.23)	83.2 (48.7, 155.2)	88.57 (0.46)	-14.8 (8.81)	-15.2 (-41.0, 9.7)	-13.85 (0.43)
Placebo (N=333)	100.7 (22.22)	95.3 (52.3, 194.5)	100.58 (0.48)	-2.1 (5.25)	-1.4 (-25.1, 15.0)	-2.24 (0.46)

Pairwise comparison	**Estimate Difference (SE)*a**	**95% CI for Difference*a**	**p-value*a**
TZP MTD vs. Placebo	-11.62 (0.63)	(-12.85, -10.38)	<0.001

Note 1: TZP MTD is tirzepatide up to 15 mg once weekly.
Note 2: Only participants with non-missing baseline value were included in analysis.
Note 3: Descriptive statistics are based on observed values.
Note 4: Missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data is not missing at Week 52 through retrieved dropout imputation method.
Note 5: Missing data was imputed 100 times.
Note 6: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

*a - ANCOVA model for endpoint measures: Variable = Baseline + HF Decompensation Within 12 Months of Screening + T2DM Status + Baseline BMI group (<35, >=35 kg/m^2) + Treatment (Type III sum of squares). *b - ANOVA model for baseline measures: Variable = Treatment (Type III sum of squares).

The applicant has also presented the cumulative distribution of change in body weight (%), which shows a clear separation between the tirzepatide and placebo curves (tirzepatide curve shifted towards greater weight loss from baseline to week 52 than placebo curve). Moreover, a plot of estimated mean for percent change in body weight by treatment and visit was presented, showing that the difference between tirzepatide and placebo arm with regard to the percentage of body weight reduction was

already significant by week 4.

Change in hsCRP from Baseline to Week 52

The LS Mean percent change in hsCRP at week 52 was -38.8% in the tirzepatide group and -5.9% in the placebo group (estimated difference: -34.9; 95% CI: -45.6, -22.2, p-value: <0.001). See **Table 16**.

Table 16. Summary and analysis of change from baseline to 52 weeks in hsCRP; ANCOVA with multiple imputation for missing data at 52 weeks using log transformation; randomized population

	Actual value at week 52 (mg/L)				% change from baseline at week 52		
Treatment	**Geometric Mean (SD)**	**Mean (SD)**	**Median (Min, Max)**	**Estimate (SE) *a*b**	**Mean (SD)**	**Median (Min, Max)**	**Estimate (SE) *a*b**
TZP MTD (N=305)	1.8 (174.39)	4.0 (8.94)	1.7 (0.2, 100.9)	1.94 (0.14)	23.3 (357.84)	-42.2 (-98.3, 5294.7)	-38.76 (4.47)
Placebo (N=298)	2.9 (166.42)	6.1 (12.79)	2.9 (0.1, 139.3)	2.98 (0.17)	53.0 (234.80)	-1.0 (-99.0, 2160.4)	-5.88 (5.25)

Pairwise comparison	**Estimate Difference (SE)*a**	**95% CI for Difference*a**	**p-value*a**
TZP MTD vs. Placebo	-34.93 (5.94)	(-45.60, -22.17)	<0.001

Note 1: TZP MTD is tirzepatide up to 15 mg once weekly.
Note 2: Only participants with non-missing baseline value were included in analysis.
Note 3: Descriptive statistics are based on observed values.
Note 4: Missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data is not missing at Week 52 through retrieved dropout imputation method.
Note 5: Missing data was imputed 100 times.
Note 6: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

*a - ANCOVA model for actual endpoint measures: log(Actual measurement) = log(Baseline) + HF Decompensation Within 12 Months of Screening + T2DM Status + Baseline BMI group (<35, >=35 kg/m^2) + Treatment (Type III sum of squares). ANCOVA model for percent change in endpoint measures: log(Actual measurement/baseline) = log(Baseline) + HF Decompensation Within 12 Months of Screening + T2DM Status + Baseline BMI group (<35, >=35 kg/m^2) + Treatment (Type III sum of squares). *b - ANOVA model for baseline measures: log(Actual measurement) = Treatment (Type III sum of squares).

Plot of estimated mean for change in hsCRP by treatment and visit

The results of change in hsCRP from baseline to week 52 (on-treatment period) calculated using MMRM are depicted in the plot below (**Figure 11**). The difference between tirzepatide and placebo arm is already significant by week 24.

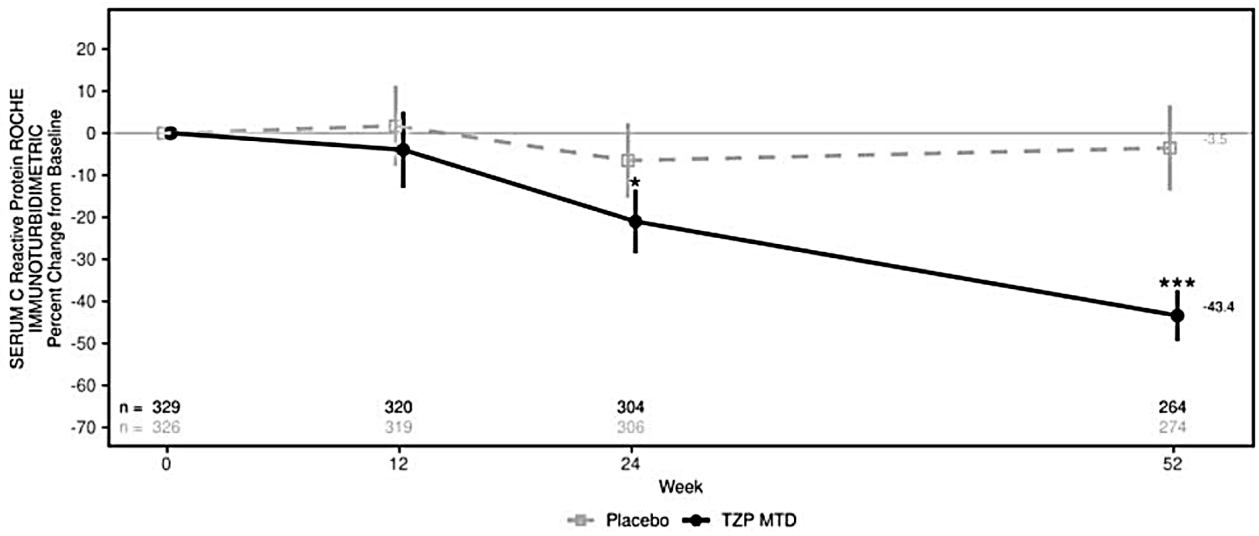


Figure 11. Plot of estimated mean for change in hsCRP by treatment and visit from baseline to week 52, randomized population.

Other Secondary Efficacy Endpoints

Hierarchical Composite Endpoint

The hierarchical composite endpoint includes the following:

- time to all-cause mortality through the end of the study
- occurrence of HF events through end of the study
- change from baseline in KCCQ-CSS category at Week 52, and
- change from baseline in the 6MWD category at Week 52.

Categories for change from baseline:

KCCQ-CSS: worsening by ≥10-points or by ≥5- but <10-points; no change (<5-points); improvement by ≥5- but <10-points, by ≥10- but <15-points or by ≥15-points.

6MWD: worsening by ≥30%, by ≥20% and <30% or by ≥10% and <20%; no change (<10%); improvement by ≥10% and <20%, by ≥20% and <30% or by ≥30%.

The data were analysed by using win ratio. Tirzepatide treatment resulted in more wins than placebo (TZP: 57.9%; placebo: 35.4%; win ratio: 1.63; 95% CI: 1.17 to 2.28; p = 0.004). A majority of the wins were determined by the KCCQ category (TZP: 31.3%; placebo: 19.0%), driven by the ≥15 point improvement category (TZP: 24.5%; placebo: 13.1%). A summary of the results is shown in **Table 17**.

Table 17: Results of the win ratio analysis for the hierarchical composite endpoint

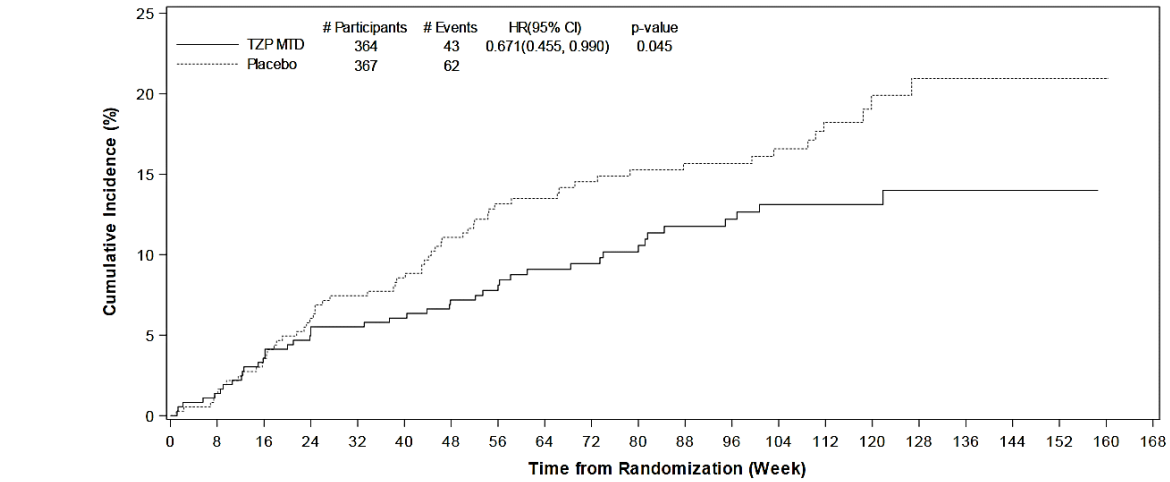
Endpoint component	TZP MTD (N=364) % Wins	Placebo (N=367) % Wins	% Ties	Win ratio (95% CI) p-value
Hierarchical Composite Endpoint	57.90	35.43	6.67	1.63 (1.17, 2.28) p = 0.004
Timing of Death during Study*a	3.65	3.85		
Timing and Frequency of HFE during Study*a	11.78	6.69		
Change from Baseline to Week 52 in KCCQ-CSS Category*b	31.27	18.98		
≥10-point worsening	0.00	0.00		
≥5-but <10-point worsening	0.19	0.44		
No change (<5-point change)	1.41	1.23		
≥5 but <10-point improvement	2.11	1.59		
≥10 but <15-point improvement	3.03	2.62		
≥15-point improvement	24.53	13.10		
Change from Baseline to Week 52 in 6MWD Category*b	11.21	5.91		
≥30% worsening	0.00	0.00		
≥20% and <30% worsening	0.01	0.05		
≥10% and <20% worsening	0.07	0.13		
No change (<10% change)	1.36	1.57		
≥10% and <20% improvement	3.89	1.36		
≥20% and <30% improvement	2.65	0.62		
≥30% improvement	3.22	2.18		

Note 1: Missing post-baseline values of KCCQ-CSS and 6MWD were imputed based on the worst 15% observed data in the same treatment arm if data is missing due to death through multiple imputation method; or missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data is not missing at Week 52 if data is missing due to other reasons through retrieved dropout imputation method.
Note 2: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

*a - Events happened up to the earlier of the two censoring times are counted in the pairwise comparisons.
*b - Baseline is the last record prior to randomization. Missing KCCQ-CSS and 6MWD at 52 weeks are imputed through multiple imputations.
*c - Win ratio, calculated as the number of pairs of tirzepatide-treated participants wins divided by number of pairs of placebo participants wins, is obtained using a non-parametric generalized pairwise comparison within each stratum that proceeded in a hierarchical fashion on the components in the order as listed in the table. Participants are stratified according to HF decompensation within 12 months of screening, type 2 diabetes status, and baseline BMI group (<35, ≥35 kg/m^2). Variance and p-value were calculated using the asymptotic normal U statistics approach.

Time to First Occurrence of HF Events or All-Cause Death

The Kaplan-Meier plot for time to first occurrence of adjudication-confirmed HF events or all-cause death shows that tirzepatide-treated participants exhibit a statistically significantly reduced risk as compared to the placebo group. The curves separate around week 24 and continue to diverge throughout follow-up – see **Figure 12**.

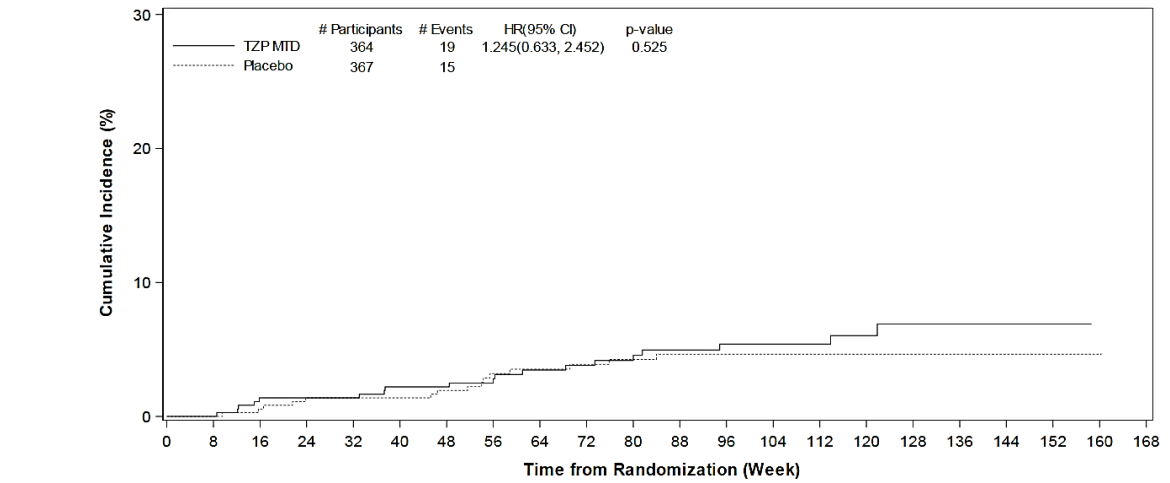


# Participants at Risk																					
TZP MTD	364	359	349	344	340	338	333	284	275	251	228	220	196	167	146	105	82	46	12	5	0	0
Placebo	367	361	349	339	332	328	318	268	259	240	219	215	195	165	145	94	73	45	11	7	1	0
Cumulative # Participants with Events																						
TZP MTD	0	5	13	20	20	22	26	29	32	33	36	39	40	42	42	42	43	43	43	43	43	43
Placebo	0	5	13	22	27	31	40	47	48	51	53	54	54	56	59	61	62	62	62	62	62	62

Figure 12. Kaplan-Meier plot of time to first occurrence of adjudication-confirmed HF events or all-cause death; randomized population

Time to All-Cause Death

The Kaplan-Meier plot for all-cause death shows that the curves of tirzepatide and placebo largely overlap. There was no increase in deaths in the placebo group after Week 88, while the number of deaths continued to increase in small increments in the tirzepatide arm – see **Figure 13**.



# Participants at Risk																					
TZP MTD	364	364	357	357	355	352	351	302	294	269	246	240	214	185	163	114	89	50	13	5	0	0
Placebo	367	366	360	356	354	354	350	294	283	265	244	240	213	181	161	106	79	50	14	7	1	0
Cumulative # Participants with Events																						
TZP MTD	0	0	5	5	5	8	8	10	12	13	15	16	17	17	17	18	19	19	19	19	19	19
Placebo	0	0	2	5	5	5	7	11	12	13	14	15	15	15	15	15	15	15	15	15	15	15

Figure 13. Kaplan-Meier plot of time to all-cause death Randomized population.

Time to First Occurrence of HF Events

The Kaplan Meier plot of time to first occurrence of adjudication confirmed HF events (**Figure 14**) shows that participants treated with tirzepatide exhibit a statistically significantly reduced risk of first occurrence of HF events compared with placebo. The curves of tirzepatide and placebo separate around week 24 and continue to diverge throughout the follow up period.

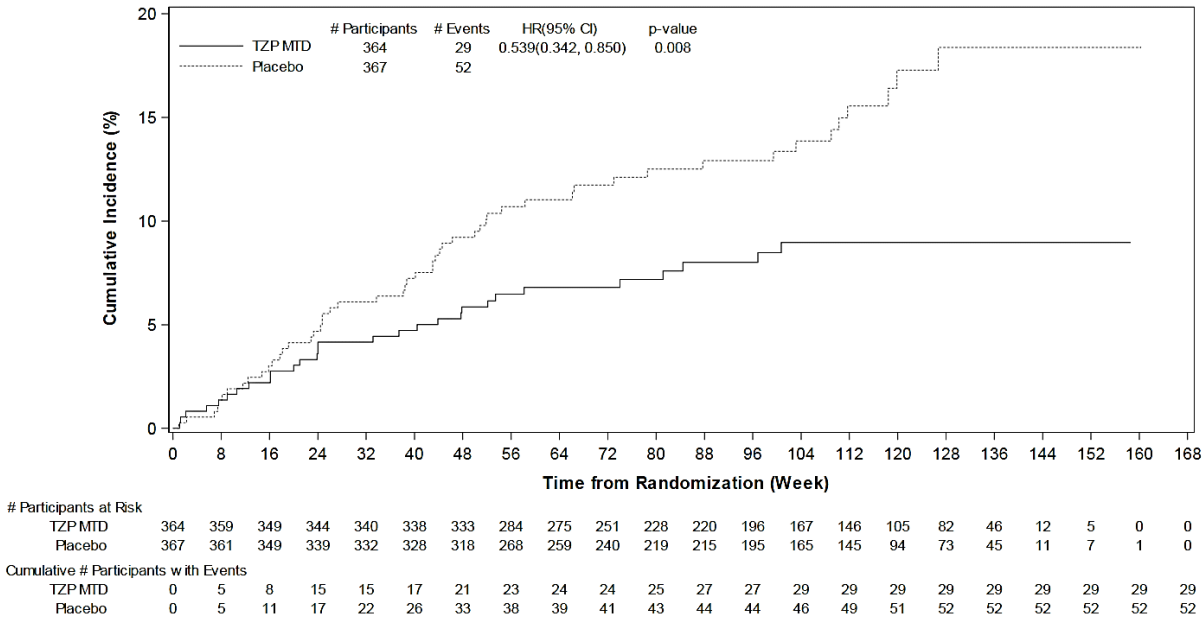


Figure 14: Kaplan-Meier plot of time to first occurrence of adjudication-confirmed HF events, randomized population

Time to Total (First and Recurrent) HF Events

No statistically significant difference was observed in total (first and recurrent) HF events across treatment groups – see **Table 18**.

Table 18. Summary and analysis of total (first and recurrent) HF events confirmed by clinical endpoint committee, randomized population

Endpoint Component ***Subcomponent***	**Tirzepatide (N = 364) n (Total Number of Events), n/100 Patient Years**	**Placebo (N = 367) n (Total Number of Events), n/100 Patient Years**	**Rate ratio (95% CI)[a]**	**p-Value[a]**
Total HF events	29 (44), 6.70	52 (68), 10.55	0.62 (0.37, 1.05)	0.077
Hospitalization for HF	12 (17), 2.52	26 (36), 5.41	0.45 (0.21, 0.98)	0.043
Urgent visit for HF	5 (7), 1.03	12 (13), 1.94	0.53 (0.16, 1.70)	0.283
Oral diuretics intensification for HF	17 (22), 3.29	21 (21), 3.15	1.02 (0.53, 1.98)	0.954

Number of HF events	**Tirzepatide (N = 364) n**	**Placebo (N = 367) n**
1	19	42
2	7	7
3	2	2
≥4	1	1

Note: Total events include first and recurrent events. A 30-day spacing rule is applied when consider recurrent events.

a Derived from LWYY model with treatment (tirzepatide versus placebo) as a fixed effect, adjusting for T2D Status, baseline probability of HFpEF (<0.8, ≥0.8), and baseline NTproBNP (<200, ≥200 ng/L).

Time to Total (First and Recurrent) Events of HF and All-Cause Death

A lower number of total (first and recurrent) HF events and all-cause death were reported in the tirzepatide group compared with placebo group; however, the results were not statistically significant. This secondary endpoint is not discussed further in this AR, as the previous analyses have already shown that tirzepatide does not reduce recurrent events of HF and all-cause mortality.

Proportion of Participants with NYHA Class improvement at Week 52

As shown in **Table 19** below, a statistically significantly greater proportion of participants treated with tirzepatide showed an improvement in the NYHA class at week 52 compared with placebo.

Table 19. Proportion of Participants with NYHA Class Improvement at Week 52

Time point Treatment	N*a	n*a	(%)* a	Proportion estimate *b	Estimate of the difference in proportions (95% CI)*b	Odds Ratio (95% CI) (Treatment/ Control)*b	Between treatment p-value *b
Week 52 (Visit 12)							
TZP MTD	328	109	33.23	33.27	12.88 (6.88, 18.89)	2.28 (1.53, 3.40)	<0.001
Placebo	327	67	20.49	20.39			

Abbreviations: BMI = body mass index; CI = confidence interval; HF = heart failure; NYHA = New York Heart Association n = number of subjects attaining NYHA meaningful within patient improvement; N = total number of participants in specified treatment arm; T2DM = type 2 diabetes mellitus; TZP MTD = tirzepatide maximum tolerated dose (up to 15 mg once weekly).

Note 1: Only subjects with non-missing baseline value and at least one non-missing post-baseline value of the response variable were included in analysis.
Note 2: Placebo was used as the control group.

*a - N, n, and (%) are based on observed value.
*b - Estimate of proportions, estimate of the difference in proportions, Odds Ratio, CI, and p-value for the odds ratio for post-baseline measures are from logistic regression model with baseline value, HF decompensation within 12 months of screening,
T2DM status, baseline BMI group (<35, >=35 kg/m^2), treatment as factors.

Categorical Analysis of KCCQ-CSS at Week 52

Proportion of Participants Attaining KCCQ-CSS MWPC Threshold (≥20 Points) at Week 52

An estimate of MWPC was empirically derived based on blinded interim analysis using two thirds of trial participants. The MWPC threshold for improvement on the KCCQ-CSS was estimated as ≥20 points.

At Week 52, a statistically significantly greater proportion of participants in the tirzepatide group achieved KCCQ-CSS MWPC threshold compared with the placebo group (**Table 20**). A visual representation of proportion of participants achieving KCCQ-CSS MWPC at Week 52, represented as vertical dotted line, can be seen in **Figure 11** (above).

Table 20. Summary and analysis of participants attaining KCCQ-CSS meaningful within-patient change threshold (≥20 points) logistic regression with multiple imputation for missing data at week 52; randomized population

Time point Treatment	N*a	n*a	(%)* a	Estimate of proportions *b	Estimate of the difference in proportions (95% CI)*b	Odds Ratio (95% CI) (Treatment/ Control)*b	Between treatment p-value *b
Week 52 (Visit 12)							
TZP MTD	301	155	51.50	47.56	12.40 (4.87, 19.94)	1.82 (1.25, 2.65)	0.002
Placebo	313	118	37.70	35.15			

Abbreviations: BMI = body mass index; CI = confidence interval; HF = heart failure; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; MWPC = Meaningful Within Patient Change; N = number of participants with baseline value and observed value at the specified timepoint; n = number of participants achieving target in observed data; T2DM = type 2 diabetes
Mellitus; TZP MTD = tirzepatide maximum tolerated dose (up to 15 mg once weekly).

Note 2: Only participants with non-missing baseline value were included in analysis.
Note 3: Missing post-baseline values were imputed based on the worst 15% observed data in the same treatment arm if data is missing due to death through multiple imputation method; or missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data is not missing at Week 52 if data is missing due to other reasons through retrieved dropout imputation method.
Note 4: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.*a - N, n, and (%) are based on observed value.

*a - N, n, and (%) are based on observed value.
*b - Estimate of Proportions, Estimate of the Difference in Proportions, Odds Ratio, CI, and p-value for post-baseline measures are
from logistic regression model with baseline value, HF decompensation within 12M of screen, T2DM status, baseline BMI group (<35, >=35 kg/m^2), treatment as factors.

Proportion of Participants Achieving ≥5, ≥10, and ≥15 Points Improvement in KCCQ-CSS

The proportion of participants achieving ≥5, ≥10, and ≥15 points improvement in KCCQ-CSS at week 52 was statistically significantly higher in the tirzepatide group compared with the placebo group (**Table 21**). A visual representation of proportion of participants achieving ≥5, ≥10, and ≥15 points improvement in KCCQ-CSS at Week 52, represented as vertical dotted line, can be seen in **Figure 11** above.

Table 21. Proportion of participants achieving KCCQ-CSS change (⩾5, ⩾10, and ⩾15 points) logistic regression with multiple imputation for missing data at 52 weeks, randomized population

Treatment Groups	N[a]	n[a]	n[a]/N[a] ×100 (%)	Odds Ratio (Treatment / Control)[b] (95% CI)	Between Treatment p-Value[b]
≥5 points improvement in KCCQ-CSS from baseline to Week 52					
Tirzepatide	301	247	82.1	1.90 (1.28, 2.83)	0.001
Placebo	313	211	67.4		
≥10 points improvement in KCCQ-CSS from baseline to Week 52					
Tirzepatide	301	219	72.8	1.87 (1.29, 2.70)	<0.001
Placebo	313	179	57.2		
≥15 points improvement in KCCQ-CSS from baseline to Week 52					
Tirzepatide	301	189	62.8	2.04 (1.41, 2.95)	<0.001
Placebo	313	141	45.1		

Abbreviation: BMI = body mass index; CI = confidence interval; HF = heart failure; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; n = number of participants achieving target in the observed data; N = number of participants with baseline value and observed value at the specified time point; T2D = type 2 diabetes mellitus.

[a] N, n, and (%) are based on observed value.

[b] Odds ratio, CI, and p-value for endpoint measures are from logistic regression model with baseline value, HF decompensation within 12 months of screening, T2D status, baseline BMI group (<35, ≥35 kg/m^2), treatment as factors.

Note 1: Only participants with nonmissing baseline values were included in the analysis.
Note 2: Missing postbaseline values were imputed based on the worst 15% observed data in the same treatment arm if data are missing due to death through multiple imputation method; or missing postbaseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data are not missing at Week 52 if data are missing due to other reasons through retrieved dropout imputation method.
Note 3: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

Change from Baseline to Week 24 in KCCQ-CSS

Participants treated with tirzepatide demonstrated a statistically significantly improvement as assessed by median change in KCCQ-CSS compared with placebo from baseline to Week 24 (see **Table 22**). For KCCQ-CSS change from baseline analysis at 52 weeks, please see primary endpoint section above.

Table 22. Summary and analysis of change from baseline to 24 weeks in KCCQ-CSS nonparametric analysis, randomized population

	Change from Baseline (observed)		TZP MTD vs. Placebo			
Treatment	**Mean (SD)**	**Median (Q1, Q3)**	**Estimated median difference *a**	**(95% CI)*a**	**(99% CI)*a**	**p-value *b**
TZP MTD (N=330)	19.3 (19.21)	17.2 (6.8, 31.3)	5.7	(3.1, 8.5)	(2.1, 9.4)	<0.001
Placebo (N=326)	13.4 (17.79)	11.2 (2.1, 25.0)				

Abbreviations: BMI = body mass index; CI = confidence interval; HF = heart failure; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; N = total number of participants in specified treatment arm; Q1 = 1st quartile; Q3 = 3rd quartile; SD = standard deviation; TZP MTD = tirzepatide maximum tolerated dose (up to 15 mg once weekly).

Note: Only participants with non-missing baseline and endpoint visit value were included in analysis.

*a - Hodges-Lehmann estimate of location shift and corresponding CI.
*b - Van Elteren test stratified by HF decompensation within 12 months of screening, type 2 diabetes status, and baseline BMI group (<35, >=35 kg/m^2).

Change from Baseline to Week 24 in 6MWD

Participants treated with tirzepatide demonstrated a statistically significantly improvement as assessed by change in 6MWD (meter) compared with placebo from baseline to Week 24 – cf. **Table 23**.

Table 23. Summary and analysis of change from baseline to 24 weeks in 6MWD (meters), nonparametric analysis, randomized population

	Change from Baseline (observed)		TZP MTD vs. Placebo		
Treatment	**Mean (SD)**	**Median (Q1, Q3)**	**Estimated median difference *a**	**(95% CI)*a**	**p-value*b**
TZP MTD (N=340)	21.5 (51.44)	16.0 (1.0, 44.0)	15.0	(10.0, 20.0)	<0.001
Placebo (N=330)	5.3 (39.58)	5.0 (-13.0, 22.0)			

Abbreviations: 6MWD = 6 minute walking distance; BMI = body mass index; CI = confidence interval; HF = heart failure; N = total number of participants in specified treatment arm; Q1 = 1st quartile; Q3 = 3rd quartile; SD = standard deviation; TZP MTD = tirzepatide maximum tolerated dose (up to 15 mg once weekly).

Note: Only participants with non-missing baseline and endpoint visit value were included in analysis.

*a - Hodges-Lehmann estimate of location shift and corresponding CI.
*b - Van Elteren test stratified by HF decompensation within 12 months of screening, type 2 diabetes status, and baseline BMI group (<35, >=35 kg/m^2).

Categorical Analysis of 6MWD at Week 52

Proportion of participants attaining 6MWD meaningful within-patient change threshold (≥25 meters) at week 52

An estimate of MWPC was empirically derived based on a blinded interim analysis using two thirds of the trial participants. The MWPC threshold for improvement on the 6MWD was estimated as ≥25 meters.
At week 52, a statistically significantly greater proportion of participants in the tirzepatide group achieved 6MWD MWPC threshold compared with the placebo group (cf. **Table 24**). A visual representation of proportion of participants achieving 6MWD MWPC at Week 52, represented as vertical dotted line, can be seen in **Figure 12**.

Table 24. Proportion of participants achieving 6MWD (meter) meaningful within-patient change (MWPC) threshold (≥25 meters) logistic regression with multiple imputation for missing data at 52 week; randomized population

Time point Treatment	N*a	n*a	(%)*a	Estimate of proportions *b	Estimate of the difference in proportions (95% CI)*b	Odds Ratio (95% CI) (Treatment/ Control)*b	Between treatment p-value *b
Week 52 (Visit 12)							
TZP MTD	326	181	55.52	51.67	17.72 (10.03, 25.42)	2.08 (1.50, 2.89)	<0.001
Placebo	314	99	31.53	33.95			

Abbreviations: BMI = body mass index; CI = confidence interval; HF = heart failure; MWPC = Meaningful Within Patient Change;

N = number of participants with baseline value and observed value at the specified timepoint; n = number of participants achieving

target in observed data; T2DM = type 2 diabetes mellitus; TZP MTD = tirzepatide maximum tolerated dose (up to 15 mg once weekly).

Note 1: Only participants with non-missing baseline value were included in analysis.

Note 2: Missing post-baseline values were imputed based on the worst 15% observed data in the same treatment arm if data is missing due to death through multiple imputation method; or missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data is not missing at Week 52 if data is missing due to other reasons through retrieved dropout imputation method.

Note 3: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

*a - N, n, and (%) are based on observed value.

*b - Estimate of Proportions, Estimate of the Difference in Proportions, Odds Ratio, CI, and p-value for post-baseline measures are

from logistic regression model with baseline value, HF decompensation within 12M of screen, T2DM status, baseline BMI group (<35, ≥35 kg/m^2), treatment as factors.

Proportion of Participants Achieving 6-Minute Walk Test Distance Change (≥10 meters, ≥20 meters, ≥30 meters)

The proportion of participants achieving ≥10, ≥20, and ≥30 meters improvement in 6MWD at Week 52 was statistically significantly higher in the tirzepatide group compared with the placebo group (cf. **Table 25** below). A visual representation of proportion of participants achieving these improvements in 6MWD at Week 52, represented as vertical dotted lines, can be seen in **Figure 12** above.

Table 25. Proportion of participants achieving 6MWD change (≥10 meters, ≥20 meters, and ≥30 meters); Logistic regression with multiple imputation for missing data at 52 weeks; randomized population

Treatment Groups	N[a]	n[a]	n[a]/N[a] ×100 (%)	Odds Ratio (Treatment/Control)[b] (95% CI)	Between Treatment p-Value[b]
≥10 meters change in 6MWD					
Tirzepatide	326	234	71.8	2.23 (1.61, 3.10)	<0.001
Placebo	314	144	45.9		
≥20 meters change in 6MWD					
Tirzepatide	326	200	61.4	2.13 (1.54, 2.94)	<0.001
Placebo	314	114	36.3		
≥30 meters change in 6MWD					
Tirzepatide	326	166	50.9	2.00 (1.43, 2.80)	<0.001
Placebo	314	90	28.7		

Abbreviation: 6MWD = 6-minute walking distance; BMI = body mass index; CI = confidence interval; HF = heart failure; n = number of participants achieving target in the observed data; N = number of participants with baseline value and observed value at the specified time point; T2D = type 2 diabetes mellitus.

[a] N, n, and (%) are based on observed value.

[b] Odds ratio, CI, and p-value for endpoint measures are from logistic regression model with baseline value, HF decompensation within 12 months of screening, T2D status, baseline BMI group (<35, ≥35 kg/m^2), treatment as factors.

Note 1: Only participants with non-missing baseline values were included in the analysis.
Note 2: Missing post-baseline values were imputed based on the worst 15% observed data in the same treatment arm if data are missing due to death through multiple imputation method; or missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data are not missing at Week 52 if data are missing due to other reasons through retrieved dropout imputation method.
Note 3: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

Proportion of Participants Achieving ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss Targets

A statistically significantly greater proportion of participants receiving tirzepatide achieved all ≥5%, ≥10%, ≥15% and ≥20% body weight loss targets from baseline to Week 52 (see **Table 26**).

Table 26: Proportion of participants achieving weight loss targets (≥5%, ≥10%, ≥15%, and ≥20%) logistic regression with multiple imputation for missing data at 52 weeks; randomized population

Treatment Groups	N[a]	n[a]	n/N ×100 (%)a	Odds Ratio (Treatment/Control)[b] (95% CI)	Between Treatment p-Value[b]
≥5% body weight reduction					
Tirzepatide	331	286	86.4	12.06 (8.09, 18.00)	<0.001
Placebo	333	89	26.7		
≥10% body weight reduction					
Tirzepatide	331	240	72.5	20.32 (12.75, 32.38)	<0.001
Placebo	333	26	7.8		
≥15% body weight reduction					
Tirzepatide	331	170	51.4	43.52 (17.32, 109.38)	<0.001
Placebo	333	4	1.2		
≥20% body weight reduction					
Tirzepatide	331	81	24.5	32.34 (9.09, 115.06)	<0.001
Placebo	333	2	0.6		

Abbreviation: CI = confidence interval; HF = heart failure; n = number of participants in the specified category; N = number of participants in the population with baseline and post-baseline value at the specified time point; T2D = type 2 diabetes mellitus.

a N, n, and % are based on observed value.
b Odds ratio, CI, and p-value for post-baseline measures are from logistic regression model with baseline value, HF decompensation within 12 months of screening, T2D status, treatment as factors.

Note 1: Only participants with non-missing baseline value were included in the analysis.
Note 2: Missing post-baseline values were imputed based on observed data in the same treatment arm from participants who discontinued treatment on or prior to Week 52 but observed data are not missing at Week 52 through retrieved dropout imputation method.
Note 3: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets.

Exploratory Efficacy Endpoints

The exploratory endpoints are summarized in **Table 27**.

Table 27. Summary of exploratory endpoint results

Exploratory Endpoint	Result
Proportion of participants with **atrial fibrillation**	Baseline: TZP: 14.8% vs. placebo: 17.4% Proportion of participants with atrial fibrillation was numerically reduced in both treatment groups at week 24 and 52 (compared to baseline), but the difference was not statistically significant.
Change in **waist circumference** (cm) from baseline to week 52	Significantly greater reduction compared with placebo from baseline to week 52 in tirzepatide-treated participants: LS mean change difference TZP MTD vs Placebo (95% CI) Week 24: -6.04 (-7.36,-4.72); p<0.001 Week 52: -10.91 (-12.32,-9.51); p<0.001
Change in the **KCCQ-TSS** (total symptom score) and **KCCQ-OSS** (overall summary score) from Baseline to week 52	Significantly greater mean improvement in KCCQ-TSS and -OSS compared with placebo from baseline to week 52 in tirzepatide-treated participants: Change difference TZP MTD vs Placebo (95 % CI) *KCCQ-TSS* Week 24: 7.74 (5.10, 10.37); p<0.001

	Week 52: 8.74 (5.89, 11.60); p<0.001 *KCCQ-OSS* Week 24: 5.74 (3.28, 8.21); p<0.001 Week 52: 8.60 (5.78, 11.41); p<0.001
Change from baseline in **EQ-5D-5L**	The EQ-5D-5L is a standardized self-administered instrument for use as a measure of health outcome, which provides a simple descriptive profile, and a single index value for health status. Compared to placebo, the tirzepatide group had significantly greater improvements from baseline in EQ-5D-5L Health State Index and EQ VAS scores at Week 24 and Week 52: Change difference TZP MTD vs Placebo (95 % CI) *Health State Index* Week 24: 0.05 (0.03, 0.08); p<0.001 Week 52: 0.06 (0.03, 0.09); p<0.001 *VAS score* Week 24: 4.34 (2.27, 6.41); p<0.001 Week 52: 5.26 (3.02, 7.50); p<0.001
% participants with improved categorical shift in **PGIS** from baseline to week 52	**PGIS** = Patient-Global Impression of Status
Overall Health	Participant-rated assessment of overall health "in the past 2 weeks" (5-point scale ranging from "1-Excellent" to "5-Poor.") **At baseline**, 60.4% of the participants in the tirzepatide group and 56.9% participants in the placebo group reported "fair" or "poor" overall health. Of the participants who reported "fair" or "poor" overall health at baseline, more participants in the tirzepatide group improved to "excellent," "very good," or "good" **at weeks 24 and 52** compared with the placebo group.
Physical Function	Participant-rated assessment of the overall impact of HF symptoms on ability to perform physical activities "in the past 2 weeks" (5-point scale ranging from "1-Not impacted" to "5-Extremely impacted, cannot perform physical activities." **At baseline**, 56.6% of the participants in the tirzepatide group and 51.5% participants in the placebo group reported "moderately impacted" physical function. Of those who reported impaired physical function at baseline (that is, "extremely impacted," "severely impacted," or "moderately impacted"), more participants in the tirzepatide group improved to "slightly impacted" or "not impacted" **at weeks 24 and 52** compared with the placebo group.
Symptom Severity	Participant-rated assessment of the overall severity of HF symptoms "in the past 2 weeks" (5-point scale ranging from "1-No symptoms" to "5-Very severe.") **At baseline**, 52.5% of the participants in the tirzepatide group and 52.0% participants in the placebo group reported having "moderate" symptom severity. Of those who had "very severe," "severe," or "moderate" symptom severity at baseline, more participants in the tirzepatide group improved to "no symptoms," or "mild" **at weeks 24 and 52** compared with the placebo group.
Change from Baseline to Week 52 in Waist-to-Height Ratio	Participants treated with tirzepatide showed a statistically significantly greater reduction in waist-to-height ratio compared with placebo from baseline to week 52: LS mean change difference TZP MTD vs Placebo (95% CI) Week 24: -0.036 (-0.044,-0.028); p<0.001 Week 52: -0.066 (-0.075,-0.058); p<0.001
Evaluation of **Pre-specified Biomarkers**	
Change in NT-proBNP from baseline to week 52	Participants treated with tirzepatide showed a greater reduction in plasma NT-proBNP compared with placebo from baseline to Week 52; however, the results were not statistically significant. Percent change difference TZP vs placebo (95 % CI) Week 12: -10.8 (-19.1,-1.5); p=0.024 Week 24: - 9.7 (-18.9, 0.5); p=0.063 Week 52: -10.5 (-20.7, 1.0); p=0.072

Change in cTNT from baseline to week 52	Participants treated with tirzepatide showed a statistically significantly greater reduction in serum cTNT compared with placebo from baseline to Week 52. Percent change difference TZP vs placebo (95 % CI) Week 12: -0.55 (-7.54, 6.96); p=0.881 Week 24: -9.83 (-15.95,-3.26); p=0.004 Week 52: -10.35 (-16.65,-3.58); p=0.003
eGFR slope from baseline to week 52	CKD-EPI equation was used by the central laboratory to estimate and report eGFR. Participants treated with tirzepatide showed a statistically significantly greater rate of change in eGFR per year compared with placebo from baseline to Week 52. Difference eGFR change rate/year TZP vs placebo (95 % CI) at week 52 (ml/min/1.73 m^2 per year): 2.53 (1.02, 4.05); p=0.001
Change from baseline to week 52 in **total blood** and in plasma **volume**	Tirzepatide-treated participants showed a significantly greater reduction in total blood and in plasma volume compared with placebo from baseline to week 52. Change difference TZP vs placebo (95 % CI) at week 52 (in ml): Total blood volume: -577.88 (-634.03, -521.72); p<0.001 Plasma volume: -315.18 (-357.76, -272.59); p<0.001

Ancillary analyses

Subgroup analyses

Subgroup Analysis of Heart Failure Outcomes

Subgroup analysis was only conducted for pre-specified categories with ≥10 events. The treatment effect on change in HF outcomes was generally consistent with the primary results across subgroups, except for those using diuretics at baseline. The p-values for the treatment and interaction effects are presented in the Forest plot below (**Figure 15**; showing only results for interaction p-values < 0.4).

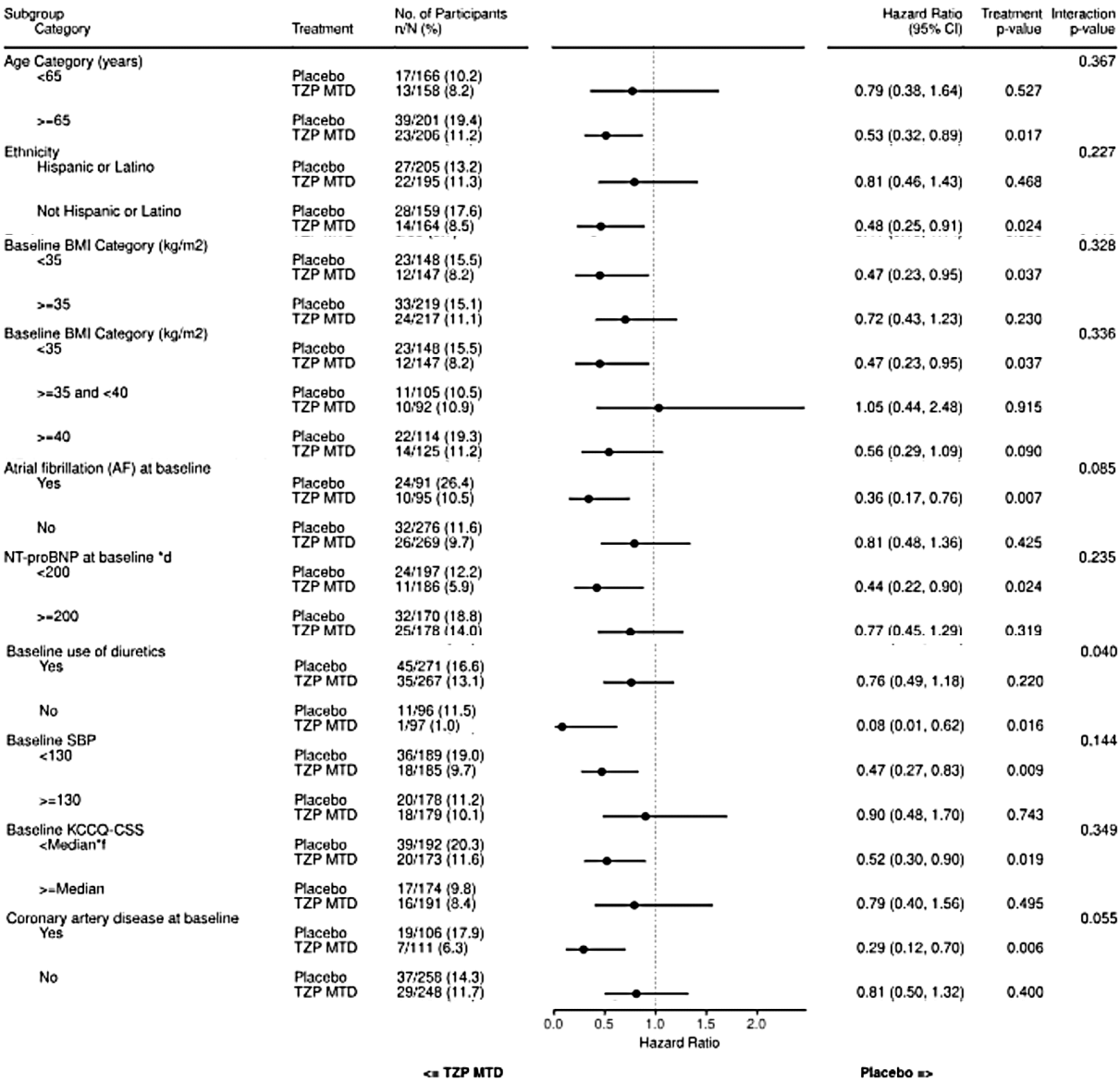


Figure 15. Subgroup analysis of first heart failure outcomes confirmed by clinical endpoint committee; randomized population – Table modified by assessor: only subgroups with interaction p-value <0.4 are shown.

Subgroup Analysis of KCCQ-CSS

Subgroup analysis was only conducted for pre-specified categories with ≥10 events. The treatment effect on change in KCCQ-CSS was consistent with the primary results across subgroups. The p-values for the treatment and interaction effects are presented in the Forest plot below (**Figure 16**; showing only results for interaction p-values <0.4).

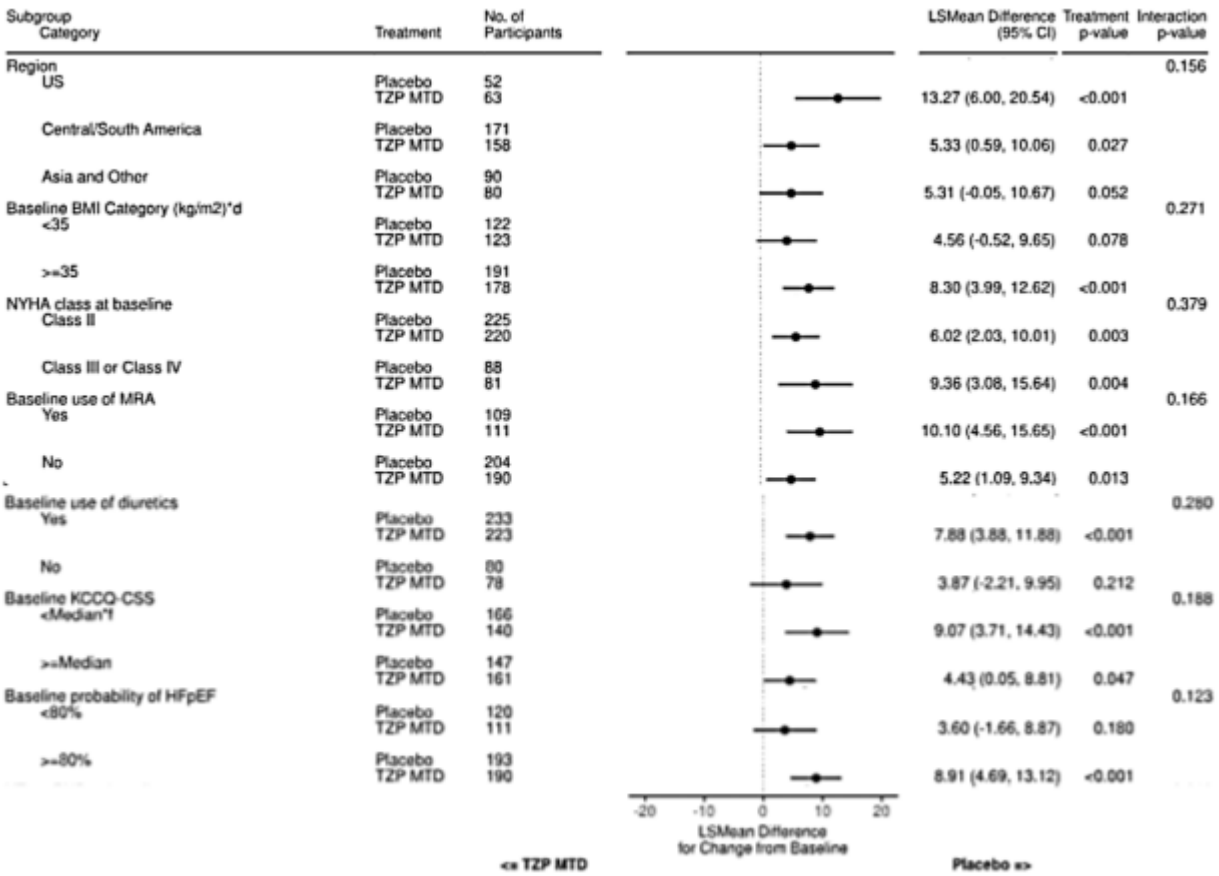


Figure 16: Subgroup analysis of change in KCCQ-CSS from baseline to week 52 ANCOVA with multiple imputation for missing data at 52 weeks; randomized population. – Table modified by assessor: only subgroups with interaction p-value <0.4 are shown.

Cardiac Magnetic Resonance Imaging Addendum Results

A subset of participants at selected sites was enrolled in the cMRI addendum to evaluate cardiac function and structure by the cMRI.

The following MRIs were recorded:

- Baseline MRI: MRI measurement taken prior to or within 7 days of the second dose of the study treatment.
- Week 52 MRI: MRI measurement taken either
  - at 52 weeks, or
  - within 105 days after 52 weeks, or
  - at the early discontinuation visit if the discontinuation occurs prior to 52 weeks.

Study disposition

The disposition of participants in the cMRI addendum was generally consistent with the main study. In the TZP MTD arm, the placebo arm and in the total population, 72/80 (90.0%), 90/95 (94.7%) and 162/175 (92.6%) participants, respectively, completed the study. Treatment was completed by 65/80 (81.2%), 85/95 (89.5%) and 150/175 (85.7) participants in the TZP MTD, placebo or total group, respectively.

Demographics of Participants in the cMRI Addendum

Demographics and baseline clinical characteristics of participants in the cMRI addendum were generally consistent with the main study – see **Table 28** for demographic characteristics and **Table 29** for baseline clinical characteristics. A total of 50 participants in the tirzepatide group and 56 participants in the placebo group had both baseline and week 52 cMRI measurements.

Table 28: Summary of Selected Baseline Demographic Characteristics; cMRI addendum

Attribute	TZP MTD (N=50)	Placebo (N=56)	Total (N=106)
Age (years), mean ± SD	66.020 ± 7.844	64.375 ± 8.721	65.151 ± 8.321
Age Category, n (%)			
<65	19 (38.0)	30 (53.6)	49 (46.2)
65-74	24(48.0)	19(33.9)	43(40.6)
75-84	7(14.0)	7(12.5)	14(13.2)
Sex, n (%)			
Female	27(54.0)	31(55.4)	58(54.7)
Male	23(46.0)	25(44.6)	48(45.3)
Region, n (%)			
US	0	1 (1.8)	1 (0.9)
Central/South America	43 (86.0)	50 (89.3)	93 (87.7)
Asia	7 (14.0)	5 (8.9)	12 (11.3)
Race, n (%)			
American Indian or Alaska Native	1 (2.0)	1 (1.8)	2 (1.9)
Asian	7 (14.0)	5 (8.9)	12 (11.3)
Black or African American	2 (4.0)	4 (7.1)	6 (5.7)
Native Hawaiian or Other Pacific Islander	2 (4.0)	1 (1.8)	3 (2.8)
White	38 (76.0)	45 (80.4)	83 (78.3)
Ethnicity, n (%)			
Hispanic or Latino	41 (82.0)	50 (89.3)	91 (85.8)
Not Hispanic or Latino	9 (18.0)	6 (10.7)	15 (14.2)

Table 29: Summary of Selected Baseline Clinical Characteristics; cMRI addendum

Attribute	TZP MTD (N=50)	Placebo (N=56)	Total (N=106)
Weight (kg), mean ± SD	96.586 ±14.315	99.841 ± 17.981	98.306 ±16.360
Waist circumference (cm), mean ± SD	116.740 ± 11.892	117.816 ± 12.580	117.308 ± 12.214
Waist to height ratio, mean ± SD	0.730 ± 0.079	0.733 ± 0.093	0.731 ± 0.086
BMI (kg/m^2), mean ± SD	37.623 ± 5.246	38.621 ± 8.410	38.150 ± 7.081
BMI category, n (%)			
<35	18 (36.0)	20 (35.7)	38 (35.8)
≥35 to <40	20 (40.0)	18 (32.1)	38 (35.8)
≥40	12 (24.0)	18 (32.1)	30 (28.3)
6MWD (meters), median (Q1, Q3)	338.0 (260.0, 381.0)	328.5 (243.0, 381.0)	335.0 (252.0, 381.0)
HF decompensation within 12 months of V1, n(%)			
No	25 (50.0)	31 (55.4)	56 (52.8)
Yes	25 (50.0)	25 (44.6)	50 (47.2)
Atrial fibrillation[a], n(%)			
No	40 (80.0)	47 (83.9)	87 (82.1)
Yes	10 (20.0)	9 (16.1)	19 (17.9)
Type 2 Diabetes, n(%)			
No	24 (48.0)	27 (48.2)	51 (48.1)
Yes	26 (52.0)	29 (51.8)	55 (51.9)
Coronary artery disease			
No	36 (75.0)	45 (80.4)	81 (77.9)
Yes	12 (25.0)	11 (19.6)	23 (22.1)
LVEF (%), mean ± SD	61.500 ± 6.348	62.607 ± 6.125	62.085 ± 6.226
NYHA class, n (%)			
NYHA class II	43 (86.0)	43 (76.8)	86 (81.1)
NYHA class III	7 (14.0)	13 (23.2)	20 (18.9)
NT-proBNP (ng/L), median (Q1, Q3)	118.5 (25.0, 343.0)	121.0 (63.5, 321.5)	121.0 (25.0, 327.0)
Cardiac Troponin T (mcg/L), mean ± SD			

Attribute	TZP MTD (N=50)	Placebo (N=56)	Total (N=106)
KCCQ-CSS score (points), median (Q1, Q3)	58.229 (44.271, 65.625)	51.562 (35.000, 66.406)	54.167 (40.104, 65.625)
hsCRP (mg/L), mean (SD)	6.699 (10.266)	4.849 (4.837)	5.739 (7.940)
eGFR (ml/min/1.73 m^2), median (Q1, Q3)	63.5 (46.0, 88.0)	65.0 (48.0, 86.5)	64.5 (46.0, 87.0)
eGFR Category, n (%)			
<60	21 (42.0)	23 (41.1)	44 (41.5)
≥60	29 (58.0)	33 (58.9)	62 (58.5)
Probability of HFpEF, mean[b] (SD)	0.823 (0.127)	0.803 (0.139)	0.813 (0.133)
Systolic BP (mmHg), mean ± SD	132.310 ± 11.892	131.500 ± 12.724	131.882 ± 12.287
Diastolic BP (mmHg), mean ±SD	78.060 ± 9.924	76.491 ± 8.756	77.231 ± 9.313
Heart Rate (beats/min), mean ±SD	69.060 ± 10.873	68.902 ± 8.667	68.976 ± 9.723

cMRI Substudy Efficacy Analysis

The cMRI substudy demonstrated (see also **Table 30**):

- a statistically significantly greater reduction in LVM with tirzepatide compared to placebo (LS mean change difference: -11.18 g)
- a statistically significantly greater reduction of pericardial fat volume (LS Mean change difference: -43.15 mL)
- a statistically significantly greater reduction of paracardiac fat volume, i.e., the sum of epicardial and pericardial fat (LS mean change difference: -45.42 mL)
- a trend towards a reduction in LVEDV
- a statistically significantly greater reduction in LVSV (LS mean change difference: -8.05 mL)

Table 30: Summary and analysis of change from baseline in cMRI endpoints

cMRI endpoints	Actual Value at Baseline (Mean)		Actual Value at Week 52 (Mean)		Change Difference: LS Mean (95% CI) [a,b]
	TZP (N = 80)	Placebo (N =95)	TZP (N = 80)	Placebo (N = 95)	
Structural and functional parameters					
Left ventricular mass (LVM) (g)	120.43	122.23	110.64	123.35	-11.18** (-18.73, -3.62)
Left ventricular mass index (LVMI) (g/m^2)	60.55	59.87	58.84	60.37	-2.21 (-6.01, 1.59)
Left ventricular end diastolic volume (LVEDV) (mL)	138.87	151.14	131.96	151.50	-7.49 (-16.49, 1.51)
Left ventricular end diastolic volume index (LVEDVI) (mL/m^2)	69.62	73.69	70.09	73.99	-0.10 (-4.60, 4.40)
Left ventricular end systolic volume (LVESV) (mL)	56.06	62.79	55.30	62.77	-1.75 (-7.67, 4.17)
Left ventricular end systolic volume index (LVESVI) (mL/m^2)	28.29	30.39	29.38	30.40	0.63 (-2.35, 3.61)
Left atrial volume (LAV) (mL)	48.11	47.72	48.89	46.36	2.07 (-5.01, 9.14)
Left atrial volume index (LAVI) (mL/m^2)	23.99	23.66	25.16	23.06	1.74 (-1.82, 5.29)
Atrium end systolic volume (AESV) (mL)	84.72	80.29	77.50	75.46	-2.15 (-10.30, 6.00)
Left ventricular ejection fraction (LVEF) (%)	59.82	60.19	58.84	60.51	-1.43 (-3.98, 1.12)
Left ventricular cardiac output (LVCO) (L/min)	5.55	5.74	5.43	5.74	-0.17 (-0.61, 0.27)
Left ventricular stroke volume (LVSV) (mL)	82.80	88.35	76.66	88.72	-8.05* (-14.23, -1.86)
Feature tracking					

Left ventricular global longitudinal strain (LVGLS) (%)	-19.12	-19.05	-18.46	-18.83	0.39 (-1.34, 2.11)
Left ventricular global circumferential strain LVGCS (%)	-20.55	-21.70	-20.50	-22.09	1.06 (-0.67, 2.80)
left apical endocardial global longitudinal strain (LAEGLS) (%)	-24.87	-24.33	-24.33	-24.85	0.74 (-1.75, 3.23)
left apical endocardial global longitudinal strain (LAGCS) (%)	-34.62	-34.78	-35.61	-37.03	1.32 (-1.86, 4.49)
Adipose tissue volumes					
Epicardial Fat Volume (EFV) (mL)	47.20	45.40	34.68	35.96	-1.91 (-8.52, 4.70)
Pericardial fat volume (PFV) (mL)	173.50	185.74	147.33	196.77	-43.15***(-65.45, -20.84)
Paracardiac fat (including epicardial and pericardial fat) volume (mL)	220.70	231.15	182.01	232.73	-45.42***(-69.25, -21.60)

Abbreviations: ANCOVA = analysis of covariance; cMRI = cardiac magnetic resonance imaging

a ANCOVA model for endpoint measures: Variable = Baseline + T2D Status + Baseline BMI group (<35, ≥35 kg/m^2) + Treatment (Type III sum of squares).
b ANOVA model for baseline measures: Variable = Treatment (Type III sum of squares).

Note 1: Reference to "left apical" refers to "left atrial"; Reference to "atrium" refers to "left atrium"
Note 2: Only subjects with non-missing baseline value and at least 1 non-missing post-baseline value of the response variable were included in analysis.

*p-Value <0.05, **p-value <0.01, ***p-value <0.001 versus placebo.

Additional analyses

Upon request, the applicant also presented an analysis of a composite endpoint consisting of

a. All cause death
b. HF events (only urgent HF visit and hospitalisation for HF)

Table 31 provides a summary and analysis of the composite endpoint consisting of first event of all-cause death or HF event (including hospitalisation for HF and urgent HF visit) confirmed by CEC and each component of the composite endpoint.

The time to first event analysis of this composite endpoint showed a HR of 0.64 (95% CI 0.40-1.01). The magnitude of risk reduction was similar to the protocol-specified primary composite endpoint with a HR of 0.62 (95% CI 0.41, 0.95). Tirzepatide demonstrated a statistically significant reduction in the risk of HF events (defined by hospitalisation for HF and urgent HF visit), with a HR of 0.41 (95% CI 0.22-0.75, p=0.004). As in the primary composite endpoint, the risk reduction was largely driven by reductions in HF hospitalisations (HR of 0.44 (95% CI 0.22-0.87, p=0.018)), which is considered clinically important being a prognostic factor for death in the HFpEF population, (Chatur et al. 2023b) with the 5-year mortality in patients hospitalised with HFpEF being 75.7% (Shah et al. 2017). In SUMMIT, the HR for all-cause death was 1.25 (95% CI 0.63-2.45). No randomised controlled trial has yet demonstrated a statistically significant reduction in mortality in patients with HFpEF (Kondo et al. 2024). In comparison to HFrEF, this might be attributed to relatively low rates of mortality events in HFpEF and a relatively larger proportion of nonmodifiable causes of death (approximately 60%) in HFpEF (Kondo et al. 2024).

Table 31. Summary and Analysis of First Heart Failure (excluding ODI) or Death Confirmed by Clinical Endpoint Committee, Randomised Population, Study I8F-MC-GPID

	TZP MTD (N=364)			Placebo (N=367)		
Endpoint Component Subcomponent	**n (%)**	**Total Person-Years of Follow-up*a**	**n/100 Person-Years of Follow-up**	**n (%)**	**Total Person-Years of Follow-up*a**	**n/100 Person-Years of Follow-up**
HF Events and Death (excluding ODI)	30 (8.2)	670.6	4.47	45 (12.3)	650.1	6.92

All Cause Death	19 (5.2)	687.3	2.76	15 (4.1)	684.2	2.19
Heart Failure	15 (4.1)	670.6	2.24	35 (9.5)	650.1	5.38
Hospitalization for Heart Failure	12 (3.3)	674.1	1.78	26 (7.1)	660.7	3.94
Urgent Visit for Heart Failure	5 (1.4)	682.4	0.73	12 (3.3)	670.2	1.79

Endpoint Component Subcomponent	**Hazard Ratio (95% CI)*b**	**p-value*b**	**ARD*c**
HF Events and Death (excluding ODI)	0.64 (0.40, 1.01)	0.057	2.45
All Cause Death	1.25 (0.63, 2.45)	0.525	-0.57
Heart Failure	0.41 (0.22, 0.75)	0.004	3.14
Hospitalization for Heart Failure	0.44 (0.22, 0.87)	0.018	2.16
Urgent Visit for Heart Failure	0.41 (0.14, 1.16)	0.093	1.06

Abbreviations: ARD = absolute risk difference; CI = confidence interval; HFpEF = heart failure with preserved ejection fraction; N = number of participants in the analysis population; NTproBNP = N-terminal pro b-type natriuretic peptide; n = number of participants in the specified category; TZP MTD = tirzepatide maximum tolerated dose.

Note 1: TZP MTD is tirzepatide up to 15 mg once weekly.
Note 2: Subjects may be counted in more than one category.
Note 3: Heart Failure Outcome is the composite endpoint of all cause death and heart failure events.

*a - The person-years of follow-up is calculated for each participant as time-to-event divided by 365.25. Time-to-event is the number of days between the date of randomization and the onset date of the event/censoring date plus 1 day.

*b - Derived from a Cox proportional-hazards model with treatment (Tirzepatide versus Placebo) as a fixed effect, adjusting for T2DM status, baseline probability of HFpEF (<0.8, >=0.8), and baseline NTproBNP (<200, >=200 ng/L). P-value is from Wald test. When the total number of outcomes is < 10, survival analysis is not performed.

*c - Absolute risk difference is calculated by subtracting the incidence rate per 100 person-years of Tirzepatide from that of Placebo.

Summary of main study

See effects table in section 7.6.

3.4.3. Discussion on clinical efficacy

Design and conduct of clinical study

Tirzepatide efficacy in the treatment of obese (BMI ≥ 30 kg/m^2) HFpEF patients was investigated in one pivotal phase 3 randomized, multicentre, international, placebo-controlled, double-blind, parallel-arm study (Study 18-F-MC-GPID; **SUMMIT**).

The participants (n=731) were randomized to receive once-weekly, injectable placebo or tirzepatide maximum tolerated dose (MTD; up to 15 mg). Sufficiently balanced groups with respect to pathology, comorbidities, and severity of disease were ensured by stratified randomization based on HF decompensation within 12 months of screening (Y/N), baseline diagnosis of T2DM (Y/N) and BMI ≥35 (Y/N). The study design is adequate and generally in line with the recommendations in the *Guideline on clinical investigation of medicinal products for the treatment of heart failure* (CPMP/EWP/235/95, Rev. 2). The treatment period of 52 weeks (20 weeks dose escalation and ≥32 weeks of maintenance) is appropriate.

In addition, a cardiac magnetic resonance imaging (cMRI) addendum was completed in a subset of 106 participants. MRI measurements were taken at baseline and at week 52. This is endorsed as it provides in-depth information on the effect of tirzepatide on cardiac structure and function.

Tirzepatide doses and background therapy
Tirzepatide was up-titrated to MTD (5, 10 or 15 mg) in a double-blind up-titration regimen with dose-escalation in 2.5 mg steps every 4 weeks until a maximum of 15 mg is reached at week 20. This strategy helps to ameliorate gastrointestinal side effects and has been used in previous studies of the T2DM and

weight management programme. Throughout the study, an acceptable strategy to interrupt/reduce dosing in case of intolerance or excessive weight loss was in place.

No lifestyle modification was advised, and participation in a structured exercise training program was even defined as an exclusion criterion. This may have led to a somewhat less pronounced weight reduction in comparison to the SURMOUNT studies, where diet and exercise were enforced. Per inclusion criteria, therapy with renin-angiotensin system inhibitors, diuretics, beta blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors was permitted, which corresponds to guideline recommendations. Treatment with incretins or GLP-1 receptor agonists was excluded, which is acceptable due to the interfering mechanism of action of these medications.

Other therapies (e.g., anti-emetic or antidiarrhoeal medications, anti-hypertensive drugs, lipid-lowering and anti-hyperglycaemic agents) were permitted. Therapies associated with weight gain and weight loss were excluded, except when the dose had been stable for ≥3 months prior to visit 1 and is expected to remain stable during the study period.

Endpoints

Two **primary efficacy endpoints** (dual endpoints) were defined, at least one of which must be met, namely (1) "change from baseline to week 52 in the KCCQ-CSS" and (2) "occurrence of the composite endpoint of CV death and/or HF events over time". KCCQ-CSS is a validated patient-reported outcome (PRO) for patients with heart failure. According to the chronic heart failure guideline (CPMP/EWP/235/95), PROs are only recommended as primary endpoint in case of high unmet medical need and for patients unable to undergo exercise testing due to physical limitations. A high unmet medical need could be assumed for the obese HFpEF population in the SUMMIT study, but it is not agreed that the patients in the SUMMIT study were unable to undergo exercise testing due to physical limitations. It is noted that the majority of participants was able to conduct the 6MWT (TZP MTD: N=326; placebo: N=314). Therefore, success as regards meeting the KCCQ-CSS endpoint is not considered sufficient. From a regulatory point of view greater weight is set to the composite endpoint of CV death/HF events. In addition, the composite endpoint of CV death and/or HF events is considered problematic, as the applicant has widened it (amendment c) by additionally including "oral diuretics intensification for HF", which may "soften" the endpoint. However, this additional subcomponent did not relevantly contribute to the overall result (see discussion of results below).

The **key secondary endpoints** (6MWD, weight loss and change in hsCRP) are endorsed. They reflect the well-established weight-reducing effect of tirzepatide and its potential effects on exercise capacity and inflammatory state. The 6MWD supports the objective evaluation of functional status and can be correlated with the KCCQ-CSS data from the primary endpoint.

The **other secondary endpoints** complement the primary and key secondary endpoints, e.g., responder analyses for 6MWD and KCCQ-CSS, analyses of all-cause mortality and/or of first/recurrent HF events, or NYHA class change. Specifically, inclusion of all-cause mortality as first component of the hierarchical composite secondary endpoint is endorsed, as the guideline for the development of heart failure medications recommends that assessment of mortality should include *both* all-cause mortality and CV mortality.

Sample size and population studied

The intended sample size was 700 patients, but eventually, 731 patients were 1:1 randomized to tirzepatide and placebo. Inclusion and exclusion criteria are largely acceptable. Inclusion of patients with BMI ≥30 kg/m^2 and HFpEF (NYHA II – IV, for ≥3 months) on stable HF medication is supported. The criterion for diagnosing HFpEF (elevated NT-proBNP *or* left atrial enlargement *or* increased filling pressure) in connection with the inclusion criterion of LVEF ≥50% is endorsed. The LVEF threshold of

50% conforms to the current ESC guideline [McDonagh TA (2021) *Eur Heart J.* **42** (36):3599-3726]. However, the lack of participants with BMI <30 kg/m^2 renders it more difficult to decide, whether the effects of tirzepatide on HF symptoms are a result of weight reduction or due to an independent cardiovascular benefit.

Using a 6MWD between 100 and 425 m and a KCCQ-CSS≤80 as inclusion criterion enables analysis of the effect on functional capacity and minimizes within-subject variability. The study population was additionally enriched by including patients with either an eGFR <70 ml/min/1.73 m^2 or HF decompensation within the past 12 months, which is considered appropriate.

Statistical methods
The primary estimand for primary and key secondary endpoints targets the treatment effect between tirzepatide and placebo regardless of whether intercurrent events occur (i.e. treatment policy strategy), which is considered relevant for the clinical and regulatory decision making, since it reflects the clinical practice.

Although the multiplicity control strategy is technically correct and the overall type I error is controlled at a 2-sided alpha level of 0.05, it is not considered relevant for the assessment. The dual primary endpoints with alpha-splitting (time to first occurrence of CV death or HF event is tested at a 2-sided alpha level of 0.04 and change from baseline in KCCQ-CSS at Week 52 is tested at a 2-sided alpha level of 0.01) mean that the study is successful as soon as at least one of the primary endpoints is significant. For example, the study is successful if change from baseline in KCCQ-CSS at Week 52 is significant regardless of whether time to first occurrence of CV death or HF event is significant or not. As this is not in line with the clinical and regulatory decision making, the assessment will not be guided by the proposed type I error control strategy for primary and key secondary efficacy analyses.

Conduct of the study

Randomized population
Demographic and baseline clinical characteristics were comparable across the treatment groups. No European patients were included in the SUMMIT study. However, the applicant has shown that inclusion criteria and concomitant medication align with relevant European guidelines. Moreover, a comparison with data from the ESC HF III registry shows that the concomitant medication in the SUMMIT study reflects European clinical reality. This was confirmed based on the patient demographic properties and baseline medications in the studies STEP-HFpEF and STEP-HFpEF DM, where a relevant proportion of European participants had been included. The mean age of the SUMMIT participants was ~65 years, which is younger than in other HFpEF studies (e.g., DELIVER [dapagliflozin] and EMPEROR-Reduced [empagliflozin]: ~72 years). Nevertheless, about 20% of the SUMMIT population was older than 75 years, i.e., a relevant number of elderly patients was included as requested by the guideline. However, only 10 patients were older than 85 years, which makes it difficult to draw conclusions on this age group. Baseline NT-proBNP was lower than in other HFpEF studies using higher cut-offs (e.g., 200 pg/ml in SUMMIT versus 300 pg/ml in DELIVER and EMPEROR-Reduced). However, this could be justified by the fact that the SUMMIT study focuses on an obese HFpEF population, where NT-proBNP levels generally tend to be lower than in non-obese HFpEF patients [Obokata M et al (2017) Circulation 136(1):6-19]. Nevertheless, the mean probability of HFpEF of 0.814 at baseline shows that a representative HFpEF patient population was enrolled. Slightly more participants randomized to tirzepatide completed the study (91.2%) and the study drug (80.8%) than participants randomized to placebo (90.2% completed study; 78.7% completed study drug). The retention rate in the placebo arm is considered reasonably high. Overall, the rates of study and study drug continuations as well as the most common reasons are considered acceptable.

Amendments

Several amendments were implemented, of which amendment c is considered to have the highest impact, because it included a widening of the HF event definition by adding the subcomponent "oral diuretics intensification for HF". This is seen critical, as it may "soften" the endpoint and artificially increase efficacy of tirzepatide. Nevertheless, the results (below) suggest that addition of the diuretics intensification component did not relevantly alter the results.

Protocol deviations and treatment compliance

Most important protocol violations were in the categories "Study procedure compliance" and "Investigational Medicinal Product and/or Investigational Device". The deviations were balanced across treatment groups (tirzepatide: 36.5%; placebo: 37.6%). Thus, no relevant influence on study results is expected. However, it is noted that, in several instances, the question whether a participant had been hospitalised due to an HF event during the past 12 months was answered with "no" in the IWRS, although the correct response would have been "yes". The applicant has ensured that there is no impact on the study results, because the correct response based on the eCRF was used instead of the incorrect response in the IWRS.

Deviations due to COVID 19 are considered negligible. Treatment compliance was defined as taking ≥75% (but ≤125%) of the required dose. Overall, study drug compliance was high (n=662; 90.6%) and similar with tirzepatide and placebo. The 15 mg dose of tirzepatide was taken as the highest dose by 77.2 % of the participants. As final dose, 65.4%, 20.4% and 7.1% of the participants took the 15 mg, 5 mg and 10 mg dose, respectively.

Efficacy data and additional analyses

Primary endpoints

HF outcome

For the primary endpoint *"Occurrence of the composite endpoint of CV death and/or HF events over time"* tirzepatide was superior to placebo (HR: 0.62, 95% CI: 0.41 to 0.95, p=0.025). However, this effect was mainly driven by a reduction in HF hospitalisations (p=0.018) and urgent visits (p=0.093). The component "*oral diuretics intensification for HF*" was practically not affected (p=0.492) and efficacy was maintained, when the results were analysed after omission of the diuretics intensification component. This suggests that widening of the HF endpoint by amendment c did not relevantly change the results. The applicant has also provided an analysis of a composite endpoint consisting of all-cause death and HF events (only urgent HF visit and hospitalisation for HF). The magnitude of risk reduction was similar to the protocol-specified primary composite endpoint. Tirzepatide did not reduce CV mortality. By contrast, twice as many CV deaths occurred with tirzepatide than in the placebo arm (10 *vs.* 5). The small study size and the small event rate renders it difficult to draw a conclusion regarding potentially increased mortality of tirzepatide-treated HFpEF patients. In this context, a potential impact of the "obesity paradox" is discussed - see safety part.

KCCQ-CSS

Tirzepatide was also superior to placebo at improving total symptoms and physical limitation in the KCCQ-CSS [estimated mean difference tirzepatide vs. placebo at 52 weeks vs. baseline: 6.9, 95% CI (3.3, 10.6), p<0.001]. Although this endpoint was formally met and the results support the analysis of the HF outcomes endpoint, the difference between tirzepatide and placebo is relatively small and only a little higher than the 5-point threshold, below which an effect would be considered as "no change". Thus, it is important to interpret these data in context with the categorical endpoint analyses presented among the secondary endpoints (see below).

Although the benefit of tirzepatide treatment in the KCCQ-CSS and the HF outcome endpoint is acknowledged, it is not entirely clear, whether the symptomatic improvement is due to weight reduction only, or whether there is an independent effect of tirzepatide on HFpEF pathophysiology. Only HFpEF patients with a BMI ≥30 kg/m^2 were included in the SUMMIT study, which renders it difficult to conclude on an effect of tirzepatide on HFpEF independently of weight reduction.

Secondary endpoints

Tirzepatide showed superiority in comparison to placebo regarding the key secondary endpoints. The improvement in 6MWD confirms the improved exercise capability suggested by the primary endpoint data, and the lowered hsCRP indicates a reduction of inflammatory processes, which may contribute to the observed reduction of HF events. As expected, tirzepatide also reduced body weight, which may by itself already be a factor, which increases exercise capacity and reduces inflammation.

The result of the win ratio analysis of the hierarchical composite endpoint was predominantly driven by the KCCQ-CSS category, specifically by the subpopulation showing ≥15 points improvement. The categorical analysis of KCCQ-CSS and 6MWD showed that the meaningful within-patient change (KCCQ-CSS: ≥20 points; 6MWD: ≥20 meters) was reached by about 52% of tirzepatide-treated patients, but also by 32 – 38% of patients in the placebo group. The positive effect of tirzepatide on exercise capacity was also reflected by a higher percentage of patients with NYHA class improvement in comparison to the placebo group.

Analysis of all-cause mortality was conducted as part of the secondary endpoints. It is noted that the between-group difference in all-cause deaths (difference of n=4) is almost the same as the difference in CV/undetermined mortality (difference of n=5), which indicates that the additional deaths observed with tirzepatide are mainly CV deaths, while non-CV deaths appear to be balanced across treatment arms (see safety section).

For KCCQ-CSS and 6MWD, the change from baseline to week 24 was also analysed as secondary endpoint. Already after 24 weeks, the difference between tirzepatide and placebo group reached 83% and 82% of the effect at week 52 for KCCQ-CSS and 6MWD, respectively. Thus, most of the improvement occurs within the first 24 weeks, with very little additional effect between week 24 and week 52. This shows that the benefit regarding 6MWD and KCCQ-CSS correlates with body weight reduction, most of which occurs in the initial phase of treatment, and suggests a potential causal relationship between body weight reduction and improvement of HF symptoms.

Cardiac magnetic resonance imaging (cMRI) addendum

A cMRI addendum was completed in a subset of 106 participants, who had similar demographic and clinical characteristics as the main study population. MRI measurements were taken at baseline and at week 52. Left ventricular mass was reduced by tirzepatide in comparison to placebo, which, according to the literature, could be a consequence of weight reduction [MacMahon S et al (1986) *N Engl J Med* **314**:334-339]. The reduction of left ventricular stroke volume could be due to a weight-loss-induced reduction of blood volume (determined as exploratory endpoint). A correlation of blood volume and stroke volume has been previously reported, e.g. in persons who experienced a training-induced increase in blood volume [Bonne TC (2014) *Am J Physiol Regul Integr Comp Physiol* **306**:R752-R760].

Most importantly, pericardial fat volume was considerably reduced by tirzepatide. Pericardial fat has been reported to be an important factor that adversely affects cardio-mechanical interaction in HFpEF [Zamani SK et al (2023) *Circulation* **148**:1410–1412]. Thus, the beneficial effect of tirzepatide in HFpEF could be due to the reduction of cardiac adipose tissue at the side of the heart. The applicant has provided an analysis, which shows that the percent change in pericardial fat volume positively correlates with left atrial volume, left atrial volume index, and left ventricular global longitudinal strain, indicating improved

ventricular systolic function. However, the applicant could not present data on ventricular interdependence or from echocardiography.

3.4.4. Conclusions on the clinical efficacy

The SUMMIT study demonstrated that once weekly administered tirzepatide at the maximum tolerated dose (up to 15 mg) significantly reduces HF events (mainly driven by a reduction in HF hospitalisations and urgent HF visits) and improves KCCQ-CSS in obese (BMI ≥30 kg/m^2) HFpEF patients. As expected, body weight reduction was more pronounced in the tirzepatide arm than in the placebo group. The beneficial effect of tirzepatide on exercise capacity was confirmed by the 6-minute walk test and by improvement in NYHA classification. In addition, a reduction in hsCRP level was observed, which was more pronounced in tirzepatide than in placebo-treated participants and indicates a positive effect on inflammatory processes.

Despite these beneficial effects, tirzepatide was not able to reduce CV mortality. Moreover, as only obese HFpEF patients were included in the study, the benefit in normal weight or overweight HFpEF patients remains unclear. Uncertainty remains on whether TZP exerts beneficial cardiovascular effects independent from weight loss. Therefore, a separate indication for HFpEF is not considered to be justified. However, inclusion of a cross-reference to section 5.1 for "heart-failure with preserved ejection fraction" is acceptable.

3.5. Clinical safety

Introduction

Safety data from Study I8F-MC-GPID (GPID; SUMMIT) was used to assess the safety profile of tirzepatide in adults with chronic HFpEF and obesity. The SUMMIT study was a randomized, outpatient, multicenter, international, placebo-controlled, double-blinded, parallel-arm, Phase 3 study with 2 study periods. The study was designed to evaluate the efficacy and safety of SC QW tirzepatide, MTD up to 15 mg, compared to placebo, in participants with HFpEF and obesity.

The safety profile of tirzepatide has been well established in several Phase 1, 2, and 3 clinical studies in other patient populations (such as T2DM and weight management). Safety data are also available from postmarketing surveillance. The population in the SUMMIT study provides controlled data specific to the HFpEF population to allow systematic assessment of safety in this population.

Patient exposure

The submission data cutoff date for the application is 09 August 2024.

Safety data in the HFpEF population were taken from the SUMMIT study. This study continued until approximately 52 weeks after the last participant was randomly assigned. The study duration of individual participation varied depending on the duration of study enrollment. Some participants received over 2 years of treatment. A total of 731 participants with HFpEF and obesity were randomly assigned.

Of these participants, 364 received at least 1 dose of tirzepatide.

The median duration of treatment exposure and total patient-year were similar between tirzepatide (90.1 weeks, 593.1 patient years) and placebo (92.0 weeks, 607.8 patient years). The median duration of study follow-up was similar between tirzepatide (104.1 weeks, 687.3 patient years) and placebo (103.6 weeks, 684.2 patient years).

The highest dose of tirzepatide at any time during the study ranged from 2.5 to 15 mg. Overall, 77.2% of the participants took 15 mg of tirzepatide as the highest dose.

The duration of exposure is summarised in the following tables.

Table 32. Summary of Duration on Study; Randomized Population; I8F-MC-GPID

	TZP MTD	Placebo	Total
Patient weeks of follow-up Number of participants	364	367	731
Mean weeks of follow-up	98.5	97.3	97.9
SD	33.41	34.42	33.90
Minimum	8.6	4.1	4.1
Q1	67.2	66.0	66.1
Median	104.1	103.6	104.0
Q3	127.1	125.1	126.0
Maximum	158.6	160.3	160.3
Total patient-year	687.3	684.2	1371.5

Table 33. Summary of Duration on Study Treatment Safety Population Study I8F-MC-GPID

Duration of exposure	TZP MTD (N=364) n (%)	Placebo (N=367) n (%)	Total (N=731) n (%)
> 0 week	364 (100.0)	367 (100.0)	731 (100.0)
>= 4 weeks	360 (98.9)	363 (98.9)	723 (98.9)
>= 8 weeks	354 (97.3)	356 (97.0)	710 (97.1)
>= 12 weeks	345 (94.8)	352 (95.9)	697 (95.3)
>= 16 weeks	335 (92.0)	338 (92.1)	673 (92.1)
>= 20 weeks	330 (90.7)	336 (91.6)	666 (91.1)
>= 24 weeks	323 (88.7)	332 (90.5)	655 (89.6)
>= 32 weeks	313 (86.0)	327 (89.1)	640 (87.6)
>= 40 weeks	303 (83.2)	321 (87.5)	624 (85.4)
>= 48 weeks	298 (81.9)	313 (85.3)	611 (83.6)
>= 52 weeks	291 (79.9)	305 (83.1)	596 (81.5)
>= 65 weeks	239 (65.7)	245 (66.8)	484 (66.2)
>= 78 weeks	209 (57.4)	218 (59.4)	427 (58.4)
>= 91 weeks	180 (49.5)	191 (52.0)	371 (50.8)
>= 104 weeks	150 (41.2)	153 (41.7)	303 (41.5)
>= 117 weeks	104 (28.6)	100 (27.2)	204 (27.9)
>= 130 weeks	66 (18.1)	56 (15.3)	122 (16.7)
>= 143 weeks	16 (4.4)	17 (4.6)	33 (4.5)
>= 156 weeks	3 (0.8)	4 (1.1)	7 (1.0)

Adverse events

Overall, a higher percentage of patients experienced at least one AE in the TZP group compared to the placebo group of the SUMMIT study. This imbalance was mainly driven by gastrointestinal (GI) events. Also, a markedly higher percentage of patients discontinued treatment due to AE in the TZP than in the placebo group. Reassuringly, the percentage of patients with at least one serious AE (SAE) was fairly balanced between TZP and placebo. However, fatal events were numerically more frequent in the TZP than in the placebo group. This is further discussed in the section on deaths and SAEs. For details on AE frequency, see the following two tables.

Table 34. Overview of Adverse Events; Safety Population

Category[a]	SUMMIT Study Safety Population		
	Tirzepatide (N = 364) n (%)	Placebo (N = 367) n (%)	Tirzepatide vs. Placebo p-value[b]
Deaths[c]	19 (5.2)	15 (4.1)	0.488
SAEs	96 (26.4)	94 (25.6)	0.866
Discontinuation from study due to AE	20 (5.5)	15 (4.1)	0.392
Discontinuation from study drug due to AE	39 (10.7)	16 (4.4)	0.001
TEAEs	313 (86.0)	279 (76.0)	<0.001

Abbreviations: AE = adverse event; CSR = clinical study report; n = number of participants with at least 1 AE per event type; N = number of participants in the treatment group; SAE = serious adverse event; TEAE = treatment-emergent adverse event; vs. = versus.
a Participants may be counted in more than 1 category.
b p-values for overall treatment effect were computed using Fisher's Exact test.
c Deaths are also included as SAEs and discontinuations due to AEs.

Table 35. Summary and Analysis of TEAEs Occurring in ≥5% of Participants in Any Treatment Group; Preferred Term by Decreasing Frequency in Tirzepatide Arm; Safety Population

Preferred Term	Tirzepatide (N = 364) n (%)	Placebo (N = 367) n (%)	Tirzepatide vs. Placebo p-value[a]
Diarrhoea	67 (18.4)	23 (6.3)	<.001
Nausea	62 (17.0)	24 (6.5)	<.001
Constipation	54 (14.8)	22 (6.0)	<.001
Decreased appetite	38 (10.4)	6 (1.6)	<.001
Vomiting	38 (10.4)	8 (2.2)	<.001
Urinary tract infection	36 (9.9)	22 (6.0)	0.056
COVID-19	34 (9.3)	41 (11.2)	0.465
Dizziness	34 (9.3)	18 (4.9)	0.021
Atrial fibrillation	23 (6.3)	12 (3.3)	0.058
Dyspepsia	23 (6.3)	8 (2.2)	0.006
Hypotension	22 (6.0)	11 (3.0)	0.051
Cardiac failure	21 (5.8)	32 (8.7)	0.153
Abdominal pain upper	20 (5.5)	7 (1.9)	0.011
Anaemia	19 (5.2)	18 (4.9)	0.868

Abbreviations: CSR = clinical study report; n = number of participants with at least 1 TEAE; N = number of participants in treatment group; TEAE = treatment-emergent adverse event; vs. = versus.
a p-values for overall treatment effect were computed using Fisher's Exact test.

Treatment differences in less frequently reported TEAEs by SOC and PT:

In addition to the most frequently reported TEAEs, treatment imbalances between tirzepatide and placebo (p-value <0.05 or odds ratio ≥2; tirzepatide count ≥4) were observed for the following TEAEs (individual PTs) reported by at least 1% before rounding in any treatment group. Again, GI events dominated. Of the non-GI events, selected ones are further discussed in the section on AEs of special interest (AESIs). Other types of AEs may be related to the decreased appetite with TZP and consecutive reduced food and water intake. Examples are dehydration, vitamin D deficiency and iron deficiency. Alopecia was discussed previously as related to weight loss.

- *Gastrointestinal disorders*
  - *Abdominal Pain* (tirzepatide, 3.0%; placebo, 0.8%)

    - *Gastroesophageal reflux disease* (tirzepatide, 3.0%; placebo, 0.8%)
    - *Colitis* (tirzepatide, 2.5%; placebo, 0.3%)
    - *Eructation* (tirzepatide, 2.5%; placebo, 0%)
    - *Impaired gastric emptying* (tirzepatide, 1.4%; placebo, 0%)
    - *Abdominal discomfort* (tirzepatide, 2.5%; placebo, 0.8%)
    - *Gastritis* (tirzepatide, 2.5%; placebo, 0.8%)
    - *Flatulence* (tirzepatide, 2.2%; placebo, 0.5%)
    - *Hemorrhoids* (tirzepatide, 1.9%; placebo, 0.8%)
    - *Large intestine polyp* (tirzepatide, 1.1%; placebo, 0.3%)
- *General disorders and administration site conditions*
    - *Injection site reactions* (tirzepatide, 3.8%; placebo, 0.5%)
    - *Asthenia* (tirzepatide, 3.6%; placebo, 1.4%)
- *Investigations*
    - *Weight decreased* (tirzepatide, 4.9%; placebo, 1.4%)
    - *Lipase increased* (tirzepatide, 4.1%; placebo, 0.8%)
    - *Amylase increased* (tirzepatide, 2.2%; placebo, 0.3%)
    - *Pancreatic enzymes increased* (tirzepatide, 1.4%; placebo, 0.3%)
    - *Blood calcitonin increased* (tirzepatide, 1.1%; placebo, 0.5%)
- *Metabolism and nutrition disorders*
    - *Hyponatremia* (tirzepatide, 1.6%; placebo, 0.8%)
    - *Vitamin D deficiency* (tirzepatide, 1.6%; placebo, 0.5%)
    - *Dehydration* (tirzepatide, 1.4%; placebo, 0.5%)
- *Nervous system disorders*
    - *Syncope* (tirzepatide, 1.4%; placebo, 0.5%)
    - *Diabetic neuropathy* (tirzepatide, 1.1%; placebo, 0.3%)
- *Cardiac Disorders*
    - *Acute myocardial infarction* (tirzepatide, 1.9%; placebo, 0.5%)
- *Vascular Disorders*
    - *Orthostatic hypotension* (tirzepatide, 1.6%; placebo, 0.3%)
- *Injury, poisoning and procedural complications*
    - *Fall* (tirzepatide, 3.3%; placebo, 1.6%)
    - *Skin laceration* (tirzepatide, 1.1%; placebo, 0.5%)
- *Hepatobiliary Disorders*
    - *Cholelithiasis* (tirzepatide, 2.5%; placebo, 1.1%)
- *Infections and Infestations*
    - *Herpes zoster* (tirzepatide, 1.6%; placebo, 0.5%)
    - *Pharyngotonsillitis* (tirzepatide, 1.1%; placebo, 0.3%)
- *Psychiatric disorders*
    - *Depression* (tirzepatide, 1.4%; placebo, 0.5%)
- *Skin and subcutaneous tissue disorders*
    - *Alopecia* (tirzepatide, 1.1%; placebo, 0.3%)
- *Blood and lymphatic system disorders*
    - *Iron deficiency anemia* (tirzepatide, 1.1%; placebo, 0.3%)
    - *Leukocytosis* (tirzepatide, 1.1%; placebo, 0.3%)
- *Ear and labyrinth disorders*
    - *Vertigo* (tirzepatide, 1.1%; placebo, 0.5%)

AEs of special interest (AESIs)

Several safety topics were selected for closer examination based on the known safety profile and pharmacological actions of GLP-1 receptor agonists (GLP-1RAs):

- Exocrine pancreas safety
- Gastrointestinal adverse events
- Hepatobiliary disorders
- Hypoglycemia

- Immunogenicity
- Hypersensitivity reactions
- Injection site reactions
- Cardiovascular safety
- Renal safety
- Orthostatic hypotension
- Thyroid safety
- Major depressive disorder / Suicidal ideation or behaviour
- Malignancy

Topics for which no events were reported are not further discussed in the following.

Pancreatitis

An independent clinical endpoint committee (CEC) for adjudication of potential pancreatitis case was established in the SUMMIT study. Criteria for sending cases for adjudication were intentionally broad to capture all potential cases of pancreatitis. These were:

- all suspected cases of acute or chronic pancreatitis, and
- AEs of severe or serious abdominal pain of unknown aetiology.

The results are tabulated below. There were more patients with investigator-reported as well as with CEC-confirmed pancreatitis in the TZP than in the placebo group. However, reassuringly, the absolute number of patients and events was low (three confirmed events in 3 patients, 0.8%).

Table 36. Summary of Investigator-Reported and Adjudicated Pancreatic Events – AESI; Safety Population

Events	**Tirzepatide (N = 364) n (%); Events**	**Placebo (N = 367) n (%); Events**
Investigator-reported events	8 (2.2), 9	2 (0.5), 2
CEC pancreatitis assessment		
No	5 (1.4); 6	2 (0.5); 2
Unknown (unable to determine)	0	0
Yes	3 (0.8); 3	0
Acute pancreatitis	3 (0.8); 3	0
Chronic pancreatitis	0	0
Diagnostic criteria used to confirm acute pancreatitis		
Symptoms and imaging	1 (0.3); 1	0
Symptoms and elevated enzymes	2 (0.5); 2	0
Imaging and asymptomatic elevated enzymes	0	0
Symptoms, imaging, and elevated enzymes	0	0

Abbreviations: AESI = adverse event of special interest; CEC = clinical endpoint committee; CSR = clinical study report; n = number of participants with at least 1 pancreatic event; N = total number of participants in the specified treatment group.

It is known from GLP-1 receptor agonists (GLP-1 RAs) that they functionally increase serum lipase and amylase in the absence of pancreatitis. This was also observed in SUMMIT. The figures below show the time course of the serum level of these enzymes. As expected, an early increase after start of treatment becomes obvious with no major change thereafter.

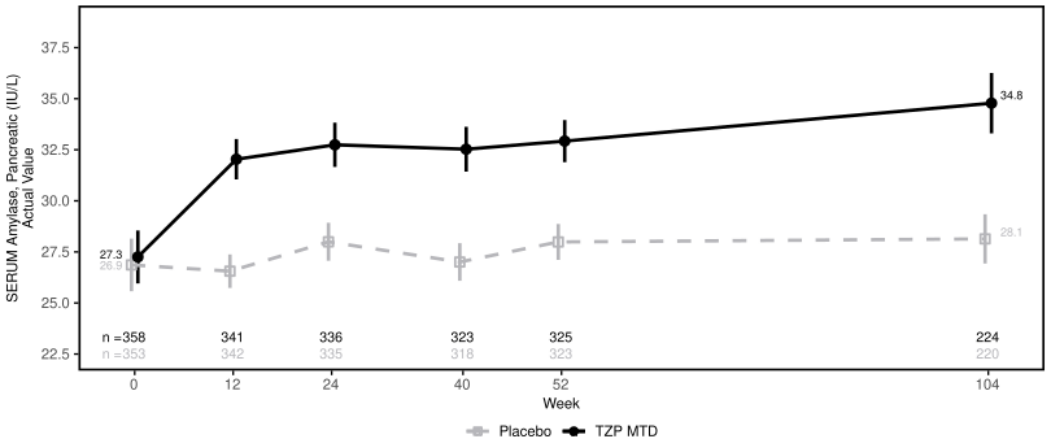


Figure 17
Variable Analysed: Actual Value of serum Amylase, Pancreatic (IU/L); Safety Population; Results are presented in LSMean +/- 1.96 SE.

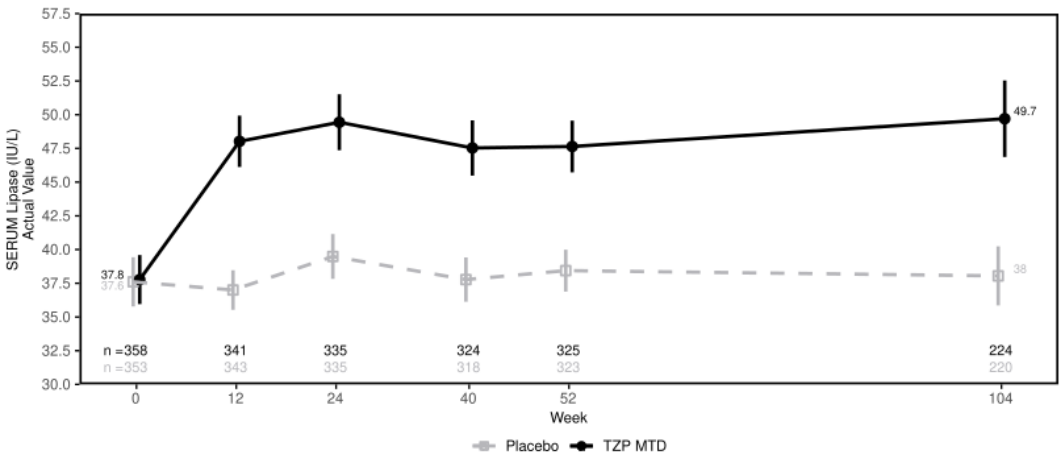


Figure 18
Variable Analysed: Actual Value of serum Lipase (IU/L); Safety Population; Results are presented in LSMean +/- 1.96 SE.

Gastrointestinal Events

The following tables provide further information on kind, severity, seriousness and prevalence of GI events. The table below shows that the events were mostly mild or moderate in severity; 4.7% of participants in the TZP group experienced a severe GI event.

Table 37: Summary of TEAEs by Maximum Severity in the Gastrointestinal Disorders SOC; Safety Population

Maximum Severity[a]	**Tirzepatide N = 364 n (%)**	**Placebo N = 367 n (%)**
Participants with ≥1 GI TEAE	197 (54.1)	96 (26.2)
Mild	96 (26.4)	67 (18.3)
Moderate	84 (23.1)	24 (6.5)
Severe	17 (4.7)	5 (1.4)

The severe or serious GI events most often were nausea, diarrhoea, vomiting or upper abdominal pain; see table below.

Table 38. Summary of Treatment-Emergent Severe or Serious Gastrointestinal Events – AESI; Preferred Term by Decreasing Frequency in Tirzepatide Arm; Safety Population

Preferred Term	Tirzepatide N = 364 n (%)	Placebo N = 367 n (%)	Tirzepatide vs. Placebo p-value[a]
Participants with ≥1 severe/serious GI TEAE	21 (5.8)	9 (2.5)	0.026
Nausea	5 (1.4)	1 (0.3)	0.122
Diarrhoea	4 (1.1)	0	0.061
Vomiting	3 (0.8)	1 (0.3)	0.372
Abdominal pain upper	2 (0.5)	0	0.248
Obstructive pancreatitis	2 (0.5)	0	0.248
Acute abdomen	1 (0.3)	0	0.498
Colitis	1 (0.3)	0	0.498
Colitis ischemic	1 (0.3)	0	0.498
Diabetic gastroparesis	1 (0.3)	0	0.498
Dyspepsia	1 (0.3)	0	0.498
Incarcerated inguinal hernia	1 (0.3)	0	0.498
Inguinal hernia	1 (0.3)	0	0.498
Intestinal ischemia	1 (0.3)	0	0.498
Intestinal obstruction	1 (0.3)	0	0.498
Intestinal perforation	1 (0.3)	0	0.498
Large intestine polyp	1 (0.3)	0	0.498
Melaena	1 (0.3)	0	0.498
Pancreatitis acute	1 (0.3)	0	0.498
Peptic ulcer haemorrhage	1 (0.3)	0	0.498
Pneumoperitoneum	1 (0.3)	0	0.498
Upper gastrointestinal haemorrhage	1 (0.3)	2 (0.5)	>.999
Varices oesophageal	1 (0.3)	0	0.498
Ascites	0	1 (0.3)	>.999
Gastric ulcer	0	1 (0.3)	>.999

As expected from previous experience with TZP or other GLP-1RAs, GI events were most frequent after start of treatment, in the dose up-titration phase. As shown in the following table, prevalence of GI symptoms was highest between Week 4 and Week 8 of treatment with 13.7% of participants experiencing a GI condition. After Week 20, the prevalence was lower, between 5 and 8 per cent. For details, see table 39.

Table 39. Prevalence of Treatment-Emergent Nausea, Diarrhoea, and Vomiting by Treatment over Time; Safety Population Study I8F-MC-GPID

Nausea / Diarrhoea / Vomiting Time Point	% of Participants	
	Tirzepatide (N = 364)	Placebo (N = 367)
0 < Weeks ≤4	10.16	4.63
4 < Weeks ≤8	13.74	3.81
8 < Weeks ≤12	10.44	2.73
12 < Weeks ≤16	9.37	2.74
16 < Weeks ≤20	9.80	2.22
20 < Weeks ≤24	8.68	2.51
24 < Weeks ≤32	7.56	2.25
32 < Weeks ≤40	5.35	1.13
40 < Weeks ≤48	7.10	0.85
48 < Weeks ≤52	5.70	1.14
52 < Weeks ≤78	7.96	3.01
78 < Weeks ≤104	7.06	2.80
104 < Weeks ≤ End of treatment	3.83	2.21
After the 1st dose	33.79	11.99

Permanent discontinuation of study drug due to GI events:

The SOC of Gastrointestinal disorders was the most common AE class leading to discontinuation of the study drug. More participants in the tirzepatide group than the placebo group discontinued study drug due to a GI event:

- tirzepatide: 4.1%, and
- placebo: 0%.

The most frequently reported GI PTs leading to permanent discontinuation of study drug in the tirzepatide group were

- Constipation (0.8%)
- Diarrhoea (0.5%)
- Dyspepsia (0.5%), and
- Vomiting (0.5%).

Hepatic events

The following diagram provides an overview of the liver parameters in serum for each individual study participant. The results are shown as transaminase level vs. bilirubin level. Three subjects showed a constellation fulfilling Hy's law. Two of them were from the placebo group. Thus, there is no hint for TZP-induced liver injury.

Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs ALT or AST); Safety Population.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of participants with a post-baseline ALT/AST and a post-baseline TBL; TBL = total bilirubin
Points do not necessarily represent values from the same blood draw.
Subjects are only included if they have non-missing post-baseline values for both TBL and ALT/AST.

Gallbladder-Related Disorders

More subjects in the TZP than in the placebo group experienced an acute gallbladder event (4.4% TZP vs. 2.7% placebo). Most of the vents were cholelithiasis or acute cholecystitis. It is known from previous experience that GLP-1RAs can increase the risk for gallbladder disease.

A total of 8 (2.2%) tirzepatide-treated participants and 5 (1.4%) placebo-treated participants reported **serious or severe** gallbladder-related events in the SUMMIT study.

Table 40. Summary of Treatment-Emergent Acute Gallbladder Disease; MedDRA Preferred Term by Decreasing Frequency within SMQ Classification; Safety Population

SMQ Scope Preferred Term	**Tirzepatide (N = 364) n (%)**	**Placebo (N = 367) n (%)**
Subjects with >=1 TEAE of *Acute gallbladder disease* PT	16 (4.4)	10 (2.7)
Subjects with >=1 *Biliary tract disorders* (SMQ) PT	3 (0.8)	4 (1.1)
Narrow	3 (0.8)	4 (1.1)
Obstructive pancreatitis	2 (0.5)	0
Biliary colic	1 (0.3)	2 (0.5)
Hyperbilirubinemia	1 (0.3)	2 (0.5)
Subjects with >=1 *Gallbladder-related disorders* (SMQ) PT	16 (4.4)	8 (2.2)
Narrow	16 (4.4)	8 (2.2)
Cholelithiasis	9 (2.5)	4 (1.1)
Cholecystitis acute	7 (1.9)	4 (1.1)
Cholecystitis	2 (0.5)	0
Biliary colic	1 (0.3)	2 (0.5)
Cholecystectomy	1 (0.3)	0
Cholecystitis chronic	1 (0.3)	0
Subjects with >=1 *Gallstone related disorders* (SMQ) PT	10 (2.7)	4 (1.1)
Narrow	10 (2.7)	4 (1.1)
Cholelithiasis	9 (2.5)	4 (1.1)
Obstructive pancreatitis	2 (0.5)	0

The MAH examined the possibility that gallbladder disease could be related to weight loss instead of being related to TZP itself. Therefore, the MAH provided a listing of gallbladder events by the degree of weight loss, see table below. Due to the low number of events, firm conclusions are not possible.

Table 41. Summary of Treatment-Emergent Acute Gallbladder Disease by Maximum Weight Reduction Categories; Safety Population

Maximum Weight Reduction Category	**Participants**		**Any TEAE of Acute Gallbladder Disease**		**Cholelithiasis**		**Cholecystitis Event[a]**	
	Tirzepatide n	**Placebo n**	**Tirzepatide m (%)**	**Placebo m (%)**	**Tirzepatide m (%)**	**Placebo m (%)**	**Tirzepatide m (%)**	**Placebo m (%)**
Weight gain	6	34	0	0	0	0	0	0
Weight loss								
≥0% to <10%	76	282	3 (3.9)	6 (2.1)	1 (1.3)	3 (1.1)	3 (3.9)	1 (0.4)
≥10% to <20%	149	41	4 (2.7)	4 (9.8)	3 (2.0)	1 (2.4)	2 (1.3)	3 (7.3)
≥20% to ≤30%	101	5	8 (7.9)	0	4 (4.0)	0	4 (4.0)	0
>30%	32	1	1 (3.1)	0	1 (3.1)	0	0	0

Hypoglycaemia

A total of 16 (2.2%) participants experienced at least 1 hypoglycaemic event with BG less than 54 mg/dL or severe hypoglycaemia during the study. The incidence of hypoglycaemia events was higher in the tirzepatide group than in the placebo group. A total of

- 11 (3.0%) in the tirzepatide group (aggregated rate per year: 0.05), and
- 5 (1.4%) in the placebo group (aggregated rate per year: 0.02).

All participants with an event of hypoglycaemia had a history of known T2D.

Depression and suicidal ideation

Participants were excluded from the SUMMIT study if they had a history of any condition such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.

The TEAEs of MDD or suicidal ideation or behaviour were identified using MedDRA PTs from SMQs narrow scope:

- Suicide/self-injury (20000037), and
- Depression, excluding suicide and self-injury (20000167).

No events of severe or serious MDD or suicidal ideation or behaviour were reported. A total of 8 (tirzepatide, 6 [1.6%]; placebo, 2 [0.5%]) participants reported at least 1 TEAE of MDD events in the SUMMIT study safety population, see table below.

Table 42. Summary of Treatment-Emergent Major Depressive Disorder/Suicidal Ideation Events; Preferred Term by Decreasing Frequency in Tirzepatide Arm within SMQ Classification; Safety Population

SMQ **Scope** **Preferred Term**	**Tirzepatide** **(N = 364)** **n (%)**	**Placebo** **(N = 367)** **n (%)**
Participants with ≥1 TEAE	6 (1.6)	2 (0.5)
Depression (excl suicide and self-injury)	6 (1.6)	2 (0.5)
Narrow	6 (1.6)	2 (0.5)
Depression	5 (1.4)	2 (0.5)
Persistent depressive disorder	1 (0.3)	0

Abbreviations: CSR = clinical study report; n = number of participants with event; N = number of participants in population; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event.

Atrial fibrillation and other cardiac conduction disorders

Supraventricular tachyarrhythmias were more frequently reported as an AE in the TZP than in the placebo group (6.6% TZP vs. 3.8% placebo). For further details on AEs related to cardiac conduction see table 43.

Table 43. Summary of Treatment-Emergent Arrhythmias and Cardiac Conduction Disorders. Preferred Term by Decreasing Frequency in Tirzepatide Group within SMQ Classification. Safety Population Study I8F-MC-GPID

Event Category or Term	**n (%)**	
	Tirzepatide (N = 364)	**Placebo (N = 367)**
Participants with ≥1 TEAE of arrythmias and cardiac conduction disorder	42 (11.5)	30 (8.2)
Arrhythmia related investigations, signs and symptoms SMQ	17 (4.7)	12 (3.3)

Broad	16 (4.4)	12 (3.3)
Palpitations	5 (1.4)	4 (1.1)
Syncope	5 (1.4)	2 (0.5)
Bradycardia	3 (0.8)	2 (0.5)
Sudden death	2 (0.5)	0
Cardiac arrest	1 (0.3)	0
Cardio-respiratory arrest	1 (0.3)	2 (0.5)
Tachycardia	1 (0.3)	0
Electrocardiogram change	0	1 (0.3)
Heart rate increased	0	1 (0.3)
Narrow	1 (0.3)	0 (0.0)
Sudden cardiac death	1 (0.3)	0
Supraventricular Tachyarrhythmias SMQ	***24 (6.6)***	***14 (3.8)***
Narrow	24 (6.6)	14 (3.8)
Atrial fibrillation	23 (6.3)	12 (3.3)
Atrial flutter	1 (0.3)	1 (0.3)
Atrial tachycardia	1 (0.3)	0
Supraventricular tachycardia	1 (0.3)	1 (0.3)
Tachyarrhythmia terms, nonspecific (SMQ)	0 (0.0)	1 (0.3)
Narrow	0 (0.0)	1 (0.3)
Tachyarrhythmia	0	1 (0.3)
Ventricular tachyarrhythmias (SMQ)	2 (0.5)	3 (0.8)
Narrow	2 (0.5)	3 (0.8)
Ventricular fibrillation	1 (0.3)	0 (0.0)
Ventricular tachycardia	1 (0.3)	1 (0.3)
Ventricular extrasystoles	0	2 (0.5)
Conduction defects (SMQ)	2 (0.5)	2 (0.5)
Narrow	2 (0.5)	2 (0.5)
Atrioventricular block first degree	1 (0.3)	0
Paroxysmal atrioventricular block	1 (0.3)	0
Atrioventricular block complete	0	1 (0.3)
Bundle branch block right	0	1 (0.3)
Cardiac conduction disorders (HLT)	2 (0.5)	2 (0.5)

SMQ = standardized MedDRA query

The MAH also performed an analysis of atrial fibrillation (AF) independent from AE reporting. The results are shown in the following table and indicate that there was no difference between TZP and placebo. In both groups, around 13 % of participants presented with AF. At baseline, the percentage was slightly higher (15% in the TZP group and 17% in the placebo group)

Table 44. Summary and Analysis of Participants with Atrial Fibrillation Status Logistic Regression by Treatment at 52 Weeks; Randomized Population Study I8F-MC-GPID

Time point				Proportion estimate *b*c	Estimate of the difference in proportions (95% CI) *b*c	Odds Ratio (95% CI) (Treatment/Control) *b*c	Between treatment p-value *b*c
Treatment	N*a	n*a	(%)*a				
Baseline							
TZP MTD	349	53	15.19	15.03	-2.29 (-7.68, 3.10)	0.87 (0.58, 1.30)	0.485
Placebo	344	59	17.15	17.32			
Week 52 (Visit 12)							
TZP MTD	335	45	13.43	13.30	-0.03 (-5.13, 5.06)	1.30 (0.67, 2.54)	0.437
Placebo	326	43	13.19	13.33			

Abbreviations: BMI = body mass index; CI = confidence interval; HF = heart failure; N = number of participants with baseline value and observed value at the specified timepoint; n = number of participants with atrial fibrillation at the specified endpoint; T2DM = type 2 diabetes mellitus; TZP MTD = tirzepatide maximum tolerated dose.

Notably, the listing of baseline characteristics (see next table) revealed a much higher percentage of AF at baseline, around 25%. Therefore, the above AF analysis appears incomplete. One problem was that not for every patient post-baseline AF results were available.

Overall, 186 (25.4%) participants had atrial fibrillation at baseline, 95 (26.1%) in the TZP group and 91 (24.8%) in the placebo group; see table below.

Table 45 (shortened). Summary of Selected Baseline Clinical Characteristics Randomized Population

Attribute	Tirzepatide (N = 364)	Placebo (N = 367)	Total (N = 731)
Atrial fibrillation[a], n (%)			
No	269 (73.9)	276 (75.2)	545 (74.6)
Yes	95 (26.1)	91 (24.8)	186 (25.4)

Additionally, the MAH performed an analysis of atrial fibrillation in the tirzepatide programmes.

In larger tirzepatide datasets, there is no indication of an imbalance in atrial fibrillation (Table 4). For example, in the overall clinical safety database (excluding Study SUMMIT and Study SURPASS-CVOT), treatment-emergent adverse events of atrial fibrillation were reported in 0.5% of tirzepatide-exposed participants and 0.4% of participants in comparator groups. In Study SURPASS-CVOT, treatment-emergent adverse events of atrial fibrillation were similar for tirzepatide and dulaglutide in both the overall population and in the subpopulation with HF history. As recently reported by Lin et al. (2025), real-world evidence data also suggest a similar risk of atrial fibrillation in subjects with HFpEF in both the tirzepatide and control groups (HR: 0.98; 95% CI: 0.91 – 1.04).

Data from 6 studies with GLP-1 RA in T2D populations showed no significant difference between GLP-1 RA and placebo regarding the incidence of atrial fibrillation reported as a serious adverse event (relative risk: 0.93; 95% CI: 0.70, 1.23) (Hamedi et al. 2021). Additionally, the data observed with semaglutide in patients with HFpEF and obesity indicated that new-onset atrial fibrillation was notably uncommon (Verma et al. 2024).

Table 46. Summary and Analysis of Serious Adverse Events and Treatment-Emergent Adverse Events of Atrial Fibrillation in Tirzepatide Programmes

Population	Events Analysed	Comparator	Tirzepatide		Comparator		Risk Difference a (95% CI)
			N	n (%)	N	n (%)	
Safety population in tirzepatide programmes b excluding Study SUMMIT	TEAEs	Pooled comparator c	9649	49 (0.5)	4898	19 (0.4)	0.24 (0.01, 0.46)

Safety population in tirzepatide programmes b excluding Study SUMMIT	SAEs	Pooled comparator c	9649	12 (0.1)	4898	5 (0.1)	0.05 (-0.06, 0.17)
Study SURPASS-CVOT safety population	TEAEs	Dulaglutide 1.5 mg QW	6647	202 (3.0)	6647	229 (3.4)	-0.41 (-1.01, 0.20)
Study SURPASS-CVOT safety population	SAEs	Dulaglutide 1.5 mg QW	6647	59 (0.9)	6647	58 (0.9)	0.02 (-0.30, 0.33)
Study SURPASS-CVOT safety population with HF history	TEAEs	Dulaglutide 1.5 mg QW	1325	73 (5.5)	1379	70 (5.1)	0.43 (-1.26, 2.12)
Study SURPASS-CVOT safety population with HF history	SAEs	Dulaglutide 1.5 mg QW	1325	23 (1.7)	1379	19 (1.4)	0.36 (-0.58, 1.29)

Abbreviations: CI = confidence interval; CWM = chronic weight management; CVOT = cardiovascular outcomes trial; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; n = number of participants with events meeting specified criteria; N = number of participants in the analysis population; OSA = obstructive sleep apnoea; QW = once weekly; SAE = serious adverse event; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

[a] Risk difference and 95% CI were calculated as tirzepatide - comparator.

[b] Tirzepatide programmes included studies for T2DM, CWM, HFpEF, OSA: GPGB, GPGH, GPGI, GPGK, GPGL, GPGM, GPGO, GPHD, GPHK, GPHL, GPHM, GPHO, GPHZ, GPIA, GPID (SUMMIT), and GPIF.

[c] Pooled comparator included dulaglutide 0.75 mg, dulaglutide 1.5 mg, insulin degludec, insulin glargine, lispro, placebo, and semaglutide 1 mg.

MACE

The MAH provided a MACE analysis, consisting of MI, cerebrovascular event, hospitalisation for unstable angina and coronary intervention. With this MACE definition, the events were numerically less frequent in the TZP than in the placebo group. However, besides the untypical definition of MACE, the number of events was too low for meaningful conclusions. Statistical significance was not reached.

Table 47. Summary of Composite MACE and its component (Investigator Reported and CEC Confirmed) Safety Population Study I8F-MC-GPID

	TZP MTD N=364 n(%)*a	**Placebo** N=367 n(%)*[a]	**HR (95% CI)*[a]**	**p-value*[b]**
MACE	14 (3.8)	20 (5.4)	0.69 (0.35, 1.37)	0.292
MI	6 (1.6)	3 (0.8)	NE	
Hospitalization for Unstable Angina	3 (0.8)	7 (1.9)	0.43 (0.11, 1.65)	
Coronary Interventions	5 (1.4)	7 (1.9)	0.71 (0.23, 2.24)	
CABG	1 (0.3)	0 (0.0)	NE	
PCI	5 (1.4)	7 (1.9)	0.71 (0.22, 2.23)	
Cerebrovascular Events	3 (0.8)	6 (1.6)	NE	
Stroke	3 (0.8)	3 (0.8)	NE	
TIA	0 (0.0)	3 (0.8)	NE	

*[a] Hazard ratio, and two-sided 95% CI for comparing combined tirzepatide arm versus placebo from Cox Proportional Hazards model.
*[b] P-value is from a Cox Proportional Hazards model: response = tirzepatide arm. When the total number of outcomes is < 10, Fisher's Exact Test is used to compare treatment groups, and Hazard Ratio is not calculated
NE = not evaluable

Renal safety

Evaluation of kidney-related AEs did not provide a hint for adverse effects of TZP towards the kidney. Glomerular filtration rate (GFR) was estimated (yielding eGFR) from serum creatinine using the CKD-EPI formula). In the placebo group, there was a slight numerical decrease in eGFR over time, and this decrease was largely prevented by TZP. At Week 52, LS mean difference between TZP and placebo in change from baseline in eGFR was 1.85 mL/min/1.73 m^2, and at Week 104 it was virtually the same (1.84 mL/min/1.73 m^2; the mean decrease from baseline in the TZP group was 0.29 mL/min/1.73 m^2 and in the placebo group 2.59 mL/min/1.73 m^2; see table below. Thus, taken together, there are no hints for a renal safety concern of TZP.

Table 48.
Variable Analysed: serum Glomerular Filtration Rate Adj for BSA CKD-EPI calculation (mL/min/1.73 m^2)

		Actual Value		Change from Baseline		
Time Point / Treatment	n	Mean (SD)	LSMean (SE) [95% CI]	Mean (SD)	LSMean (SE) [95% CI]	Within treatment p-value
Week 104 (Visit 16)						
TZP MTD	224	66.9 (24.19)	64.8 (0.707) [63.4,66.2]	***-0.29*** (11.985)	-0.36 (0.707) [-1.75,1.03]	0.613
Placebo	220	63.4 (25.35)	62.9 (0.713) [61.5,64.3]	***-2.59*** (11.052)	-2.19 (0.713) [-3.59,-0.79]	0.002

Calcitonin

In rodents, GLP-1RAs lead to increased calcitonin secretion and consecutive hyperplasia of the parafollicular cells (C-cells) in the thyroid gland. Ultimately, C-cell adenomas or carcinomas can result. In humans, pure GLP-1RAs did not lead to an increase of serum calcitonin. In the original MAA of TZP (indications T2D and weight management), a slight increase in serum calcitonin in response to treatment became obvious. This was again observed in the SUMMIT study. As shown in the table below, the increase in serum calcitonin was most pronounced at Week 52 (4.17 ng/L with TZP vs. 3.73 ng/L with placebo).

Table 49 (shortened): Summary and Analysis of Calcitonin Using Conventional Units MMRM by Treatment and Visit from Baseline to Week 104 Using Log Transformation Safety Population Study I8F-MC-GPID; Variable Analysed: Actual Measurement of serum Calcitonin (ng/L)

Time Point Treatment	n	Mean (SD)
Baseline		
TZP MTD	346	3.61 (4.559)
Placebo	342	3.94 (5.084)
Week 52 (Visit 12)		
TZP MTD	321	4.17 (5.518)
Placebo	323	3.73 (4.658)
Week 104 (Visit 16)		
TZP MTD	226	3.74 (4.351)
Placebo	215	3.52 (4.246)

No instances of thyroid malignancies, including medullary thyroid cancer, were observed during the SUMMIT study.

Diabetic retinopathy

Two participants (**0.5%**) in the placebo group and 4 (**1.1%**) in the tirzepatide group experienced ≥1 TEAE of potential diabetic retinopathy complications during the study. Three of these participants had baseline fundus examination performed, none of whom had any pathology at baseline. None of the TEAEs of potential diabetic retinopathy complications were serious or severe.

Malignancy

The percentage of subjects reporting an event of malignancy or malignant tumour was balanced between TZP and placebo, see table below.

Table 50 (shortened): Summary of Treatment-Emergent Malignancies Preferred Term by Decreasing Frequency in Tirzepatide Group within SMQ Classification Safety Population Study I8F-MC-GPID

	TZP MTD (N=364)	Placebo (N=367)
TERM	n (%)	n (%)
Subjects with >=1 TEAE of Malignancies PT	10 (2.7)	9 (2.5)
Subjects with >=1 Malignant tumours (SMQ) PT	9 (2.5)	9 (2.5)

Orthostatic hypotension

Events of orthostatic hypotension were markedly more frequent (around two-fold) in the TZP than in the placebo group, and were also rather frequent in absolute terms (16% in the TZP group vs. 8% in the placebo group). As further described in the section of vital signs, TZP increased heart rate (HR) by around 2.8 bpm and decreased systolic blood pressure (SBP) by around 5 mmHg. Increase in HR is a known side-effect of GLP-1RAs. which can be accompanied by drop in SBP.

Table 51: Summary of Treatment-Emergent Hypotension, Orthostatic Hypotension, and Syncope MedDRA Preferred Term by Decreasing Frequency Safety Population Study I8F-MC-GPID

	TZP MTD (N=364)	Placebo (N=367)	p-values
Preferred Term	n (%)	n (%)	Overall*a
Subjects >=1 TEAE of Hypotension, Orthostatic Hypotension, and Syncope	60 (16.5)	30 (8.2)	<.001
Dizziness	34 (9.3)	18 (4.9)	0.021
Hypotension	22 (6.0)	11 (3.0)	0.051
Orthostatic hypotension	6 (1.6)	1 (0.3)	0.068
Syncope	5 (1.4)	2 (0.5)	0.285
Presyncope	1 (0.3)	1 (0.3)	>.999

Immunogenicity

Anti-drug antibodies (ADA) - binding

Method of ADA determination:

The antibody assay is the same as used for supporting the weight management indication. Test were performed to confirm that the assay cut-points used in the obesity population are also appropriate for the HFpEF population.

Definition of ADA status:

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

TE ADA+ participant: An evaluable participant who had a

- baseline status of ADA not present and at least 1 post-baseline status of ADA present with titre ≥2 × minimum required dilution (MRD), where the MRD is the minimum required dilution of the ADA assay, or
- baseline and post-baseline status of ADA present, with the post-baseline titre being 2 dilutions (4-fold) greater than the baseline titre. That is, the participant has baseline (B) status of ADA present, with titre 1:B, and at least 1 post-baseline (P) status of ADA present, with titre 1:P, with P/B ≥4.

A titre was expected when ADA assay result was detected. On occasion, the corresponding assay could not be performed, in which case a titre value was imputed for the purpose of TE ADA determination. A baseline sample with detected ADA and no titre, the titre was imputed to be the MRD, while a post-baseline sample with ADA detected and no titre, the titre was imputed to be one dilution above the MRD.

TE ADA inconclusive participant

- If at least 20% of the evaluable participant's post-baseline samples, drawn pre-dose, were ADA inconclusive and all remaining post-baseline samples were ADA not present.

TE ADA-negative (TE ADA-) participant

- If the evaluable participant was not TE ADA+ and not TE ADA inconclusive.

Incidence of ADA:

During the planned treatment period, 162 of 359 TE ADA-evaluable participants (45.1%) were

TE ADA+, of which

- 156 (43.5%) were classified as treatment-induced, and
- 6 (1.7%) were classified as treatment-boosted.

For further details, see table below.

Table 522: Summary of Treatment-Emergent Tirzepatide ADA Status During Planned Treatment Period; Safety Population

Category	Tirzepatide (N = 364) n (%)
Participants evaluable for TE ADA	359 [98.6]
Baseline ADA present	17 (4.7)
Postbaseline TE ADA+ (during the planned treatment period)	162 (45.1)
Postbaseline TE ADA inconclusive	0
Postbaseline TE ADA-	197 (54.9)

Time course:

Among the 162 TE ADA+ participants, 80.9% developed an ADA+ titre within 40 weeks, and 86.4% developed an ADA+ titre within 52 weeks.

ADA titres:

For most participants, the ADA titres were between 20 and 640, see Figure 19 below.

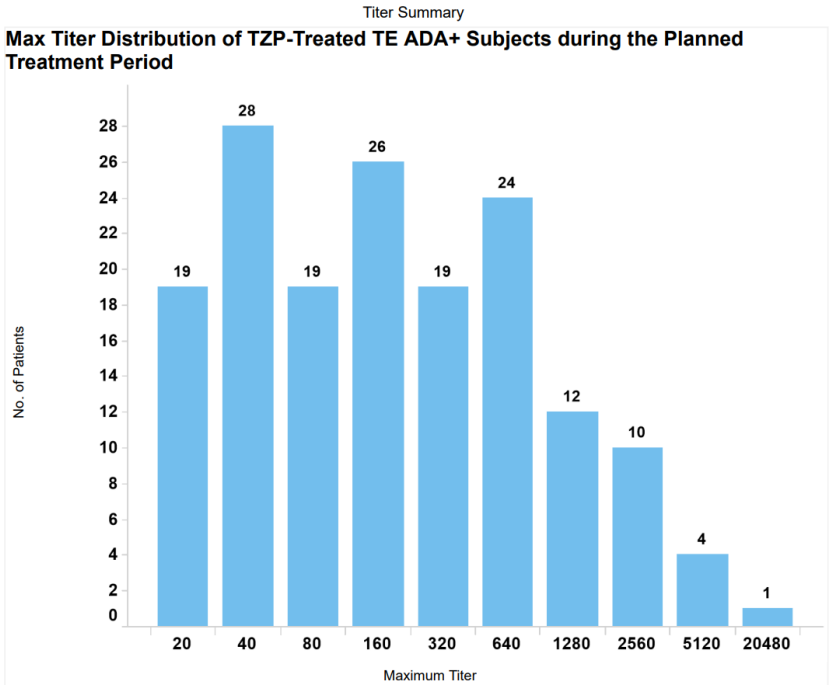


Figure 19. Maximum titer distribution of tirzepatide TE ADA+ participants during the planned treatment period.

Neutralising antibodies (Nab):

Method of Nab determination:

The antibody assay is the same as used for supporting the weight management indication. Test were performed to confirm that the assay cut-points used in the obesity population are also appropriate for the HFpEF population.

Results:

The following table lists the frequency of TE ADA+ patients who were found positive for 1) cross-reactive antibodies against native GIP and GLP-1; 2) neutralising antibodies against tirzepatide and; 3) by in-silico prediction, cross-reactive, neutralising antibodies against native GIP and GLP-1. The findings are similar to those made in the T2D and weight management studies.

Table 53. Summary of Cross-Reactive and Neutralizing Antibodies from Tirzepatide-Treated Participants with TE ADA; Safety Population, Excluding Sites in China

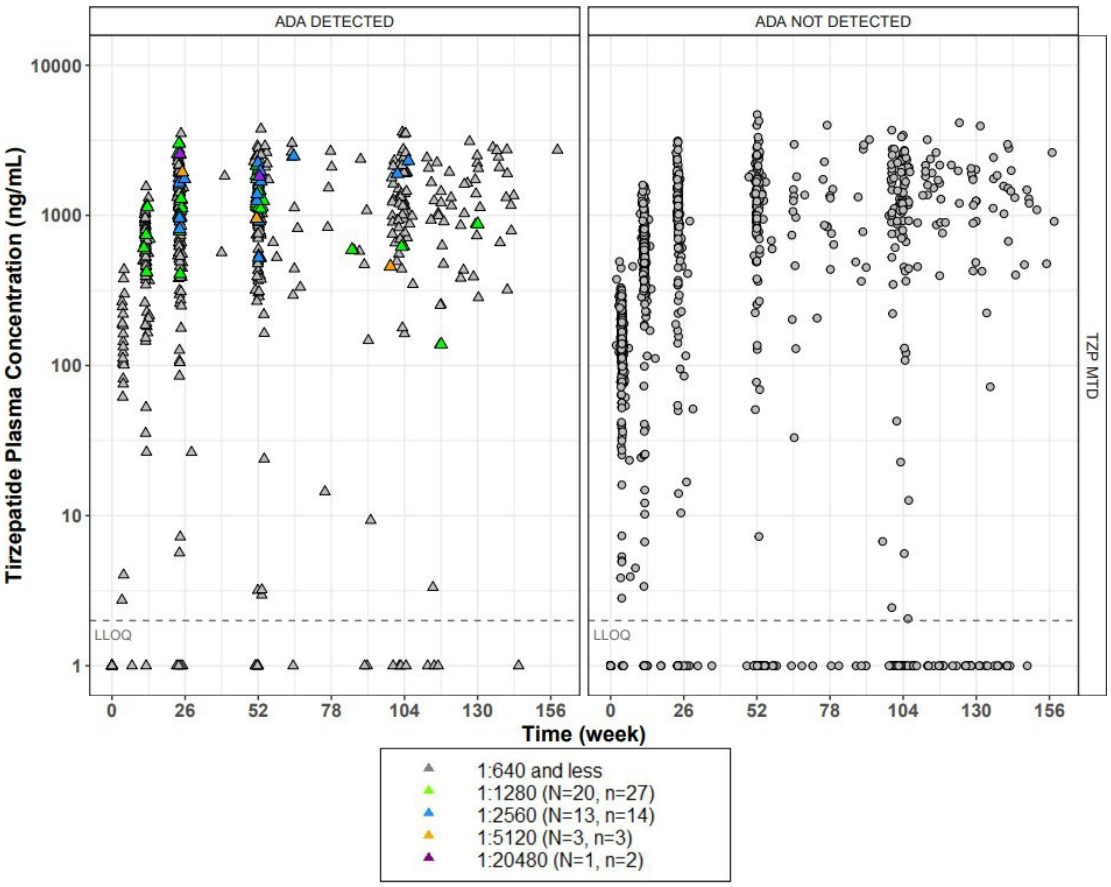
Category	TZP MTD (N=339) n (%)
Patients Postbaseline TE ADA+ *b	153 (45.8)
Neutralizing TZP for GIPR	10 (3.0)
Neutralizing TZP for GLP-1R	2 (0.6)
GIP Cross-Reactive	86 (25.7)
In Silico Neutralizing to Native GIP	4 (1.2)
GLP-1 Cross-Reactive	34 (10.2)
In Silico Neutralizing to Native GLP-1	1 (0.3)

Abbreviations: ADA = anti-drug antibodies; N = total number of participants in specified treatment group; n = number of participants in specified category; TE = treatment-emergent; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor; TZP = tirzepatide.
Note: Denominator for percent (%) is the total number of patients who are TE ADA Evaluable in the TZP treatment group (N=334).
*a A participant is TE ADA Evaluable if there is at least one non-missing test result for TZP ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of TE ADA Evaluable participants in the TZP treatment group.

*b A TE ADA Evaluable participant is considered to be TE ADA+ if the participant has at least one postbaseline titer that is a 4- fold or greater increase than titer from baseline measurement (treatment boosted). If baseline result is ADA NOT Present, then the participant is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= (treatment-induced).

Effect of antibodies on PK:

No relevant effect of ADA on PK of TZP was detected, see Figure 20.



Abbreviations: ADA = anti-drug antibodies; BQL = below quantifiable limit; LLOQ = lower limit of quantitation; MTD = maximum tolerated dose; n = number of observations; N = number of participants; TZP = tirzepatide.
Note: BQL samples were assigned a value of LLOQ/2 to be included in the figure.

Figure 20. Comparison of observed tirzepatide concentrations from participants with detectable (left panel) and nondetectable (right panel) tirzepatide ADA titers in the SUMMIT study.

Effect of antibodies on efficacy:

The figure 21 presents the Kaplan-Meier curve showing time-to-first occurrence of adjudication-confirmed HF event and CV death. Comparison of the Kaplan-Meier estimates of time-to-composite endpoint (CV death or HF event) showed no impact of TE ADA status on the risk of developing CV death or HF event.

Visual assessment of time-to-first occurrence of any component of CV death or HF event suggests the presence of ADA is not associated with loss of efficacy of tirzepatide. TE-ADA+ patients had numerically less events.

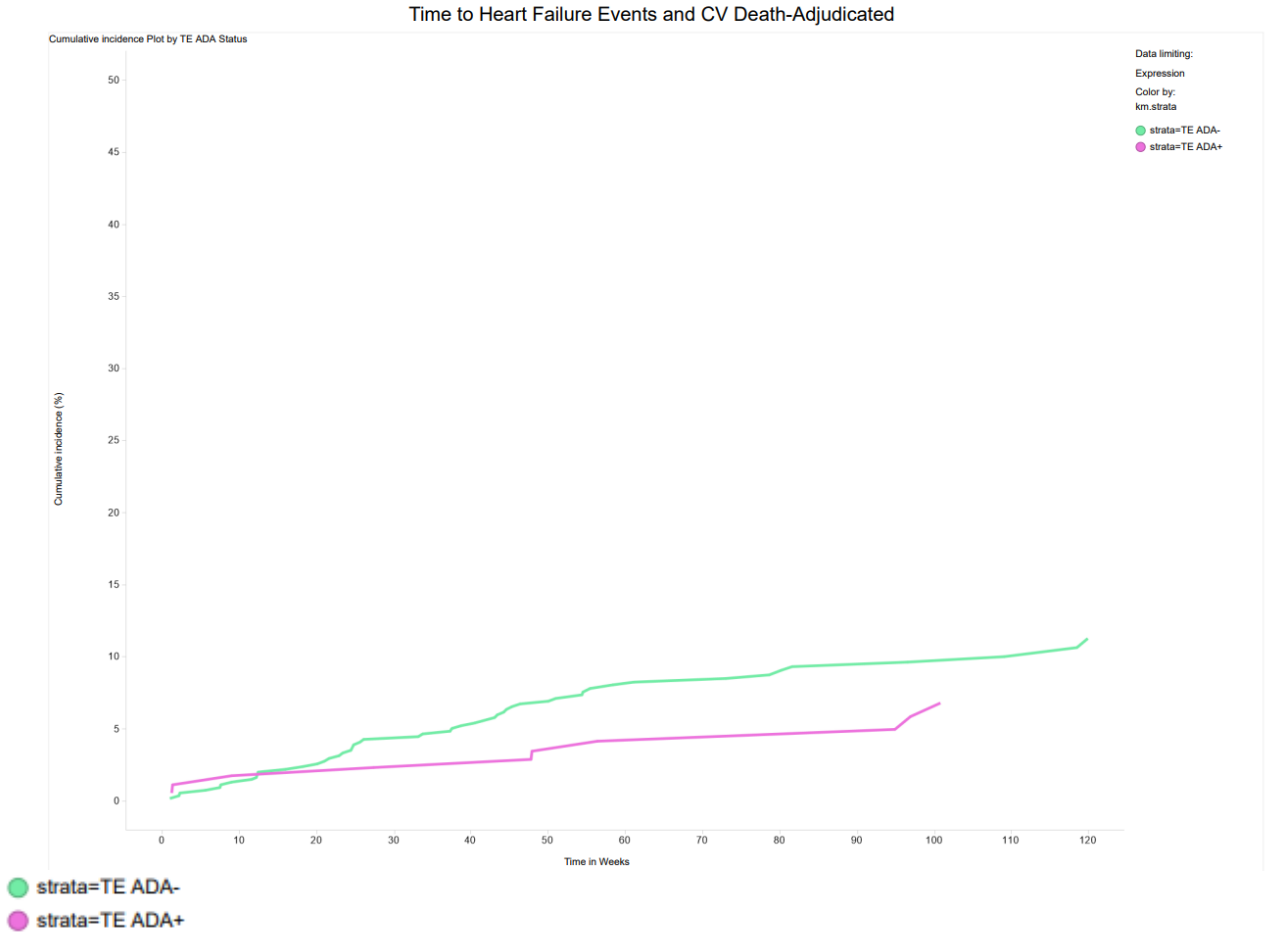


Figure 21. Kaplan-Meier plot of the time-to-first occurrence of adjudication-confirmed heart failure event or CV death

Injection site reactions

TEAEs identified by the following SMQs and HLTs were summarized to address injection site reactions:

- Injection site reaction HLT,
- Infusion site reaction HLT, and
- Administration site reaction HLT.

Injection site reactions by ADA status:

A markedly higher percentage of tirzepatide-treated TE ADA+ participants (10.5%) experienced injection site reactions compared to TE ADA- participants (2.5%), see table below.

Table 54. Summary of Injection Site Reactions by TE ADA Status During the Planned Treatment Period; Safety Population

	Tirzepatide (N = 364)	
TE ADA Status	M	m (%)
TE ADA+	162	17 (10.5)
TE ADA-	197	5 (2.5)
Not evaluable	5	0

m = number of participants in specified category (TE ADA+, TE ADA-, or not evaluable with hypersensitivity reaction); M = total number of participants in specified TE ADA status; N = total number of participants in specified treatment group

Systemic hypersensitivity reactions

Immediate hypersensitivity, including anaphylaxis, and nonimmediate hypersensitivity were assessed as follows:

- immediate hypersensitivity (Time Period A) included all TEAEs that occurred within 24 hours of study drug administration, and
- nonimmediate hypersensitivity (Time Period B) included all TEAEs that occurred more than 24 hours after study drug administration, but prior to the next administration of the study drug.

The hypersensitivity cases were identified based on the following:

- narrow and algorithm terms in Anaphylactic reaction SMQ (20000021) (analysis for algorithm term only applicable for Time Period A)
- narrow terms in Angioedema SMQ (20000024)
- narrow terms in Severe cutaneous adverse reactions SMQ (20000020)
- narrow terms in Hypersensitivity SMQ (20000214), and
- narrow terms in Vasculitis SMQ (20000174).

Summaries and analyses of the incidence of TEAEs for the following SMQ searches were provided for immediate and nonimmediate hypersensitivity time periods:

- any narrow terms from any one of the 5 SMQs, that is, a combined search across narrow terms of all 5 SMQs, and
- any narrow scope term within each SMQ, separately (that is, narrow SMQ search). In addition, for immediate hypersensitivity, any term from the Anaphylactic reaction SMQ algorithm was included.

The following table lists the reported potential hypersensitivity reactions. There was a slight numerical imbalance disfavouring TZP (4.7% for TZP vs. 3.5% for placebo). No specific kind of immune reaction dominated. Thus, this evaluation does not provide a clear hint for a relationship of TZP and hypersensitivity reactions.

Table 55 (shortened): Summary of Treatment-Emergent Hypersensitivity Events; Safety Population, I8F-MC-GPID

Event Category	Preferred Term	TZP MTD (N=364) n (%)	Placebo (N=367) n (%)
Participants with >=1 TEAE of Hypersensitivity Reactions		17 (4.7)	13 (3.5)
Anaphylactic reaction (Algorithm) *a		0	1 (0.3)
	Anaphylactic shock	0	1 (0.3)
Anaphylactic reaction (Narrow)		0	1 (0.3)
	Anaphylactic shock	0	1 (0.3)
Anaphylactic reaction (Algorithm, not Narrow)		0	0
Hypersensitivity (Narrow)		16 (4.4)	13 (3.5)

	Distributive shock	2 (0.5)	0
	Rash	2 (0.5)	3 (0.8)
	Rash pruritic	2 (0.5)	0
	Swelling face	2 (0.5)	1 (0.3)
	Allergic reaction to excipient	1 (0.3)	0
	Bronchospasm	1 (0.3)	0
	Drug hypersensitivity	1 (0.3)	0
	Eczema	1 (0.3)	0
	Hypersensitivity	1 (0.3)	3 (0.8)
	Injection site rash	1 (0.3)	0
	Rash papular	1 (0.3)	0
	Urticaria	1 (0.3)	2 (0.5)
	Anaphylactic shock	0	1 (0.3)
	Dermatitis	0	1 (0.3)
	Dermatitis atopic	0	1 (0.3)
	Iodine allergy	0	1 (0.3)
	Rash erythematous	0	1 (0.3)
	Scrotal dermatitis *e	0	1 (0.6)
Angioedema (Narrow)		3 (0.8)	3 (0.8)
	Swelling face	2 (0.5)	1 (0.3)
	Urticaria	1 (0.3)	2 (0.5)
Severe cutaneous adverse reactions (Narrow)		0	0
Vasculitis (Narrow)		1 (0.3)	0
	Polymyalgia rheumatica	1 (0.3)	0

Hypersensitivity reactions by ADA status:

TEAEs identified by the following SMQs and HLTs were summarized to address injection site reactions:

- Anaphylactic reaction SMQ (narrow and algorithm terms)
- Hypersensitivity SMQ (narrow terms)
- Angioedema SMQ (narrow terms)
- Severe cutaneous adverse reactions SMQ (narrow terms), and
- Vasculitis SMQ (narrow terms).

Presence of ADA did not increase the incidence of systemic hypersensitivity reactions; in fact, these reactions were numerically slightly less frequent when ADA were present, see table below.

Table 56. Summary of Hypersensitivity Reactions by TE ADA Status during the Planned Treatment Period; Safety Population

	Tirzepatide (N = 364)	
TE ADA Status	M	m (%)
TE ADA+	162	6 (3.7)
TE ADA-	197	10 (5.1)
Not evaluable	5	1 (20.0)

m = number of participants in specified category (TE ADA+, TE ADA-, or not evaluable with hypersensitivity reaction); M = total number of participants in specified TE ADA status; N = total number of participants in specified treatment group

Serious adverse event/deaths/other significant events

SAEs

The percentage of participants reporting at least 1 SAE was similar in the tirzepatide (26.4%) and placebo (25.6%) groups, and the SOC with the highest percentage of SAEs was Cardiac disorders, which was higher in placebo compared to tirzepatide (tirzepatide, 8.2%; placebo, 12.5%). The most frequent cardiac event was Cardiac failure, which was higher in the placebo group (tirzepatide, 3.3%; placebo, 4.9%).

Atrial fibrillation and acute myocardial infarction (which are listed under Cardiac disorders) were numerically higher in the tirzepatide group (1.9% and 1.6%, respectively) compared to the placebo group (0.8% and 0.5%, respectively). Atrial fibrillation and acute myocardial infarction are discussed in the section on AESIs

Deaths

CV death and all-cause death were included as efficacy endpoints. As such, all deaths that were reported by the investigator during the study were adjudicated by the CEC.

In the SUMMIT study, the overall number of deaths was 34 including

- 19 (5.2%) deaths in the tirzepatide group, and
- 15 (4.1%) deaths in the placebo group

Death due to CV / undetermined causes, as adjudicated by CEC (or as confirmed by CEC adjudication), occurred in 10 participants (out of 364, i.e. **2.74%**) in the tirzepatide group and 5 participants (out of 367. i.e. **1.36%**) in the placebo group.

At the end of the study, there were 15 participants with unknown vital status (4 participants in the tirzepatide group and 11 participants in the placebo group).

The figure 22 shows a Kaplan-Meier plot of mortality. This plot clearly reveals that the increase in mortality with TZP compared to placebo occurs late in the study, at around Week 90. At this time-point, the number of subjects for evaluation decreases, making the findings less reliable. Furthermore, some of the subjects had already stopped taking TZP before the fatal event.

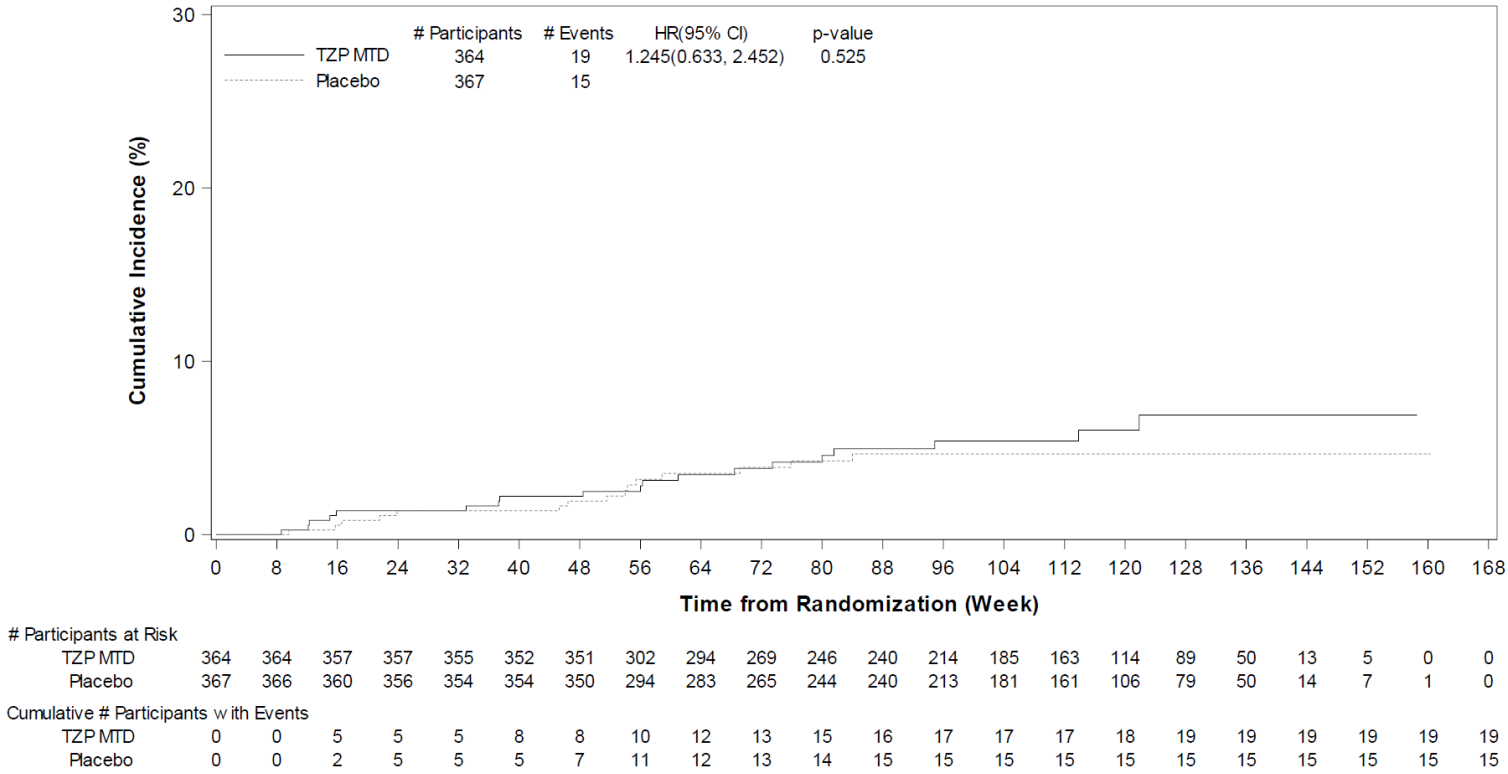


Figure 22. Kaplan-Meier plot of time to all-cause death; randomized population.

Case reports of the patients experiencing CV death in the TZP group of the SUMMIT study were submitted. The immediate cause was related to the underlying cardiac disease as expected. Some of the subjects had stopped taking TZP long before the fatal event.

To address uncertainties regarding tirzepatide-associated mortality (all-cause and CV deaths) in Study SUMMIT, the applicant also provided the following information:

- results from the recent CV outcome trial comparing tirzepatide versus dulaglutide, I8FMC-GPGN (GPGN, also known as Study SURPASS-CVOT), focusing on all-cause and CV mortality analyses in participants with and without HF history
- a summary of published literatures estimating the representation of patients with HFpEF among those with HF in the SURPASS-CVOT population, to support the relevance of the SURPASS-CVOT study results for the HFpEF population of interest (Section 1.4.2.2), and
- supporting evidence from a real-world, retrospective data analysis evaluating mortality outcomes in patients with HFpEF treated with tirzepatide.

Analysis of Mortality in Participants with or without HF History Using Study SURPASS-CVOT

SURPASS-CVOT was a Phase 3, event-driven, randomised, double-blind, active comparator, parallel-group study. It evaluated the effect of once-weekly tirzepatide (up to 15 mg) compared to once-weekly dulaglutide (1.5 mg) on CV outcomes when added to standard of care in patients with

- T2D
- a BMI of 25 kg/m² or higher
- established CV disease, and

- an elevated risk of MACE.

CV Benefit of the Active Comparator, Dulaglutide, as Established in Study REWIND

Dulaglutide (Trulicity), the active comparator in Study SURPASS-CVOT, is indicated in the EU for the treatment of patients 10 years and above with insufficiently controlled T2D as an adjunct to diet and exercise. In the long-term CV outcome study REWIND, (Gerstein et. al. 2019) dulaglutide has demonstrated superiority in preventing MACE-3 (non-fatal myocardial infarction, non-fatal stroke, and CV death) compared with placebo (HR: 0.88, 95% CI: 0.79 – 0.99; p = 0.026). Each component contributed to the reduction of MACE-3 (Trulicity SmPC). In an exploratory analysis in patients with and without HF history in Study REWIND, (Branch et al. 2022) treatment with dulaglutide also showed a numerical reduction in MACE-3, mortality, and HF events. Table 57 presents the CV and all-cause deaths for dulaglutide and placebo in all participants by HF history status.

Table 57. Mortality (All-Cause and CV Deaths) Analysis in Participants from Study REWIND

Population in Study REWIND	N		All-Cause Deaths n (%)			CV Deaths (Including Death with Undetermined Cause) n (%)		
	Dula	Placebo	Dula	Placebo	HR (95% CI)	Dula	Placebo	HR (95% CI)
Total population	4949	4952	536 (10.8)	592 (12.0)	0·90 (0·80–1.01)	317 (6.4)	346 (7.0)	0.91 (0.78–1.06)
Participants with HF historya	421	432	84 (20)	93 (21.5)	0.92 (0.69–1.24)	53 (12.6)	61 (14.1)	0.89 (0.61–1.28)
Participants without HF historya	4509	4500	450 (10)	495 (11.0)	0.90 (0.79–1.02)	263 (5.8)	283 (6.3)	0.92 (0.78–1.09)

Abbreviations: CI = confidence interval; CV = cardiovascular; Dula = dulaglutide; HF = heart failure; HR = hazard ratio; n = number of participants with event of interest in the population; N = number of participants in the population.

a Clinical history of HF events was determined by investigators at baseline, based on clinical assessment and review of available health records. Baseline heart failure was not known in 39 participants.

Sources: Gerstein et al. (2019); Branch et al. (2022).

Evaluation of Mortality with Tirzepatide in All Participants and Those with or without a History of HF: Findings from the Study SURPASS-CVOT

Lilly conducted mortality analyses (all-cause and CV deaths) for tirzepatide using data from Study SURPASS-CVOT, focusing on the subgroup of patients with HF history, and compared the results with mortality outcomes in the overall study population and in patients without a history of HF.

Study SURPASS-CVOT analyses in participants with HF history were prespecified. Participants with HF history were defined as those with documented prior hospitalisation for HF in the CV-related medical history form, and/or a history suggestive of HF in the general medical history form (that is, an event with the Medical Dictionary for Regulatory Activities high-level group term equal to "Heart failure"). Since Study SURPASS-CVOT did not collect data to specifically differentiate between HFpEF and HFrEF,

Section 1.4.2.2 of this response presents literature findings on the assessment of representation of HFpEF among patients with HF studied in Study

SURPASS-CVOT.

Of the 13165 participants in Study SURPASS-CVOT, 2678 participants (20%) reported a HF history at study entry and were distributed evenly across the 2 treatment arms. In the HF subpopulation, participants had a mean age of 64.8 years and a mean BMI of 33.5 kg/m2, with the percentage of each New York Heart Association class as follows: NYHA Class I = 17.9%, NYHA Class II = 59.2%, and Class III/IV = 10.1%.

Tirzepatide was not associated with increased risk for mortality compared with dulaglutide in patients with HF history (Table 58). In the overall population, as well as in participants with and without HF history, the HR for all-cause death favoured tirzepatide over dulaglutide, suggesting a decreased risk for mortality with tirzepatide compared with dulaglutide. The HR for CV death was also numerically lower for tirzepatide versus dulaglutide across all populations analysed, including the subgroup of patients with HF history. A prespecified indirect comparison of tirzepatide versus placebo, using the overall Study SURPASS-CVOT and matched Study REWIND populations, showed that tirzepatide reduced the risk of all-cause death (HR: 0.61, 95% CI: 0.42 – 0.82) and CV death (HR: 0.75, 95% CI: 0.52 – 1.09) compared with putative placebo. In participants with HF history, the HRs for tirzepatide versus dulaglutide were similar to and numerically lower than the HRs observed in participants without HF history for both all cause and CV deaths. These results indicate that there was no difference with respect to tirzepatide's effect on mortality between patients with or without HF history and that tirzepatide was not associated with an increased risk of mortality in either patients with or without HF history.

Table 58. Mortality (All-Cause and CV Deaths) Analysis in Participants from the Study SURPASS-CVOT

Population in Study SURPASS-CVOT	N		All-Cause Deaths			CV Deaths (Including Death with Undetermined Cause)		
			n (%)			n (%)		
	TZP	Dula	TZP	Dula	HR (95% CI)	TZP	Dula	HR (95% CI)
mITT population[a]	6586	6579	566 (8.59)	669 (10.16)	0.84 (0.75 - 0.94)	367 (5.57)	408 (6.20)	0.89 (0.77 - 1.02)
Participants with HF history	1310	1368	177 (13.51)	229 (16.74)	0.80 (0.65 - 0.97)	117 (8.93)	151 (11.03)	0.80 (0.63 - 1.02)
Participants without HF history	5276	5211	389 (7.37)	440 (8.44)	0.86 (0.75 - 0.99)	250 (4.74)	257 (4.93)	0.95 (0.80 - 1.13)

Abbreviations: CI = confidence interval; CV = cardiovascular; Dula = dulaglutide; HF = heart failure; HR = hazard ratio; mITT = modified intent to treat; n = number of participants with event of interest in the population; N = number of participants in the population; TZP = tirzepatide.

a mITT population includes all randomly assigned patients, excluding those who were inadvertently randomly assigned in the study.

HFpEF Representation among Patients with HF History in Study

SURPASS-CVOT: Literature-Based Assessment Published data from clinical trials enrolling study populations similar to those in Study SURPASS-CVOT were reviewed to assess the likely proportion of patients with HFpEF among patients with HF history in Study SURPASS-CVOT. As discussed below, evidence from these trials suggests that participants with HF history in the Study SURPASS-CVOT are representative of patients with HFpEF.

According to the Cardiovascular Resource Group, the incidence of HFpEF diagnosis among all HF diagnoses ranges from 31.6% to 58.3%, with higher incidences in the US and Japan populations compared with EU population (CVrg 2025). Of patients with HFpEF, approximately 80% have obesity, 20% to 45% have T2DM and 30% have both obesity and T2DM (Elsanhoury et al. 2021; Lam et al. 2011).

In the SELECT study with semaglutide, approximately 17000 participants with overweight or obesity without diabetes, and with prior myocardial infarction, stroke, and/or peripheral artery disease were randomised. In SELECT, CHF was reported at baseline in 4274 participants (24.3%). As expected in this population with overweight or obesity, more than half of the cases of CHF were categorised by the investigators as having HFpEF (53.1%), HFrEF (31.4%), or unknown CHF (15.5%) (Lingvay et al. 2023).

To further substantiate this estimate, insights on HFpEF frequency were derived from a systematic review and meta-analysis that was conducted across 15 global, large (more than 1000 participants) trials of sodium-glucose co-transporter-2 inhibitors in patients with HF, T2DM, chronic kidney disease, atherosclerotic cardiovascular disease, or any combination of these diseases (Usman et al. 2024). From these 15 trials, 3 trials included participants with HFpEF and HFrEF (6965 participants with HF) (Usman M. S. et. al. 2024) with a median or mean BMI ranging between 30.4 to 32.1 kg/m2 (Table 59). Across these 3 trials, approximately 45% of participants had HFpEF at baseline (Raz et al. 2018; Cannon et al. 2020; Usman et al. 2024; Aggarwal et al. 2025).

Table 59. Prevalence of HFpEF among Participants with HF, T2DM, and CVD Risk in SGLT2 Inhibitors Trials

Study	Total Enrolled	HF at Baseline	HFpEF at Baseline	% of Participants with HF and HFpEF
DECLARE-TIMI 58 (NCT01730534)	17160	1724	671	38.90
SCORED (NCT03315143)	10584	3283	1972	60.00
VERTIS CV (NCT01986881)	8246	1958	478	24.40
Total	35990	6965	3121	44.8

Abbreviations: CVD = cardiovascular disease; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

Source: Usman et. al. (2024).

Variations in inclusion/exclusion criteria amongst the 3 studies (DECLARE-TIMI 58, SCORED, VERTIS-CV) likely account for the differences in the percentage of participants with HF and HFpEF (Wiviott et al. 2019; Cannon et al. 2020; Bhatt et al. 2021). The patient population of the DECLARE-TIMI 58 study is considered most comparable to the Study SURPASS-CVOT, as both enrolled participants with established CV disease and T2DM (Wiviott et al. 2019; Nicholls et al. 2024). In the DECLARE-TIMI 58 study, 6974 (40.6%) of the 17160 participants had established CV disease. The remaining participants

had no established CV disease but were enrolled based on the presence of at least 2 CV risk factors (Wiviott et al. 2019; Usman et al. 2024). The HFpEF status between these 2 subpopulations was not reported. In summary, based on insights from the SELECT and DECLARE-TIMI 58 studies and given the high prevalence of co-morbidities, such as established CV disease, T2DM, and obesity or overweight, approximately 50% of all patients with HF history in Study SURPASS-CVOT were expected to have HFpEF.

Laboratory findings

Haematology / serum chemistry

Serum markers related to liver, kidney, pancreas and thyroid C-cells are discussed in the respective part of the AESI section. Otherwise, there were no relevant laboratory findings in respect to safety.

Vital signs

As expected from previous studies, TZP caused a mean increase in heart rate (HR) and a mean decrease in blood pressure (BP), particularly systolic BP (SBP). In SUMMIT, mean HR increase by around 2.8 beats/minute (bpm), and SBP decreased by around 4.7 mmHg. For details, see the following three tables

Systolic blood pressure (SBP):

Table 60. Variable Analyzed: Average Sitting Systolic Blood Pressure (mmHg); Week 52

		Actual Value	Change from Baseline	Pairwise Comparison
	n	Mean (SD)	Mean (SD)	LSMean Change Difference (95% CI)
TZP MTD	331	123.4 (15.54)	-4.64 (14.681)	-4.67 (-6.79,-2.54) p <.001
Placebo	334	128.3 (16.07)	0.22 (15.77)	

Diastolic blood pressure (DBP):

Table 61. Variable Analyzed: Average Sitting Diastolic Blood Pressure (mmHg); Week 52

		Actual Value	Change from Baseline	Pairwise Comparison
	n	Mean (SD)	Mean (SD)	LSMean Change Difference (95% CI)
TZP MTD	331	74.9 (9.257)	-0.94 (10.234)	-0.92 (-2.29,0.45) p = 0.189
Placebo	334	76.4 (10.899)	-0.40 (10.718)	

Heart rate (HR):

Table 62. Variable Analysed: Average Heart Rate (beats/min); Week 52

		Actual Value	Change from Baseline	Pairwise Comparison
	n	Mean (SD)	Mean (SD)	LSMean Change Difference (95% CI)
TZP MTD	331	74.0 (11.042)	2.86 (10.903)	2.77 (1.27,4.27) p <.001
Placebo	334	71.2 (11.419)	0.16 (11.530)	

Despite mean increase in HR, the percentage of patients having high (>100) HR post-baseline, with an increase by at least 15 bpm from baseline, was not higher in the TZP than in the placebo group. Fewer

subjects had high SBP (≥140; after an increase from baseline of at least 20 mmHg) in the TZP than in the placebo group. Accordingly, low SBP (≤90 after a decrease of at least 20 mmHg) was more frequent with TZP than with placebo. For further details, see table below.

Table 63 Summary of Participants with Selected Abnormal Vital Sign Thresholds By Treatment and Visit Safety Population Study I8F-MC-GPID

Parameter	n (%)	
	Tirzepatide (N = 364)	Placebo (N = 367)
Baseline		
Pulse rate (bpm)		
Low: <50	5 (1.4)	2 (0.5)
High: >100	6 (1.6)	2 (0.5)
SBP (mmHg)		
Low: ≤90	0	0
Medium ≥129	246 (67.6)	250 (68.1)
High: ≥140	111 (30.5)	119 (32.4)
DBP (mmHg)		
Low: ≤50	4 (1.1)	0
High: ≥90	57 (15.7)	65 (17.7)
Any postbaseline value		
Pulse rate (bpm)		
Low: <50 and CFB ≤-15	5 (1.4)	2 (0.6)
High: >100 and CFB ≥15	12 (3.3)	13 (3.6)
SBP (mmHg)		
Low: ≤90 and CFB ≤-20	19 (5.2)	5 (1.4)
Medium≥129 and CFB ≥20	35 (9.6)	67 (18.5)
High: ≥140 and CFB ≥20	26 (7.1)	56 (15.4)
DBP (mmHg)		
Low: ≤50 and CFB ≤-10	4 (1.1)	8 (2.2)
High: ≥90 and CFB ≥10	30 (8.2)	51 (14.0)

Abbreviations: CFB = change from baseline; DBP = diastolic blood pressure; n = number of participants in the specified category; N = number of participants in the analysis population; SBP = systolic blood pressure.

ECG:

ECG was collected locally in the SUMMIT study and the purpose was to assist in collecting atrial fibrillation information (see section on respective AESI). Further evaluation such as QT duration was not performed.

Safety in special populations

The following table presents a summary of AE categories by age group for the SUMMIT study safety population. In general, in both treatment groups the percentage of participants reporting events increased with increasing age groups.

Table 64. Overview of Adverse Events by Age Category; Safety Population; Study I8F-MC-GPID

	TZP MTD				Placebo			
Event Category	<65 years (N=158) n (%)	65-74 years (N=130) n (%)	75-84 years (N=72) n (%)	>=85 years (N=4) n (%)	<65 years (N=166) n (%)	65-74 years (N=124) n (%)	75-84 years (N=71) n (%)	>=85 years (N=6) n (%)
Total TEAEs	129 (81.6)	113 (86.9)	67 (93.1)	4 (100.0)	125 (75.3)	93 (75.0)	55 (77.5)	6 (100.0)
SAEs	30 (19.0)	35 (26.9)	29 (40.3)	2 (50.0)	30 (18.1)	38 (30.6)	22 (31.0)	4 (66.7)
Fatal	4 (2.5)	7 (5.4)	8 (11.1)	0 (0.0)	3 (1.8)	4 (3.2)	8 (11.3)	0 (0.0)
Hospitalization	28 (17.7)	31 (23.8)	28 (38.9)	2 (50.0)	26 (15.7)	35 (28.2)	19 (26.8)	4 (66.7)

Life-threatening	6 (3.8)	4 (3.1)	4 (5.6)	0 (0.0)	4 (2.4)	8 (6.5)	7 (9.9)	0 (0.0)
Disability	1 (0.6)	1 (0.8)	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.4)	0 (0.0)
Other	3 (1.9)	6 (4.6)	5 (6.9)	0 (0.0)	4 (2.4)	5 (4.0)	4 (5.6)	0 (0.0)
AEs leading to study treatment discontinuation	9 (5.7)	12 (9.2)	18 (25.0)	0 (0.0)	4 (2.4)	5 (4.0)	7 (9.9)	0 (0.0)
Accidents and injuries (SMQ)	16 (10.1)	8 (6.2)	10 (13.9)	0 (0.0)	7 (4.2)	13 (10.5)	10 (14.1)	3 (50.0)
Cardiac disorders (SOC)	20 (12.7)	22 (16.9)	19 (26.4)	1 (25.0)	26 (15.7)	34 (27.4)	16 (22.5)	3 (50.0)
Infections and infestations (SOC)	42 (26.6)	50 (38.5)	30 (41.7)	3 (75.0)	69 (41.6)	50 (40.3)	25 (35.2)	5 (83.3)
Nervous system disorders (SOC)	20 (12.7)	27 (20.8)	19 (26.4)	1 (25.0)	23 (13.9)	16 (12.9)	6 (8.5)	2 (33.3)
Psychiatric disorders (SOC)	6 (3.8)	11 (8.5)	6 (8.3)	0 (0.0)	9 (5.4)	2 (1.6)	4 (5.6)	0 (0.0)
Vascular disorders (SOC)	16 (10.1)	18 (13.8)	15 (20.8)	1 (25.0)	13 (7.8)	14 (11.3)	8 (11.3)	0 (0.0)
Central nervous system vascular disorders (SMQ)	2 (1.3)	1 (0.8)	0 (0.0)	1 (25.0)	4 (2.4)	4 (3.2)	0 (0.0)	0 (0.0)
Anticholinergic syndrome (PT)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fractures*a	3 (1.9)	2 (1.5)	5 (6.9)	0 (0.0)	1 (0.6)	4 (3.2)	6 (8.5)	1 (16.7)
Hypotension, falls, fractures (LCQ)*b	11 (7.0)	18 (13.8)	17 (23.6)	1 (25.0)	7 (4.2)	9 (7.3)	10 (14.1)	2 (33.3)

Abbreviations: AE = adverse event; HLGT = high level group term; LCQ = lilly customized query; 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 = standardized MedDRA queries; SOC = system organ class; TEAE = treatment emergent adverse event; TZP MTD = tirzepatide maximum tolerated dose.
Note: TZP MTD is tirzepatide up to 15 mg once weekly.
*a Fractures includes 6 HLTs: 'Fractures and dislocations NEC', 'Limb fractures and dislocations', 'Pelvic fractures and dislocations', 'Skull fractures, facial bone fractures and dislocations', 'Spinal fractures and dislocations', and 'Thoracic cage fractures and dislocations'.
*b LCQ includes the 6 HLTs for fractures, 'Decreased and nonspecific blood pressure disorders and shock' HLGT, and 'Fall' PT.

Discontinuation due to adverse events

The following table presents a summary and analysis of AEs that were reported by at least 1 tirzepatide-treated participant as the reason for discontinuation of the study drug in the study.

- The percentage of participants discontinuing the study drug due to an AE was higher in the tirzepatide group than placebo.
- The most frequently reported AEs leading to discontinuation of tirzepatide were in the Gastrointestinal disorders SOC (4.1%).

These results are generally consistent with the known safety profile of tirzepatide.

Table 65. Summary of Adverse Events Reported by ≥1 Tirzepatide-Treated Participant as Primary Reason for Treatment Discontinuation; Safety Population

System Organ Class Preferred Term	Tirzepatide (N = 364) n (%)	Placebo (N = 367) n (%)	Tirzepatide vs. Placebo p-value a
Participants with ≥1 DCAE	39 (10.7)	16 (4.4)	0.001
Cardiac disorders	**4 (1.1)**	**2 (0.5)**	**0.450**
Acute myocardial infarction	3 (0.8)	0	0.123
Cardiac arrest	1 (0.3)	0	0.498
Eye disorders	**1 (0.3)**	**0**	**0.498**
Xerophthalmia	1 (0.3)	0	0.498
Gastrointestinal disorders	**15 (4.1)**	**0**	**<.001**
Constipation	3 (0.8)	0	0.123

Diarrhoea	2 (0.5)	0	0.248
Dyspepsia	2 (0.5)	0	0.248
Vomiting	2 (0.5)	0	0.248
Abdominal pain	1 (0.3)	0	0.498
Colitis	1 (0.3)	0	0.498
Intestinal ischemia	1 (0.3)	0	0.498
Nausea	1 (0.3)	0	0.498
Obstructive pancreatitis	1 (0.3)	0	0.498
Pancreatitis acute	1 (0.3)	0	0.498
General disorders and administration site conditions	**5 (1.4)**	**0**	**0.030**
Death	2 (0.5)	0	0.248
Sudden death	2 (0.5)	0	0.248
Sudden cardiac death	1 (0.3)	0	0.498
Immune system disorders	**1 (0.3)**	**0**	**0.498**
Hypersensitivity	1 (0.3)	0	0.498
Infections and infestations	**4 (1.1)**	**4 (1.1)**	**>.999**
Septic shock	3 (0.8)	1 (0.3)	0.372
Urinary tract infection	1 (0.3)	0	0.498
Investigations	**3 (0.8)**	**1 (0.3)**	**0.372**
Blood calcitonin increased	2 (0.5)	0	0.248
Amylase increased	1 (0.3)	0	0.498
Metabolism and nutrition disorders	**1 (0.3)**	**0**	**0.498**
Decreased appetite	1 (0.3)	0	0.498
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**2 (0.5)**	**>.999**
Biliary neoplasm	1 (0.3)	0	0.498
Respiratory, thoracic and mediastinal disorders	**2 (0.5)**	**2 (0.5)**	**>.999**
Acute pulmonary oedema	1 (0.3)	1 (0.3)	>.999
Respiratory failure	1 (0.3)	0	0.498
Skin and subcutaneous tissue disorders	**1 (0.3)**	**0**	**0.498**
Rash papular	1 (0.3)	0	0.498
Vascular disorders	**1 (0.3)**	**0**	**0.498**
Orthostatic hypotension	1 (0.3)	0	0.498

Abbreviations: CSR = clinical study report; DCAE = discontinuation of study drug due to AE; n = number of participants with at least 1 event; N = number of participants in the treatment group; vs = versus.
a p-values for overall treatment effect were computed using Fisher's Exact test.

Post marketing experience

Tirzepatide was first approved on 13 May 2022 in the US as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. Tirzepatide has been approved for T2DM in 51 countries, including those in the EU, the US, Canada, Australia, Japan, and Switzerland. Tirzepatide was also approved in the US on 08 November 2023 in the US as an adjunct to a reduced calorie diet and increased physical activity for CWM in adults with obesity, or overweight with weight-related comorbidities. Tirzepatide has been authorized in the EU, UK, and US, and is approved or under review in other countries for weight management.

This summary of tirzepatide postmarketing data includes spontaneous reports of AEs/SAEs and deaths, and spontaneous reports for important potential risks with tirzepatide as of 30 April 2024. Additional information from most recent postmarketing data does not alter the overall safety profile of tirzepatide, and no safety signals were identified specific to an underlying comorbidity of HFpEF.

Exposure

Worldwide sales of tirzepatide following first approval (May 2022) have been collected for the cumulative period ending on 30 April 2024. An estimated 4,498,400 patients have been exposed to tirzepatide (any dose) with 2,233,100 patient-years of exposure.

Overall postmarketing adverse events

Postmarketing data for tirzepatide are reviewed on a bimonthly basis by a cross functional team including safety surveillance scientists, safety medical representatives, safety physicians, and pharmacoepidemiologists. These reviews comprise regulatory, and valid / nonvalid spontaneous reports, disproportionality analysis of Lilly Safety System, reviews of individual case reports, as necessary, and published literature. Cumulatively through 30 April 2024, there have been 116,019 AEs reported from 43,262 postmarketing cases. Among these, 6014 were SAEs reported from 3081 postmarketing cases. The most frequently reported SAEs in the postmarketing setting by individual MedDRA PT were

- Incorrect dose administered (n = 10382; reporting rate: 0.23%)
- Off label use (n = 9976; reporting rate: 0.22%)
- Nausea (n = 8273; reporting rate: 0.18%)
- Injection site pain (n = 7239; reporting rate: 0.16%)
- Diarrhoea (n = 3447; reporting rate: 0.08%)
- Injection site haemorrhage (n = 2994; reporting rate: 0.07%)
- Decreased appetite (n = 2896; reporting rate: 0.06%)
- Vomiting (n = 2850; reporting rate: 0.06%)
- Injection site erythema (n = 2519; reporting rate: 0.06%), and
- Extra dose administered (n = 2423; reporting rate: 0.05%).

Deaths

There were 126 deaths in the postmarketing report.

- 65 cases had limited information regarding medical history, concomitant medications, autopsy details, or the cause of death for an adequate medical assessment, and
- 47 cases were confounded by underlying conditions/diseases such as smoking, tobacco use, type 1 diabetes, vascular disorders, different types of cancer, renal disorders, previous inappetence, and cardiopathies.

No pattern in the cause of death was observed.

3.5.1. Discussion on clinical safety

The MAH has provided a safety evaluation of TZP in HF patients from the SUMMIT study. In general, the safety profile in the HFpEF population was very similar to the profile known from previous trials in T2M subjects or subjects with obesity.

In brief, the predominant side effects were gastrointestinal (GI) symptoms such as nausea, diarrhoea, vomiting and abdominal pain. These were observed in 54.1% of the TZP-treated subjects and in only 26.2% of the placebo subjects. As expected, the prevalence of GI effects was highest during the dose up-titration phase. Other potential side effects of TZP are pancreatitis (reassuringly observed infrequently, in 0.8% of TZP subjects vs. none in placebo subjects) and gallbladder disease such as cholecystitis (4.4% with TZP vs. 2.7% with placebo). As expected, TZP caused a mean increase in heart rate (HR, by 2.8 bpm) and a decrease in systolic blood pressure (SBP, by 4.7 mmHg). The latter was accompanied by an increase in events of orthostatic hypotension. Furthermore, TZP caused a slight increase in serum calcitonin as in previous studies. TZP was immunogenic; around 45% of study

participants in the TZP group developed ADA. This again is in line with previous findings. ADA formation was associated with an increased incidence of injection site reactions. Otherwise, no adverse effects of ADA formation were observed. Particularly, PK and efficacy were unaffected in TE ADA+ patients and in the small percentage of patients who were positive for neutralising antibodies against tirzepatide.

Unlike in previous studies, more subjects with TZP than with placebo reported at least one event of depression (1.6% TZP vs. 0.5% placebo). Reassuringly, the number of affected subjects was rather low, and suicidal ideation was absent. The MAH assumed that HF patients are more susceptible to depression than previously studied patient populations (overweight/obese subjects with or without T2D) because of the poor prognosis and the marked impairments experienced in daily life with HF.

Another special safety topic of TZP was diabetic retinopathy. In the SUMMIT study, two participants (0.5%) in the placebo group and 4 (1.1%) in the tirzepatide group experienced ≥1 TEAE of potential diabetic retinopathy complications (e.g. vision blurred) during the study. None of the TEAEs of potential diabetic retinopathy complications were serious or severe. The low number of events probably is due to the fact that subjects with more severe diabetic retinopathy were excluded from the study. The respective exclusion criterion reads: "*a history of proliferative diabetic retinopathy, diabetic maculopathy, or severe nonproliferative diabetic retinopathy that requires acute treatment*". Thus, the SUMMIT study is not suited to enable firm conclusions of the effects of TZP on diabetic retinopathy.

The applicant has also provided an analysis of AEs of atrial fibrillation (AF) across the TZP phase 3 programme. No relevant differences between TZP and pooled comparator became obvious. Thus, if an effect of TZP on AF incidence exists, it appears to be small. AF is frequently present in HFpEF patients. Thus, the treating physician will be aware of this condition. AF can contribute to reduced heart function, but this is covered by the study endpoints, addressing the net effect of TZP treatment on heart function. Taken together, the CHMP agreed that mentioning a potential small effect of TZP on AF in the SmPC is not necessary.

The most important safety finding was the numerical increase in all-cause mortality in the TZP group compared to placebo. In the TZP group 19 subjects (5.2%) died vs. 15 subjects (4.1%) in the placebo group. This difference was driven by cardiovascular (CV) mortality, which also included mortality of unknown cause. In the TZP group, 10 subjects (2.74%) experienced CV death versus 5 subjects (1.36%) in the placebo group. The MAH presented a Kaplan-Meier plot of mortality, and this revealed that the increase in mortality occurs late in the course of the study, at around Week 90. Before this time-point, the curves for TZP and placebo were virtually indistinguishable.

The MAH has provided the narratives of the CV deaths, but this did not provide further insight. Being adjudicated as CV death, these fatal events were related to the underlying cardiac disease, and in part were explicitly considered by the investigator as not related to TZP. Some of the fatal CV events occurred long (up to 22 months) after the last dose of TZP. This is regarded by the MAH as a further argument for being not related to TZP. It is agreed with the MAH that the increased mortality most likely was not due to a direct adverse effect of TZP on heart or vasculature. Although no completed CV outcome study for TZP is available at the time of this variation, a meta-analysis of existing phase 3 trials with TZP in the T2D or weight management indication does not provide any hint that TZP could increase the CV risk in this patient population (Sattar et al. 2022, Nature Medicine 28:591-598). Accordingly, the SURPASS-4 study, which contributed a large part to the meta-analysis, showed a dose-dependent decrease in MACE-4 (consisting of cardiovascular death, myocardial infarction, stroke, and hospitalisation for unstable angina) with TZP (Del Prato et al. 2012, Lancet 398: 1811–1824).

However, changes in body weight can have long-term effects. Thus, TZP could affect mortality indirectly via rapid changes in body weight. Whereas normal body weight is favourable in respect to CV risk, epidemiological data indicate that in case of manifest heart failure a higher BMI can be associated with

improved survival. This was called the obesity paradox (Kalantar-Zadeh et al. 2004, J Am Coll Cardiol 43: 1439–1444; Oreopoulos et al. 2008, Am Heart J 156: 13-22). It was reported that weight loss leads to increased mortality in HF patients (Padwal et al. 2014, Int. J. Obes 38: 1110–1114; Zamora et al. 2016, J Am Heart Assoc 5: e002468). Follow-up in these studies was 3 years, underscoring the long-term effect of weight reduction. A similar study reported increased mortality after rapid weight loss in the elder population in general, after a 4.4-year follow-up (Hussain et al. 2023, JAMA Network Open 6:e237482). The reason for this obesity paradox is unclear, and it was noted in the cited publications that it could not be distinguished between voluntary and involuntary weight loss although a lifestyle with healthy diet and physical exercise was recommended. Thus, weight loss could have been an early indicator of the presence of various life-shortening diseases. On the other hand, an early study (Sours et al. 1981, Am J Clin Nutr 34: 453-461) described the link between a voluntary low-calorie, high-protein diet and events of sudden CV death so that a causal relationship between rapid or extensive weight loss and increased risk of CV death cannot be excluded. Another published study (Mariotti et al. 2004, Eur Heart J Suppl 6: F87–F90) investigated the correlation between weight loss and clinical outcome in HF. In line with the results of the MAH's SUMMIT study, Mariotti found beneficial effects of weight loss on clinical outcomes. However, survival was not studied by these authors.

Thus, published data indicate that TZP may increase mortality in HF patients indirectly via inducing a rapid and large weight loss, which may be unfavourable in case of HF (irrespective of the type, HFrEF or HFpEF, Padwal et al. 2014). Published data also indicate that fatal events can occur long after the weight loss; Kaplan-Meier analyses performed by Padwal et al. (2014) and Zamora et al. (2016) revealed decreased survival for two years (later time-points were not obtained) after one year of weight loss. Consequently, a fatal event months after cessation of TZP treatment can still be related to TZP. On the other hand, mortality appeared unexpectedly low in the placebo group of the SUMMIT study at later time points; from study week 84 onwards (i.e. to Week 160, the end of observation), no deaths were reported in the placebo group compared to three fatal events in the TZP group. This late study period mainly contributes to the observed difference in mortality between placebo and TZP. Thus, a chance finding cannot be excluded. It should also be noted that no follow-up data are available from 11 placebo patients compared to 4 TZP patients. This imbalance in missing data could also contribute to the apparent difference in mortality. For further clarification, the MAH provided mortality data from patients of the SUMMIT study who previously were lost in follow-up. Two additional fatality cases were reported, one in the TZP and one in the placebo group so that in total 20 deaths in the TZP and 16 deaths in the placebo group resulted. Furthermore, the MAH provided a meta-analysis of HF patients in previous phase 3 studies, conducted in the indications of diabetes, obesity and sleep apnoea. This meta-analysis did not reveal an increased mortality with TZP compared to placebo. Nevertheless, HR for all-cause- and for CV mortality (TZP vs. placebo) was numerically higher in the HF subpopulation than in the total analysis population. In this meta-analysis, it was not possible to distinguish between HFrEF and HFpEF, but since HFpEF preferably occurs in conjunction with Type 2 diabetes (T2D) and obesity, it is likely that the majority of subjects in the meta-analysis had HFpEF. For further clarification, the applicant submitted an analysis of mortality in HF patients vs. non-HF patients in a large CV outcome trial (SURPASS-CVOT) in T2DM patients. The comparator was dulaglutide at a rather low dose. Unlike TZP, dulaglutide did not lead to a strong and rapid weight loss. The main concern is that rapid weight loss is unfavourable in HF patients. Therefore, dulaglutide is a suitable comparator. The analysis clearly showed that TZP had a numerical survival benefit compared to dulaglutide in HF patients. Reference to other studies in similar populations suggested that around half of the HF patients in SURPASS-CVOT had HFpEF, i.e. a relevant fraction. The results of the HF subpopulation of SURPASS-CVOT were somewhat biased by the fact that glycaemic control was markedly better in the TZP than in the comparator (dulaglutide) group. This improves survival. Furthermore, several deaths in the comparator group were due to infection. The reason is not clear. It could be a chance finding, again favouring TZP. Nevertheless, these interfering effects most likely were too small for fully explaining the observed beneficial survival effects of TZP in

the HF subpopulation of SURPASS-CVOT. Thus, the unfavourable findings of SUMMIT could not be reproduced in SURPASS-CVOT.

3.5.2. Conclusions on clinical safety

The safety profile of TZP in patients with HFpEF was highly similar to the established profile in the T2DM and weight management indication.

3.5.3. 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.

4. Risk management plan

The MAH submitted an updated RMP version with this application: version 4.2.

Rationale for submitting an updated RMP was to include the proposed new indication of treatment of symptomatic chronic heart failure with preserved ejection fraction (HFpEF) in adults with obesity. The main proposed RMP changes were the following:

- A proposed new indication of HFpEF is included along with relevant information on incidence, prevalence, demography, main existing treatment options, natural history of the condition, and important comorbidities.
- Updated overall cumulative exposure in tirzepatide clinical trial programme and post-authorisation exposures.
- Updated incidence and exposure-adjusted incidence from Study I8F-MC-GPID (SUMMIT) for important potential risks.

The proposed updates in the RMP mainly concern the background information on the new applied indication for tirzepatide (Mounjaro) regarding HFpEF in adults with obesity.

The MAH did not propose new safety concerns and no new pharmacovigilance activities or risk minimization measures were proposed for the new proposed indication.

CHMP did not agree on including a separate indication in HFpEF in adults with obesity in SmPC section 4.1,and therefore changes to the RMP related to this new indication were not acceptable. The applicant submitted an updated RMP version 4.2 and was requested to remove the information on the new indication of HFpEF. No new RMP version 4.3 has been submitted with the response. However, in procedure EMA/VR/0000271898, RMP version 6.1 was submitted. In this version, no information on HFpEF is present. This is accepted.

The PRAC considered that this is acceptable to address any remaining administrative updates resulting from the current procedure in a future RMP update.

Also the following changes in the RMP were proposed by the MAH:

- Removal of follow-up form #1: Hypocalcaemia hypokalaemia hypomagnesaemia hypophosphataemia (safety concern: Medullary thyroid cancer)

The PRAC considered that the removal of the follow-up form is acceptable. Another follow-up form for Medullary thyroid cancer remains.

- Changes in pharmacovigilance plan regarding the database linkage study to evaluate the important potential risk of MTC (I8F-MC-B014)

The assessment of protocol version 1.0 of the Medullary Thyroid Carcinoma database linkage study is ongoing (procedure MEA 005.3). The proposed update in study number, from I8F-MC-B013 to I8F-MC-B014, is in line with the study number of the study protocol, and therefore accepted. The proposed updates in primary and secondary objectives, in study population and in milestones of study I8F-MC-B014 in RMP version 4.2 are in line with the protocol of study I8F-MC-B014 and are therefore acceptable. The protocol of study I8F-MC-B014 is included in Annex 3 of the RMP, which is accepted.

- Changes in pharmacovigilance plan regarding the Tirzepatide Pancreatic Malignancy Study (I8F-MC-B011)

The assessment of protocol version 1.0 of the Database Study to Evaluate the Risks of Pancreatic Cancer In Patients Exposed to Tirzepatide (I8F-MC-B011) is ongoing (procedure MEA002.2). The proposed update on rationale, the primary and secondary objectives, study population and milestones of study I8F-MC-B014 in RMP version 4.2 are line with protocol version 1.0 of study I8F-MC-B014, and are therefore acceptable. The protocol of study I8F-MC-B011 is included in Annex 3 of the RMP, which is accepted.

- Changes in pharmacovigilance plan regarding Retinopathy addendum to SURPASS-CVOT (I8F-MC-GPGN)

The MAH updated the milestone for clinical study report, reflecting the projected date for readout following occurrence of the predefined 1614 positively adjudicated events for the primary endpoint, and this update is therefore acceptable. The information on the rationale and study objectives, study design and study population is updated in version 4.2 of the RMP in line with the protocol addendum of study I8F-MC-GPGN in Annex 3 of the RMP, and is therefore acceptable.

Overall conclusion on the RMP

The changes to the RMP are acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

5. Changes to the Product Information

As a result of this variation, sections 4.1, 4.8 and 5.1 are intended to be updated. Other minor updates have been introduced in section 4.2 and 6.6. Please refer to Attachment 1 which includes all agreed changes to the Product Information.

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:

User testing was previously performed and accepted by CHMP on the package leaflet for Mounjaro solution for injection in prefilled pen, as part of the initial marketing authorisation application (MAA) concerning the type 2 diabetes mellitus indication.

The proposed text modifications to the package leaflet resulting from the addition of these data are minor and do not include text that is significantly different from that already user tested. Overall, the structure and design of the revised Mounjaro Package Leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability.

5.1.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Mounjaro (tirzepatide) was already included in the additional monitoring list at the time of marketing authorisation. Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

5.1.2. Quick Response (QR) code

N/A

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous disorder including different but partially overlapping pathophysiologic phenotypes. HFpEF is defined as HF with an LVEF of 50% or higher at diagnosis (Redfield and Borlaug 2023). Approximately 50% of patients with HF have HFpEF. HFpEF is associated with various comorbidities including hypertension, AF, T2DM, and obesity. Some authors assume that there is a distinct obesity phenotype (obesity-related HFpEF), where increased ectopic adiposity coupled with metabolic derangements and plasma volume expansion play a causal role (Kitzman and Shah 2016; Packer 2018; Borlaug et al. 2022).

HFpEF affects 32 million people worldwide and is known to occur more in females and older patients (Redfield and Borlaug 2023). Its incidence and prevalence continue to rise (Balestrieri et al. 2024). The obesity phenotype is the most common phenotype. Approximately 50% of patients with HFpEF are estimated to have obesity. Patients with the obesity phenotype are about a decade younger than patients without obesity (Borlaug et al. 2022).

HFpEF is associated with high hospitalisation and mortality rates and significant patient burden. Patients with HFpEF present signs and symptoms such as dyspnoea, fatigue, and peripheral oedema, which severely impair patients' daily activities. HFpEF is a progressive condition characterized by variable durations of symptomatic stability often interrupted by decompensation episodes with worsening symptoms, requiring interventions, such as hospitalisation, the use of intravenous drugs in an urgent care setting, or the intensification of oral diuretics. Worsening HF is an important identifier of subsequent demise (Shah et al. 2017; Chatur et al. 2023).

Patients with obesity-related HFpEF have significant degrees of exercise intolerance and a markedly impaired quality of life and health status compared with patients without obesity (Reddy et al. 2020), and abdominal obesity is associated with increased morbidity and mortality (Tsujimoto and Kajio 2017; Chen et al. 2021).

The burden on patients with HFpEF and obesity is multifaceted and extends beyond the symptoms of the disease.

6.1.2. Available therapies and unmet medical need

Current guidelines emphasize the importance of managing comorbidities, such as hypertension, volume control, AF, T2DM, and obesity (Heidenreich et al. 2022; McDonagh et al. 2023). The goal of treatment is to relieve symptoms, improve quality of life, prevent hospitalisations and clinical worsening, and decrease mortality.

Some treatment options are available that specifically target obesity-related HFpEF. A multidisciplinary approach used for treatment includes weight management, diuretics for fluid management, management of AF, and medications for comorbidities such as hypertension and diabetes (Heidenreich et al. 2022). SGLT2 inhibitors have shown benefits in patients with HF across the broad range of LVEF, whereas the efficacy of sacubitril-valsartan was more evident in patients with HFpEF whose LVEF is less than 57% (Solomon et al. 2019) Recently, finerenone was shown to reduce the risk of HF worsening in patients

with HFmrEF and HFpEF (Solomon et al. 2024). Semaglutide also showed some benefits in HFpEF both in heart failure symptoms and physical function.

6.1.3. Main clinical studies

The efficacy conclusions are derived from the results of the SUMMIT study, the only phase 3 study submitted with this application.

6.2. *Favourable effects*

The SUMMIT study demonstrated that once weekly administered tirzepatide at the maximum tolerated dose (up to 15 mg) significantly reduced HF events (mainly driven by a reduction in HF hospitalisations and urgent HF visits) and improved KCCQ-CSS in obese (BMI ≥30 kg/m^2) HFpEF patients. As expected, body weight reduction was more pronounced in the tirzepatide arm than in the placebo group. The beneficial effect of tirzepatide on exercise capacity was confirmed by 6MWT data and by improvement in NYHA classification. In addition, a reduction in hsCRP level was observed, which was more pronounced in tirzepatide- than in placebo-treated participants, indicating a positive effect on inflammatory processes.

A cMRI addendum was completed in a subset of 106 participants and revealed that left ventricular mass, left ventricular stroke volume, and pericardial fat volume was significantly reduced by tirzepatide in comparison to placebo.

6.3. Uncertainties and limitations about favourable effects

Overall, the study size and the event rate are considered too small to allow reliable conclusions on the effect of tirzepatide on CV mortality in obese HFpEF patients. Moreover, only obese HFpEF patients were included in the study.

Uncertainty remains as regards a benefit of TZP in normal- or overweight HFpEF patients. It is unclear in how far TZP exerts a weight-reduction independent benefit in HF patients.

6.4. Unfavourable effects

The MAH has provided a safety evaluation of TZP in HF patients from the SUMMIT study. In general, the safety profile in the HF population was very similar to the profile known from previous trials in Type 2 diabetics or subjects with obesity.

In brief, the predominant side effects were gastrointestinal (GI) symptoms such as nausea, diarrhoea, vomiting and abdominal pain. These were observed in 54.1% of the TZP-treated subjects and in only 26.2% of the placebo subjects. As expected, the prevalence of GI effects was highest during the dose up-titration phase. Other potential side effects of TZP are pancreatitis (reassuringly observed infrequently, in 0.8% of TZP subjects vs. none in placebo subjects) and gallbladder disease such as cholecystitis (4.4% with TZP vs. 2.7% with placebo). As expected, TZP caused a mean increase in heart rate (HR, by 2.8 bpm) and a decrease in systolic blood pressure (SBP, by 4.7 mmHg). The latter was accompanied by an increase in events of orthostatic hypotension. Furthermore, TZP cause a slight increase in serum calcitonin as in previous studies. TZP was immunogenic; around 45% of study participants in the TZP group developed ADA. This again is in line with previous findings. ADA formation was associated with an increased incidence of injection site reactions. Otherwise, no adverse effects of

ADA formation were observed. Particularly, PK and efficacy were unaffected in TE ADA+ patients and in the small percentage of patients who were positive for neutralising antibodies against tirzepatide.

Unlike in previous studies, more subjects with TZP than with placebo reported at least one event of depression (1.6% TZP vs. 0.5% placebo). Reassuringly, the number of affected subjects was rather low, and suicidal ideation was absent.

6.5. Uncertainties and limitations about unfavourable effects

There was a numerical increase in all-cause mortality in the TZP group compared to placebo. This difference was driven by cardiovascular (CV) mortality, which also included mortality of unknown cause, but the absolute number of events was low. In the TZP group 10 subjects (2.74%) experienced CV death and 5 subjects (1.36%) in the placebo group. Furthermore, in most cases death occurred long after cessation of treatment with TZP (around 1 month to around 22 months after the last dose), making a relationship to TZP appear unlikely. However, published studies indicate that weight loss in HF patients can lead to increased mortality despite clinical improvement, and increased mortality was observed for up to two years after the weight loss. Therefore, it cannot be excluded that TZP contributed to the mortality in the SUMMIT study by an indirect effect, i.e. via induction of weight loss. In consequence, although previous studies of TZP in other indications (T2D and weight management) do not indicate a CV safety concern of TZP, it was questionable whether this finding can be transferred to the HF population. With the response to the first RSI, the applicant has provided a meta-analysis of HF patients in previous phase 3 studies (indications were diabetes, obesity and sleep apnoea). This meta-analysis did not reveal an increased mortality with TZP compared to placebo. Nevertheless, HR for all-cause- and for CV mortality (TZP vs. placebo) was numerically higher in the HF subpopulation than in the total analysis population. The numerical increase in mortality with TZP was not reproduced in an evaluation of subjects suffering from HF in a large CV outcome trial with TZP (SURPASS-CVOT; comparator, low-dose dulaglutide, which cause only small weight reduction). Furthermore, a clear biological mechanism for increased mortality with TZP in HF patients could not be established. Therefore, the observed increase in mortality in the TZP group of the SUMMIT study most likely was a chance finding.

6.6. Effects Table

Table 66. Effects Table for Mounjaro, treatment of HFpEF in obese patients

Effect	Short description	Unit	Treat-ment	Control	Uncertainties / Strength of evidence	Ref
Favourable Effects						
Δ baseline to week 52 in KCCQ-CSS	Primary EP 1	Mean Score (SD)	22.4 (21.45)	14.4 (19.70)	p<0.001	SUMMIT study
		Est. median Diff (95% CI)	6.9 (3.3, 10.6)			
Composite of CV/undetermined death and/or HF events over time	Primary EP 2	n (%)	36 (9.9)	56 (15.3)	p=0.026	SUMMIT trial
		HR (95% CI)	0.62 (0.41, 0.95)			
CV/undeter-mined death	Primary EP 2; component	n (%)	10 (2.7)	5 (1.4)	p=0.211	
		HR (95% CI)	1.99 (0.68, 5.81)			
HF events	Primary EP 2; component	n (%)	29 (8.0)	52 (14.2)	p=0.008	
		HR (95% CI)	0.54 (0.34, 0.85)			

Effect	Short description	Unit	Treat-ment	Control	Uncertainties / Strength of evidence	Ref
Hospitalization for HF	Primary EP 2; HF sub-Component	n (%)	12 (3.3)	26 (7.1)	p=0.018	
		HR (95% CI)	0.44 (0.22, 0.87)			
Urgent visit for HF	Primary EP 2; HF sub-component	n (%)	5 (1.4)	12 (3.3)	p=0.093	
		HR (95% CI)	0.41 (0.14, 1.16)			
Oral diuretics intensification for HF	Primary EP 2; HF sub-component	n (%)	17 (4.7)	21 (5.7)	p=0.492	
		HR (95% CI)	0.80 (0.42, 1.52)			
		Est. median Diff (95% CI)	15.0 (10.0, 20.0)			
Unfavourable Effects						
Any AE	Percent of participants with at least one event	%	86.0	76.0		SUMMIT study
Serious AE		%	26.4	25.6		
Death		%	5.2	4.1	difference driven by CV death; number of events is low precluding firm conclusions; however, published data support the possibility that weight loss in HF could increase mortality despite clinical benefit	
Discontinuation due to AE		%	10.7	4.4	mainly GI AEs	
AEs of special interest:						
GI event (mainly nausea, vomiting, diarrhoea, abdominal pain)		%	54.1	26.2	mainly during dose up-titration; known effect of GLP-1RAs	
Pancreatitis		%	0.8	0	known effect of GLP-1RAs	
Gallbladder disorder		%	4.4	2.7	known effect of GLP-1RAs	
Depression		%	1.6	0.5	Not observed in previous studies; number of events is low precluding firm conclusions	
Diabetic retinopathy complications		%	1.1	0.5	Number of events is low precluding firm conclusions	

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects:

The most important favourable effect to be demonstrated in HF studies would be a reduction of mortality, which, however, was not shown in the SUMMIT study. Nevertheless, tirzepatide caused a significant reduction in HF hospitalisations, and there was some tendency towards reduction of urgent HF visits. Despite the lack of mortality reduction, these endpoints are considered important, as they represent an improvement of the patients' haemodynamic situation resulting in an amelioration of HF symptoms and an improvement of quality of life. This is supported by the KCCQ-CSS data as well as by the improvements in 6MWD and NYHA category.

The tirzepatide-induced reduction of pericardial adipose tissue might be important, as it may help to explain the mechanisms underlying the improvement of cardiac function in tirzepatide-treated obese HFpEF patients. The observed reduction in hsCRP levels is acknowledged and could contribute to the above-mentioned clinical effects.

The MAH initially submitted an extension of indication to include treatment of symptomatic chronic heart failure with preserved ejection fraction (HFpEF) in adults with obesity as a separate indication in section 4.1 of the SmPC. This was not endorsed by the CHMP, since the newly proposed use of tirzepatide for the treatment of HFpEF in patients with obesity (BMI $\geq$ 30 kg/m^2) is considered as already covered by the existing indications of Mounjaro. Obesity (BMI $\geq$ 30 kg/m^2) as such already qualifies for the approved weight management indication. Therefore, it is concluded that the use of tirzepatide in patients with HFpEF and obesity is already covered by the weight management indication in the current label.

The applicant provided several arguments to support the hypothesis that the risk reduction in the primary heart failure/CV death endpoint is due to effects beyond weight reduction. These arguments are discussed below.

The applicant stated that the reduction of blood pressure occurred faster than the body weight reduction, specifically in the beginning of tirzepatide treatment. However, for the following reasons, this argumentation cannot be followed:

Compared to baseline,

- body weight was reduced in the tirzepatide group by 2.2 kg at week 4 and by 4.1 kg at week 8
- SBP was reduced by 3.83 mmHg at week 4 and by 4.39 mmHg at week 4.
- DBP was reduced by 1.45 mmHg at week 4 and by 1.6 mm Hg at week 8.

Thus, the blood pressure reduction per kg body weight reduction was

- for SBP: 1.74 mmHg/kg at week 4 and 1.07 mmHg/kg at week 8.
- for DBP: 0.66 mmHg/kg at week 4 and 0.39 mmHg/kg at week 8.

According to a meta-analysis of 25 RCTs published in 2003 [Neter JE et al (2003) *Hypertension* **42**(5):878-884], blood pressure is reduced by -1.05 mm Hg (95% CI, -1.43 to -0.66) systolic and -0.92 mm Hg (95% CI, -1.28 to -0.55) diastolic for each kilogram of weight loss (achieved with caloric restriction and/or exercise). A similar relationship between weight loss and blood pressure reduction is seen in the SUMMIT trial. Although the SBP reduction during the first four weeks (1.74 mmHg per kg weight loss) is somewhat more pronounced in SUMMIT as described by Neter et al (2003), the effect goes down to 1.1 mmHg/kg, when the first 8 week-period is considered. Moreover, the effect on DBP at week 8 is less pronounced than described in the meta-analysis by Neter et al (2003). In conclusion, the additional weight reduction-independent effect on blood pressure claimed by the applicant seems to be negligible. The blood pressure reduction per kg body weight loss is largely similar to the blood pressure effects reported for other (non-pharmacological) weight reduction approaches (Neter et al, 2003).

Moreover, most of the improvement in the KCCQ-CSS and 6MWD endpoints occurs within the first 24 weeks, with very little additional effect between week 24 and week 52. This shows that the benefit regarding 6MWD and KCCQ-CSS correlates with body weight reduction, most of which occurs in the

initial phase of treatment, and suggests a potential causal relationship between body weight reduction and improvement of HF symptoms

The applicant also argued that the effect of tirzepatide on insulin resistance is partially independent of weight reduction. In fact, it is discussed in the literature that GLP-1 may improve uptake and utilization of glucose in muscle and adipose tissues [Zheng Z et al (2024) *Signal Transduct Target Ther.* **9**(1):234]. However, since these effects on insulin resistance contribute to the antidiabetic effect of tirzepatide, they are already covered by the diabetes indication. A positive effect on HFpEF would then be an indirect consequence of the action of tirzepatide on blood glucose homeostasis.

The applicant also showed an analysis, which suggests that the HR of the composite endpoint of HF events or CV death is largely independent of baseline BMI. However, the reliability of the underlying model may be limited by the small study size. Moreover, the HR prediction for BMI<30 kg/m^2 at baseline should be interpreted with caution, since the SUMMIT study has only included patients with a BMI of ≥30 kg/m^2.

The CHMP considered that some of the applicant's arguments might support a weight reduction-independent effect of tirzepatide on HFpEF. First, the changes of both NT-proBNP and Troponin-T (biomarkers related to worsening HF) did not correlate with weight loss. Second, a mediation analysis of the on-treatment dataset suggests that almost 70% of the observed risk reduction in the composite endpoint of HF events or CV death is mediated by effects other than weight loss and third, GLP1 agonists may have a natriuretic effect, which could be beneficial in HFpEF.

However, when considering the totality of the presented evidence, the CHMP considered a weight reduction-independent effect of tirzepatide on HFpEF is still doubted and a separate HFpEF indication is not supported. Nonetheless, in view of the clinical importance of the results, the CHMP supported the inclusion of the data in SmPC section 5.1, and the addition of a reference to these data in SmPC section 4.1.

Importance of unfavourable effects:

The most prominent unfavourable effects of TZP were gastrointestinal AEs. This is well established for GLP-1 receptor agonists (GLP-1 RAs). If it leads to tolerability problems, the dose escalation can be stopped early (i.e. treatment is done with a sub-maximal dose) so that this is not a safety concern. Less frequent AEs of TZP and other GLP-1 RAs such as gallbladder disorders or pancreatitis are considered manageable, particularly when patient and prescriber are aware of these possible side effects so that diagnosis is made early. Side effects for which a relation to TZP was not fully established such as depression were infrequent, are therefore less important and are most likely also manageable. The numerically increased mortality with TZP compared to placebo most likely was a chance finding as outlined in Section 7.5 above.

6.7.2. Balance of benefits and risks

The benefit-risk-balance remains positive.

6.7.3. Additional considerations on the benefit-risk balance

The MAH initially submitted a variation application under category C.I.6.a of the variation classification Guideline with the scope to include:

"Extension of indication to include treatment of symptomatic chronic heart failure with preserved

ejection fraction (HFpEF) in adults with obesity for MOUNJARO, based on results from the Phase 3 trial I8F-MC-GPID (SUMMIT). SUMMIT was a randomized, multicenter, international, placebo-controlled, double-blind, parallel-arm study in participants with HFpEF and obesity. The study was designed to evaluate the effect of tirzepatide compared with placebo on both clinical and symptomatic or functional outcomes. As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted."

Based on the assessment of the data contained in the application, and the additional information provided during the procedure, the CHMP is of the view that the following changes to the MA should be introduced:

"*Update of sections 4.1, 4.8 and 5.1 of the SmPC based on final results from the Phase 3 trial I8F-MC-GPID (SUMMIT). SUMMIT was a randomized, multicenter, international, placebo-controlled, double-blind, parallel-arm study in participants with HFpEF and obesity. The study was designed to evaluate the effect of tirzepatide compared with placebo on both clinical and symptomatic or functional outcomes. The Package Leaflet is updated accordingly. Version 4.2 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI."*

These changes fall under category C.1.4 of the variation classification Guideline.

In reply to a Request for Supplementary Information during the procedure, the MAH updated the product information accordingly.

As requested, with the responses the MAH has made an amendment in SmPC section 4.1 to include a cross reference to the trial results with respect to HFpEF in SmPC section 5.1. It is considered acceptable to add the trial results with respect to HFpEF to section 5.1 of the SmPC, and to add to the wording of the current indication a reference to SmPC section 5.1, where the effects on HFpEF are described.

6.8. Conclusions

The benefit/risk balance remains positive.