EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 December 2025
EMADOC-1700519818-2704504
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mounjaro

International non-proprietary name: Tirzepatide

Procedure No. EMA/VR/0000281937

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

ADA	antidrug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic chemical
BG	blood glucose
BMI	body mass index
CI	confidence interval
CRF	case report form
CRO	clinical research organization
CSR	clinical study report
DBP	diastolic blood pressure
ECG	electrocardiogram
EQ-5D-Y-3L	EQ-5D-Youth-3 Levels version Questionnaire
ERA	environmental risk assessment
FAS	full analysis set
FG	fasting glucose
FSG	fasting serum glucose
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
ICF	informed consent form
IEC	independent ethics committee
IG	immunogenicity
IQR	interquartile range
IRB	Institutional Review Board
ITT	intent-to-treat
LDL	low-density lipoprotein
LS	least sqares
MAR	missing at random
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
MNAR	missing not at random
OGTT	oral glucose tolerance test
Plc	placebo
PedsQL	Pediatric Quality of Life Inventory
PI	principal investigator
PK	pharmacokinetics
PT	preferred term
PY	patient years
PYE	patient years of exposure

QTcF	Fridericia's corrected QT interval
QT interval	The portion of an electrocardiogram between the onset of the Q wave and the end of the T wave
QW	once weekly
RA	Receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SDS	standard deviation score
SMBG	self-monitored blood glucose
SMQ	standardised MedDRA query
SOC	system organ class
T2DM	type 2 diabetes mellitus
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TG	triglycerides
TZP	tirzepatide
UACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal
VAS	visual analog scale

Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 27 June 2025 an application for a variation.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise for MOUNJARO, based on final results from study I8F-MC-GPGV (SURPASS-PEDS); this is a study to evaluate efficacy, safety, and pharmacokinetics/pharmacodynamics of tirzepatide compared to placebo in paediatric and adolescent participants with type 2 diabetes mellitus inadequately controlled with metformin, or basal insulin, or both. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, the 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) EMA/PE/0000237950 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000237950 was completed.

The PDCO issued an opinion on compliance for the PIP EMA/PE/0000237950.

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 did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig Co-Rapporteur: Not applicable

Timetable	Actual dates
Submission date:	27 Jun 2025
Start of procedure:	19 Jul 2025
CHMP Rapporteur's preliminary assessment report circulated on:	18 Sep 2025
PRAC Rapporteur's preliminary assessment report circulated on:	18 Sep 2025
PRAC outcome:	2 Oct 2025
Joint Rapporteur's updated assessment report circulated on:	9 Oct 2025
Request for supplementary information adopted by the CHMP on:	16 Oct 2025
MAH's responses submitted to the CHMP on:	11 Nov 2025
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	12 Nov 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 Nov 2025
PRAC outcome:	27 Nov 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	04 Dec 2025
CHMP opinion:	11 Dec 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Type 2 diabetes mellitus is a metabolic disorder characterized by insulin resistance and relative insulin deficiency, leading to chronic hyperglycaemia. It results from impaired cellular response to insulin and inadequate pancreatic beta-cell function. Key features include dysregulated glucose homeostasis and progressive beta-cell dysfunction. Major risk factors are obesity, sedentary lifestyle, genetic predisposition, and aging. Chronic hyperglycaemia can cause microvascular and macrovascular complications. Management involves lifestyle modification, glucose-lowering medications, and monitoring to prevent complications.

As obesity increases in the paediatric population, the prevalence of T2DM has increased as well. Among children and adolescents, T2DM is a more aggressive disease than in adults (Amutha et al. 2017; Savic Hitt and Katz 2020; TODAY Study Group 2021), with higher insulin resistance, more rapid decline in β-cell function, and higher risk of microvascular and macrovascular complications at a younger age (TODAY Study Group 2021). Based on these factors, better outcomes can be expected with early detection and early intervention (ISPAD 2024).

Currently, Mounjaro is approved in adults in the following indications:

Type 2 diabetes mellitus
Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

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

For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.

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

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

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

State the claimed therapeutic indication

The MAH is proposing to extend the Type 2 diabetes mellitus indication to the paediatric population as follows (**in bold**):

Type 2 diabetes mellitus
*Mounjaro is indicated for the treatment of adults**, adolescents and children aged 10 years and above** with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise*

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

For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.

Epidemiology

European-based studies, inclusive of children from birth, have found prevalence of T2DM in the EU ranging from 0.006 to 0.029 per 1000 persons, considerably lower than those estimated in the US (Khanolkar et al. 2016; Oester et al. 2016; Neu et al. 2018).
In the US, the prevalence of T2DM among the pediatric population aged 10 to 19 years has approximately doubled from 2001 to 2017, rising from 0.34 to 0.67 per 1000 persons. The highest prevalence was among American Indian and Black youth, and the greatest absolute increases were observed among non-Hispanic Black (1.80 per 1000 persons) and Hispanic (1.03 per 1000 persons) youths (Lawrence et al. 2021). Between 2014 and 2015, 5758 new cases were diagnosed in this age group (CDC [WWW]). Moreover, the SEARCH for Diabetes in Youth study reported an annual incidence of T2DM of 17.9 per 100,000 people aged 19 years or less, with peak diagnosis at age 16 (Wagenknecht et al. 2023).

Clinical presentation and diagnosis

Type 2 diabetes presents with a gradual onset of polyuria, polydipsia, polyphagia, fatigue, and blurred vision. Early-stage patients may be asymptomatic. Complications include recurrent infections, delayed wound healing, peripheral neuropathy, and in severe cases, hyperosmolar hyperglycaemic state.

Four diagnostic tests for T2DM are currently recommended, including measurement of fasting plasma glucose, 2-hour (2-h) post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT), HbA1c and a random blood glucose in the presence of signs and symptoms of diabetes.

People with fasting plasma glucose values of ≥7.0 mmol/L (126 mg/dl), 2-h post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl), HbA1c ≥ 6.5% (48 mmol/mol) or a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) in the presence of signs and symptoms are considered to have diabetes (WHO 2019).

Management

The recommended treatment for paediatric T2DM is similar to the one in adults, with emphasis on a step-wise approach starting with lifestyle modifications, particularly diet and exercise, followed by the use of a single medical therapy and later by two therapies in combination. The aim is that the patient achieves and maintains low levels of glucose in the blood in order to prevent long-term complications.

Youth with T2DM have fewer approved glucose-lowering treatments available compared to adults (ADA 2025). The currently approved therapies for the proposed indication include:

- metformin
- insulin
- liraglutide 1.2 and 1.8 mg QD SC
- exenatide 2 mg QW SC
- dulaglutide 0.75 and 1.5 mg QW SC
- dapagliflozin 5 and 10 mg QD orally, and
- empagliflozin 10 and 25 mg QD orally.

Despite the proven safety and efficacy of these agents for the paediatric and adolescent population, there is generally less glycaemic efficacy, and a higher rate of treatment failure compared to adults with T2DM (Lee Jia Jia et al. 2024). In recent Phase 3 trials of the approved GLP-1 RAs, the percentage of participants who did not achieve HbA1c <7% and ≤6.5%, respectively, at 6 months, was 49% and 53.3% in the pooled dulaglutide groups, approximately 68% and 80% in the exenatide treatment group, and 36.3% (only HbA1c <7% was reported) in the liraglutide treatment group. Furthermore, after initial improvements in HbA1c and FSG, there was subsequent worsening of glycaemic control through Week 52 in these trials (Tamborlane et al. 2019, 2022; Arslanian et al. 2022). Additionally, no approved therapy in this population has been found to have a significant or clinically meaningful effect on weight-related parameters when compared with placebo (ADA 2025). Consequently, more efficacious treatment options are needed to help paediatric and adolescent patients with T2DM achieve their treatment goals safely.

2.1.2. About the product

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. It is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

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

Tirzepatide received initial marketing authorization on 15 September 2022 in the EU as a once-weekly (QW) subcutaneous injection to improve glycaemic control in adult participants with type 2 diabetes mellitus (T2DM). Tirzepatide has been authorized in adult participants with T2DM in 63 countries with additional applications under review in other regions. Tirzepatide is also approved in the EU for weight management in adults with obesity, or overweight with weight-related comorbidities.

The proposed therapeutic indication is for the use of tirzepatide for the treatment of paediatric patients 10 years and older with T2DM as an adjunct to diet and exercise.

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

Compliance with paediatric investigation plan (PIP)

This application has completed all commitments of the agreed PIP for tirzepatide (Mounjaro) for the condition of treatment of T2DM (EMA/PE/0000237950), in accordance with Regulation (EC) No 1901/2006. A Positive Opinion of the Paediatric Committee on compliance with a PIP was issued on 20-June-2025 (EMA/PE/0000265085). The study submitted with this application (GPGV) corresponds to "Study 2" of the original PIP.

General comments on compliance with GLP, GCP

GCP

The clinical study included in this submission was conducted and reported in accordance with the ethical principles originating from the Declaration of Helsinki and in accordance with ICH Good Clinical Practice guidelines, the applicable regulatory requirements and in compliance with the study protocol. The applicant also declares that Study I8F-MC-GPGV (EudraCT: 2021-003612-31), which was conducted in centres outside the European Union (Australia, Brazil, India, Israel, Italy, Mexico, United Kingdom, and United States of America) meets the ethical requirements of Directive 2001/20/EC or Regulation (EU) No 536/2014.

GLP

The bioanalytical part was conducted at Q2 Solutions (19 Brown Road, Ithaca, NY 14850). The content of the bioanalytical report has been reviewed for completeness, accuracy, and scientific integrity. The bioanalytical analysis was conducted in accordance with applicable Q2 Solutions SOPs, the bioanalysis plan and amendments, and the protocol. Moreover, the Quality Assurance Unit has reviewed the bioanalytical analyses and raw data, and has determined that the results reported accurately reflect the raw data generated during the conduct of this study.

2.2. Non-clinical aspects

Besides an environmental risk assessment (ERA), no new non-clinical data have been submitted in this application, which is considered acceptable.

A toxicity study in juvenile rats was already submitted and assessed with the original MAA; study number 00353469, title, "A Subcutaneous Injection Juvenile Toxicity Study in Sprague Dawley Rats Administered Tirzepatide Every Three Days from Postnatal Day 21 through 84". The effects of TZP seen in juvenile rats were similar to those observed in adult animals.

2.2.1. Ecotoxicity/environmental risk assessment (ERA)

The ERA provided is considered complete and acceptable. Tirzepatide is administered in parenteral form and has been described not to be excreted in intact form. 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.

2.2.2. Discussion on non-clinical aspects

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.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of tirzepatide. Considering the above data, tirzepatide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Number of randomly assigned participants	99
Patient population	Paediatric patients (≥10 to<18 years of age) with type 2 diabetes mellitus (T2DM).
Total treatment duration	52 weeks (30 weeks double-blind period and 22 weeks open-label extension)
Randomization ratio	1:1:1 (TZP 5 mg: TZP 10 mg: placebo)

Number of participants receiving at least 1 dose	Total: N=99 Plc/TZP 5 mg: N=34 TZP 5 mg: N=32 TZP 10 mg: N=33
Study design	Randomized, double blind, placebo-controlled, 3-arm (tirzepatide 5 mg and 10 mg, and placebo), parallel group, multi-center phase 3 study

Abbreviations: T2DM: Type 2 diabetes mellitus; TZP: tirzepatide

2.3.2. Pharmacokinetics

Population pharmacokinetic analysis

Data

The paediatric Phase 3 study, I8F-MC-GPGV (GPGV; SURPASS-PEDS), investigated the effects of tirzepatide in children and adolescents with T2DM aged between 10 to less than 18 years who had inadequate glycemic control, despite diet and exercise, with metformin and/or basal insulin. The doses of tirzepatide 5 and 10 mg QW SC were evaluated as maintenance doses for efficacy and safety in paediatric patients compared to placebo (patients in placebo arm transitioned to 5 mg of tirzepatide QW after 30 weeks). There were 22 participants aged 10 to 13 years (23.7%) and 71 participants aged 14 to 17 years (76.3%). Approximately half of participants were 10 to 15 years old (n=53, 57%) and half of participants were 16 to 17 years old (n=40, 43%).

Tirzepatide PK data

Four post-dose samples from each participant taken at four different visits during randomly assigned time windows. Specifically, at the Week 0 visit, the sample was collected at any time after the first dose on that same day. For visits in Week 7, 16, and 29, each participant was assigned via interactive web-response system (IWRS) to one of the sampling PK time windows of 1 to 24 hours, 24 to 96 hours, or 120 to 168 hours post-dose. A PK sample was also taken at any early termination (ET) visit.

The current analysis population included 93 participants contributing 664 tirzepatide concentration measurements; of these, 599 (90.2%) were non-BLQ observations, and 65 (9.8%) were BLQ samples.

The majority of BLQ PK samples were from the PK sampling windows of greater than 168 hours after dose, or 0 to 24 hours after dose (Table S3). Given the low percentage of BLQ samples (< 10%), the BLQ records were ignored in this population PK analysis (M1 method).

The estimated glomerular filtration rate (eGFR) in adults and adolescents 16 years and older was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (2021 version). In children up to 16 years of age, eGFR was calculated using the Bedside Schwartz equation as follows:

$$\mathrm{eGFR} = 0.413 \cdot \mathrm{HT}/\mathrm{Scr}$$

where: eGFR = estimated glomerular filtration rate ($\mathrm{mL/min/1.73m^2}$), HT = height (cm), Scr = serum creatine (mg/dL).

Anti-tirzepatide antibodies

A majority of the positive anti-tirzepatide antibody observations occurred in the tirzepatide 10 mg treatment arm (120 observations), with 84 positive observations occurring in the tirzepatide 5 mg treatment arm and the remaining 54 positive observations occurring in the placebo/tirzepatide 5 mg treatment arm. There were no apparent trends between antibody status and PK profile, or between antibody titer and PK profile.

Model building

A population PK model was previously developed using data from multiple clinical studies of tirzepatide as a treatment of T2DM in adult participants. The tirzepatide PK was well described using a two-compartment model with first-order absorption and linear clearance. The influence of body weight on clearance and volume parameters was implemented with fixed exponents (0.8 for clearance and 1 for volume).

The model structure and parameter estimates from the previous model were used to inform the base model of the current analysis which uses sparse PK data from SURPASS-PEDS alone. The parameter estimates of apparent intercompartmental clearance (Q/F) and apparent peripheral volume of distribution (V3/F) from the adult model were used as informative priors to support the estimation of Q/F and V3/F in the current paediatric PK analysis due to the lack of data during the distribution phase. Interindividual variability (IIV) was described using an exponential error model, the multivariate vector of IIV random effects (across parameters within each individual) had a variance-covariance matrix OMEGA (Ω). Residual variability (ε) was modeled with a proportional error term using the variance-covariance matrix of the residual random errors (Σ, SIGMA). IIV (η) was also included on the residual error.

The individual parameter values for CL/F, Q/F, V2/F, and V3/Fin the paediatric model were described as a function of individual time-varying body weight, normalized by 70 kg with a fixed exponent of 0.8 (θ6) for clearance terms and a fixed exponent of 1 (θ7) for anatomical volumes (Equations 18 and 19).

The individual parameter values for CL/F are also described as a function of individual baseline age. The age was normalized by the reference value of 15 (the median baseline age in the current analysis dataset) with an estimated exponent θ8 (Equation 20).

$$\text{WTCOV1} = \left(\frac{\text{Body weight}}{70}\right)^{\theta_6} \quad (18)$$

$$\text{WTCOV2} = \left(\frac{\text{Body weight}}{70}\right)^{\theta_7} \quad (19)$$

$$\text{AGECL} = \left(\frac{\text{Age}}{15}\right)^{\theta_8} \quad (20)$$

The parameter estimates of the final model are listed in Table 1.

Table 1: PK final model: summary of fixed and random effect parameter estimates

			Estimate	Shrinkage (%)	95% CI
Structural model parameters					
CL/F (L/h)	θ_1	Apparent clearance	0.0450	-	0.0422, 0.0479
V2/F (L)	θ_2	Apparent central volume of distribution	2.45	-	1.58, 3.31
Q/F (L/h)	θ_3	Apparent intercompartmental clearance	0.126	-	0.107, 0.145
V3/F (L)	θ_4	Apparent peripheral volume of distribution	3.95	-	3.64, 4.26
k_a (h^{-1})	θ_5	First-order absorption rate constant	0.0367	-	0.0254, 0.0481
Covariate effect parameters					
CL/F ~ Weight	θ_6	Effects of time-varying weight on CL/F and Q/F	0.800	-	FIXED
V/F ~ Weight	θ_7	Effects of time-varying weight on V2/F and V3/F	1.00	-	FIXED
CL/F ~ Age	θ_8	Effect of baseline age on CL/F	-0.439	-	-0.969, 0.0911
Interindividual variance parameters					
IIV-CL/F	$\Omega_{(1,1)}$	Variance of apparent clearance	0.0649 [CV%=25.9]	7.85	0.0109, 0.119
IIV-V2/F	$\Omega_{(2,2)}$	Variance of apparent central volume of distribution	0.622 [CV%=92.9]	20.3	0.124, 1.12
IIV-ResErr	$\Omega_{(6,6)}$	Variance of residual error	0.169 [CV%=43.0]	9.21	0.0353, 0.303
Residual variance					
Proportional	$\Sigma_{(1,1)}$	Variance	0.134 [CV%=36.6]	4.41	0.0946, 0.173

CI: confidence interval; CV: coefficient of variation; IIV: interindividual variability; SE: standard error.
Confidence intervals = estimate ± 1.96 · SE.
CV% of log-normal omegas = sqrt(exp(estimate) - 1) · 100.
CV% of sigma = sqrt(estimate) · 100.
Source code: pk-param-table.R
Source file: pk-param-combined-217.tex

Dose-normalized concentrations versus time after dose for the different doses administered including LOESS function-lines are depicted below.

Solid circles represent the individual observations. Lines represent LOESS smooth lines through the data. Individual observations beyond 300 hours after dose are not shown in the plot.

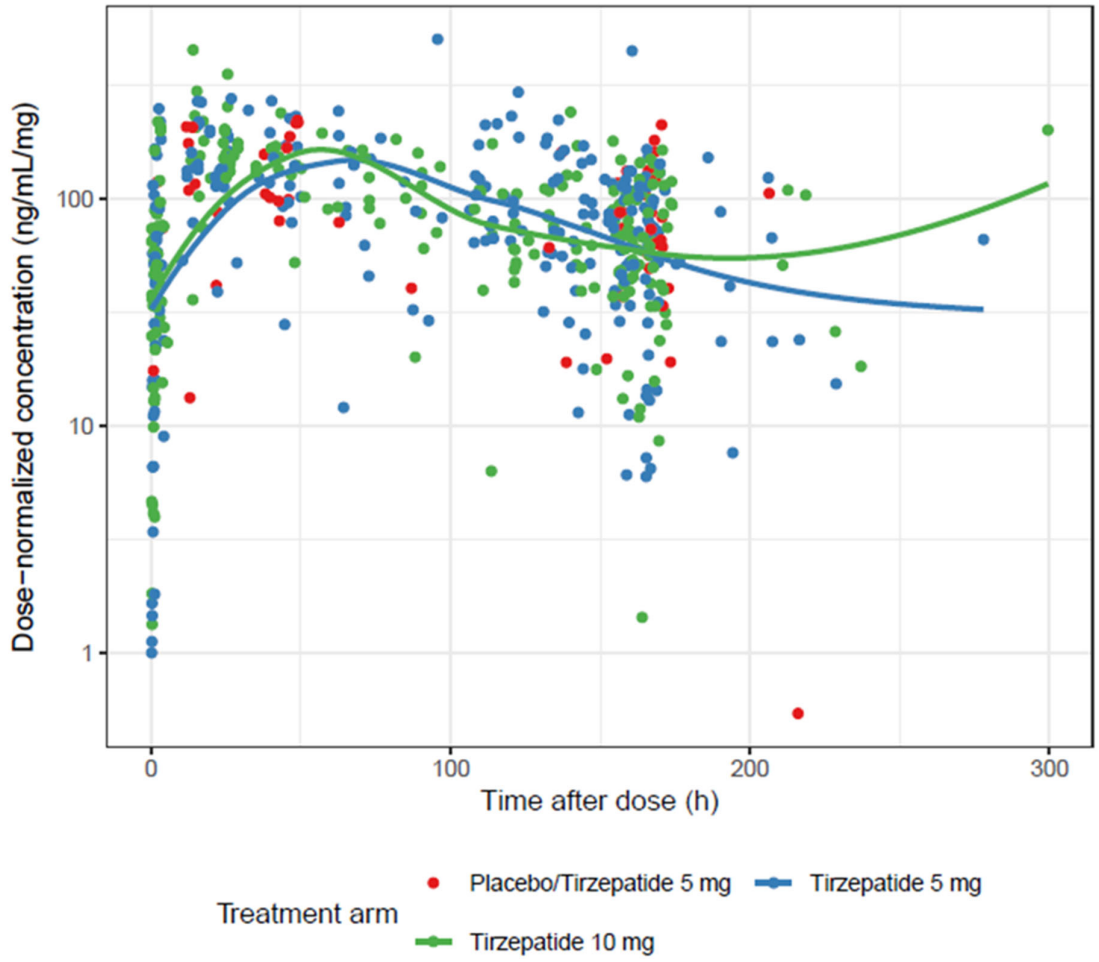


Figure 1: PK: dose-normalized tirzepatide concentration versus time after dose

Figure 2 presents the prediction-corrected VPC of the final model for all doses and separated by treatment in Figure 3.

Observed values are indicated by black circles. Black lines represent the median (solid) or 5th and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (gray) or 5th and 95th percentiles (blue) of the simulated data.

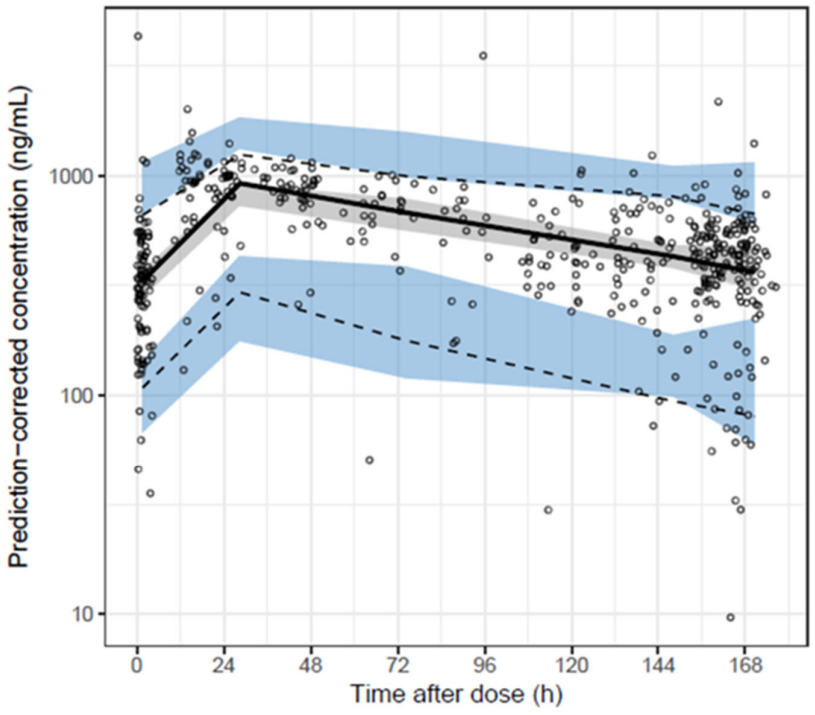


Figure 2: PK final model: prediction corrected visual predictive check of tirzepatide concentrations versus time after dose within one week

Observed values are indicated by black circles. Black lines represent the median (solid) or 5th and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (gray) or 5th and 95th percentiles (blue) of the simulated data.

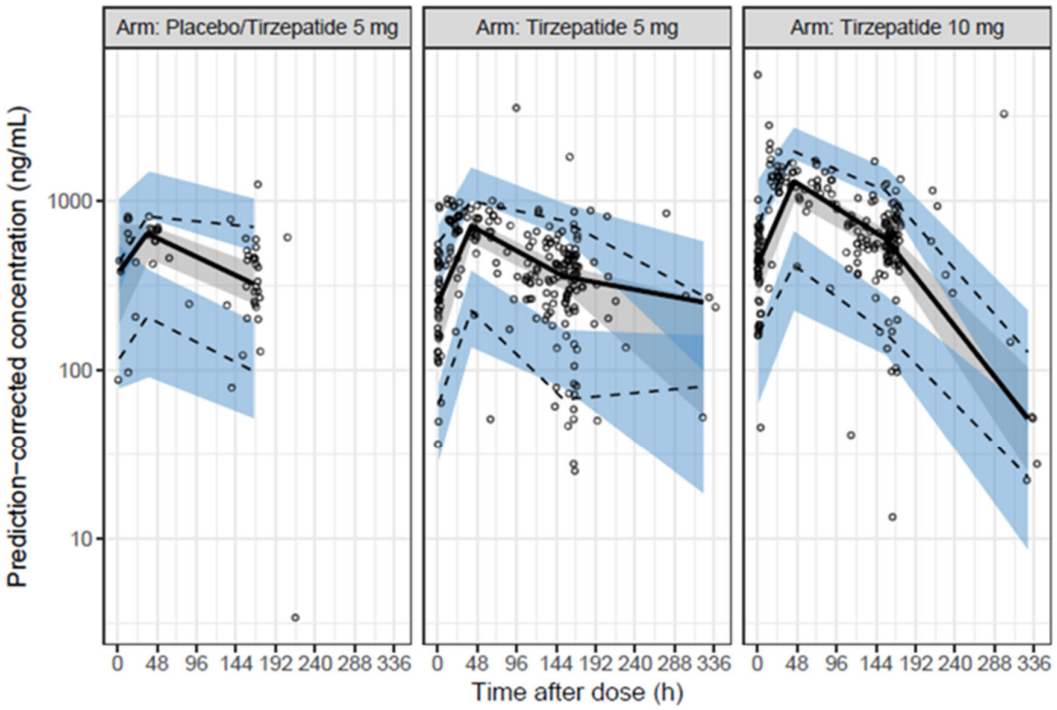


Figure 3: PK final model: prediction corrected visual predictive check of the tirzepatide concentrations versus time after dose stratified by treatment arm

A comparison of simulated exposures (AUC and Cmax) in adult and paediatric patients is given in Figure 4 for the two different doses.

The median is designated by a solid line in the center of the box. The box indicates the interquartile range (IQR) with whiskers extending to 1.5 · IQR. The notch around the median line represents approximately the 95% confidence interval of the median. Mean baseline body weight in simulated data was 95.9 kg for pediatrics and 89.8 kg for adults. Mean baseline age in simulated data was 14.8 years for pediatrics and 58.2 years for adults.

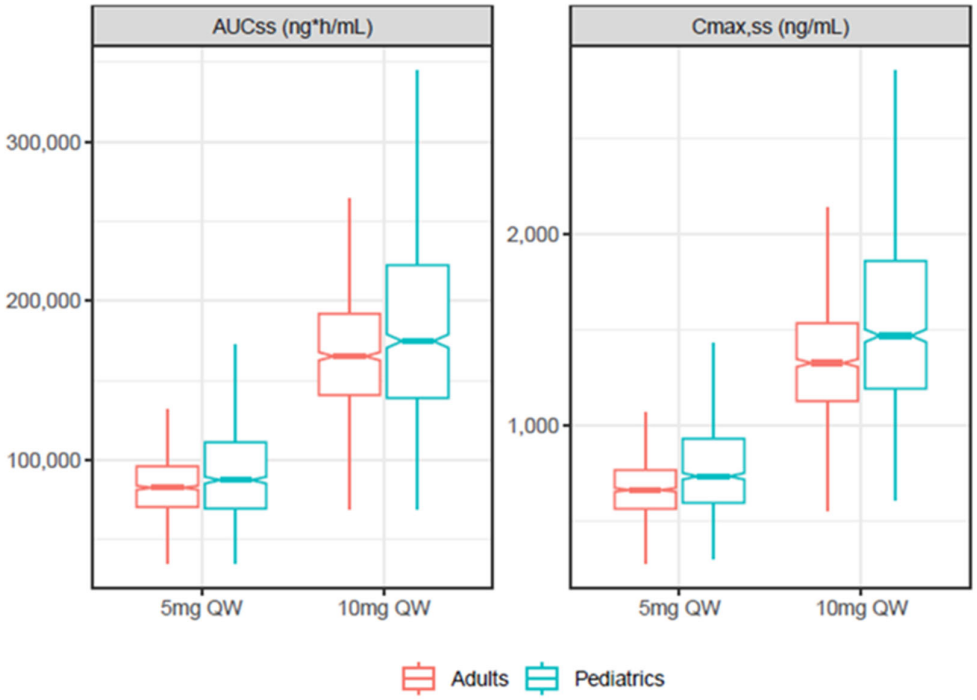
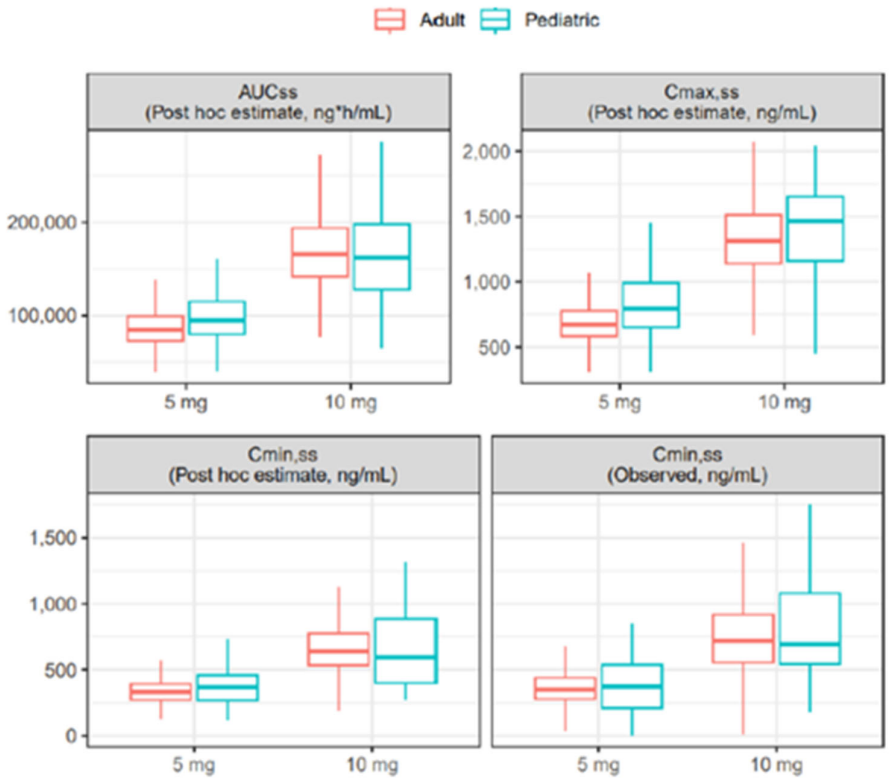


Figure 4: PK final model: simulated tirzepatide area under the concentration-time curve over the dosing interval at steady state (AUC_{ss}) and maximum concentration in the dosing interval at steady state ($C_{max,ss}$) in paediatrics and adults

Figure 5 shows boxplots of post hoc predicted exposure for AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, as well as Study I8F-MC-GPGV "trough" concentrations collected at steady state, which are observed $C_{min,ss}$. The tirzepatide exposures are stratified by doses of 5 mg and 10 mg for adult and paediatric participants.



Source code: script/pk/pk-ema-qns.R
Source graphic: deliv/figure/pk/ema/pk-box-obs-v2.pdf

Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; Cmax,ss = maximum concentration in the dosing interval at steady state; Cmin,ss = minimum concentration in the dosing interval at steady state; IQR = interquartile range.
Median values are designated by a solid line in the centre of the box. Boxes indicate the IQR with whiskers extending to 1.5 * IQR.

Figure 5: Post hoc estimates and observed values of tirzepatide exposures for paediatric and adult participants

Tirzepatide exposure was simulated across the range of paediatric body weight in Study GPGV. The body weight percentiles used for the summary were based on the minimum weight of each subject at any time during the study. The percentile bins and corresponding body weight ranges used for stratification were:

- Minimum up to fifth percentile: 47.5 kg to 50.3 kg

- Fifth percentile up to 25th percentile: 50.3 kg to 63.1 kg

- 25th percentile up to 75th percentile: 63.1 kg to 106 kg

- 75th percentile up to 95th percentile: 106 kg to 131 kg, and

- 95th percentile up to maximum: 131 kg to 143 kg.

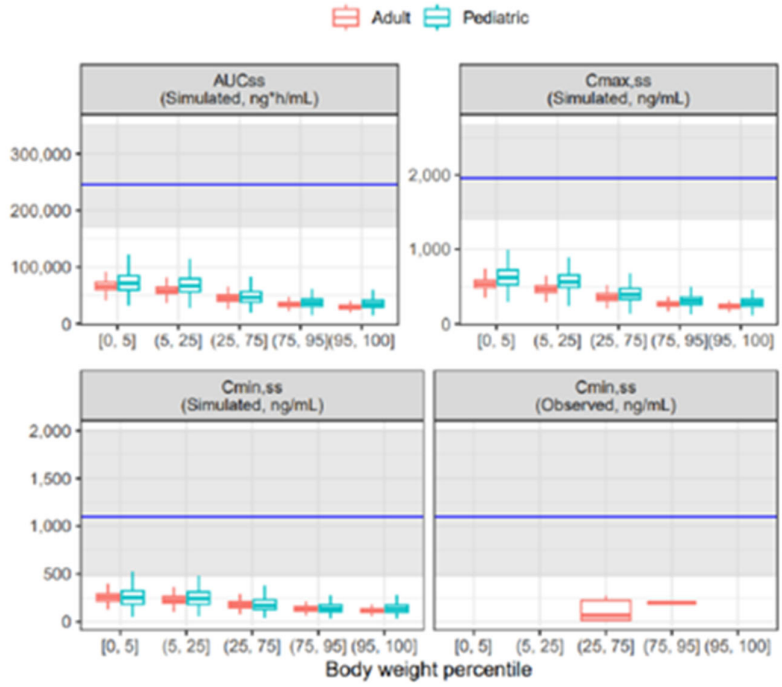
The simulated steady-state tirzepatide exposures for once-weekly tirzepatide in paediatric participants are shown in

- Figure 6: for tirzepatide 2.5 mg

- Figure 7: for tirzepatide 5 mg, and

- Figure 8: for tirzepatide 10 mg.

Figure 9 shows the simulated tirzepatide exposures for once-weekly tirzepatide in paediatric participants for ages 10, 15, and 17 years, which represent the minimum age allowed by the protocol, the median age, and the maximum age of participants, respectively. Appendix 1 includes tables of summary statistics of the simulated steady-state tirzepatide exposures in paediatric and adult participants at different body weight percentiles and a table of simulated steady-state tirzepatide exposures in paediatric participants at different ages. The simulated paediatric exposures stratified by age or body weight were below or comparable to the maximum adult dose of tirzepatide 15 mg. In summary, simulated paediatric exposures up to 10 mg were generally below or comparable to the maximum adult dose of tirzepatide 15 mg across the assessed body weight ranges, and all doses fell within the range associated with clinically meaningful HbA1c reductions. Therefore, Lilly does not believe that any addition to the Warnings and Precautions for Use in Section 4.4 of the SmPC specific to the paediatric population is warranted based on the exposure data presented.



Source code: script/pk/pk-ema-qns.R
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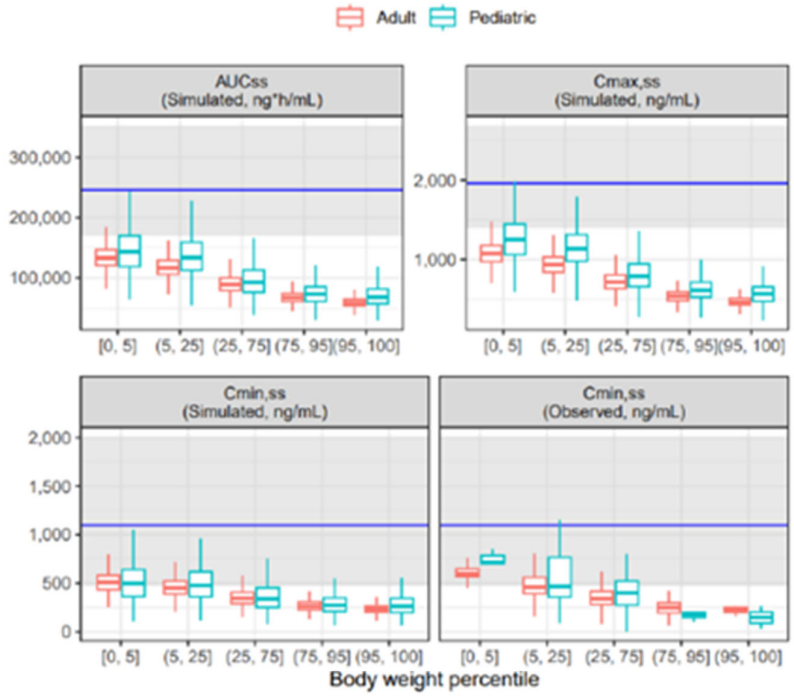
Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; Cmax,ss = maximum concentration in the dosing interval at steady state; Cmin,ss = minimum concentration in the dosing interval at steady state; IQR = interquartile range.
Median values are designated by a solid line in the centre of the box. Boxes indicate the IQR with whiskers extending to 1.5 * IQR. Observed values (for Cmin,ss) or post hoc estimates (for Cmax,ss and AUCss) for adults treated with tirzepatide 15 mg once weekly are represented by the grey region (fifth and 95th percentiles) and blue horizontal lines (medians). For each participant, the observed Cmin,ss is the median of all concentrations 7 days after the previous dose (±2 days), taken after at least 4 consecutive doses. Body weight percentiles are based on the minimum weight of each participants in Study GPGV: [0,5]: 47.5 to <50.3 kg; [5, 25]: 50.3 to <63.1 kg; [25, 75]: 63.1 to <106 kg; [75, 95]: 106 to <131 kg; [95, 100]: 131 to <143 kg.

Figure 6: Simulated and observed exposures for tirzepatide 2.5 mg once weekly in paediatric and adult participants at different body weight percentiles



Source code: script/pk/pk-ema-qns.R
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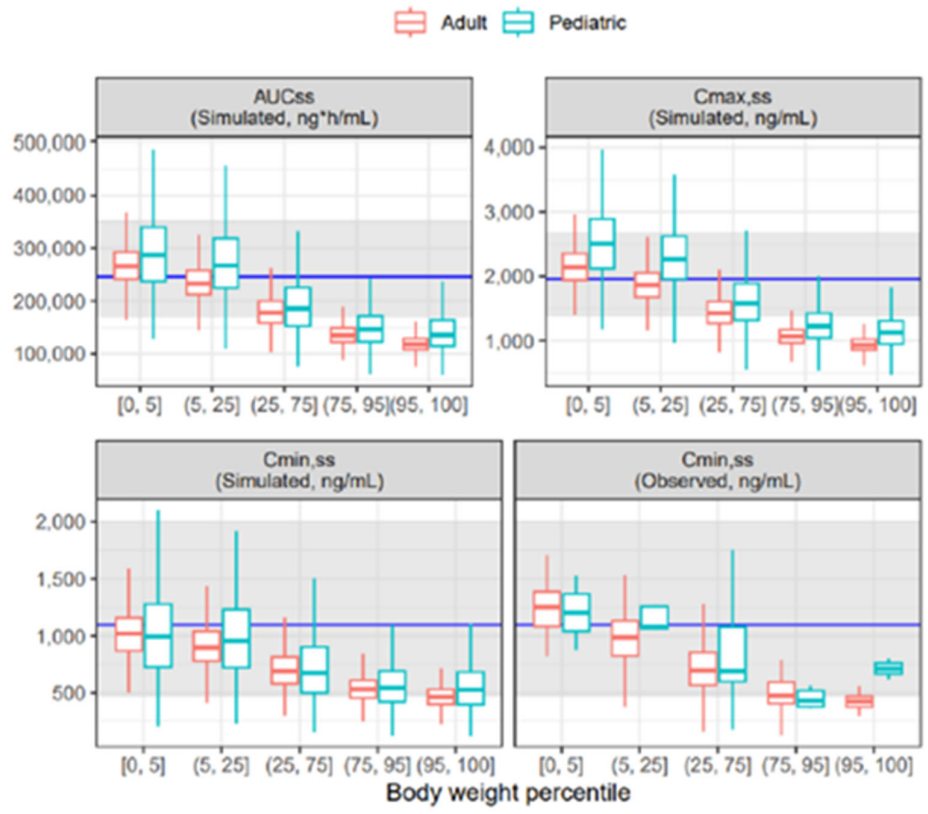
Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; Cmax,ss = maximum concentration in the dosing interval at steady state; Cmin,ss = minimum concentration in the dosing interval at steady state; IQR = interquartile range.
Median values are designated by a solid line in the centre of the box. Boxes indicate the IQR with whiskers extending to 1.5 * IQR. Observed values (for Cmin,ss) or post hoc estimates (for Cmax,ss and AUCss) for adults treated with tirzepatide 15 mg once weekly are represented by the grey region (fifth and 95th percentiles) and blue horizontal lines (medians). For each participant, the observed Cmin,ss is the median of all concentrations 7 days after the previous dose (±2 days), taken after at least 4 consecutive doses. Body weight percentiles are based on the minimum weight of each participant in Study GPGV: [0,5]: 47.5 to <50.3 kg; [5, 25]: 50.3 to <63.1 kg; [25, 75]: 63.1 to <106 kg; [75, 95]: 106 to <131 kg; [95, 100]: 131 to <143 kg.

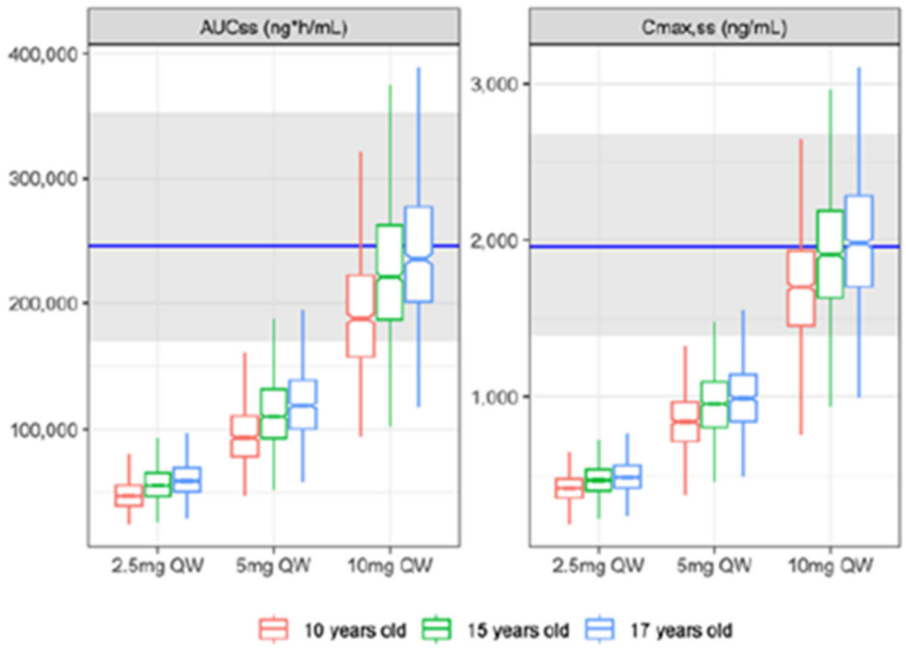
Figure 7: Simulated and observed exposures for tirzepatide 5 mg once weekly in paediatric and adult participants at different body weight percentiles



Source code: script/pk/pk-ema-qns.R
Source graphic: deliv/figure/pk/ema/pk-box-sim-10mg-v2.pdf

Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; Cmax,ss = maximum concentration in the dosing interval at steady state; Cmin,ss = minimum concentration in the dosing interval at steady state; IQR = interquartile range.
Median values are designated by a solid line in the centre of the box. Boxes indicate the IQR with whiskers extending to 1.5 * IQR. Observed values (for Cmin,ss) or post hoc estimates (for Cmax,ss and AUCss) for adults treated with tirzepatide 15 mg once weekly are represented by the grey region (fifth and 95th percentiles) and blue horizontal lines (medians). For each participant, the observed Cmin,ss is the median of all concentrations 7 days after the previous dose (±2 days), taken after at least 4 consecutive doses. Body weight percentiles are based on the minimum weight of each participant in Study GPGV: [0,5]: 47.5 to <50.3 kg; [5, 25]: 50.3 to <63.1 kg; [25, 75]: 63.1 to <106 kg; [75, 95]: 106 to <131 kg; [95, 100]: 131 to <143 kg.

Figure 8: Simulated and observed exposures for tirzepatide 10 mg once weekly in paediatric and adult participants at different body weight percentiles

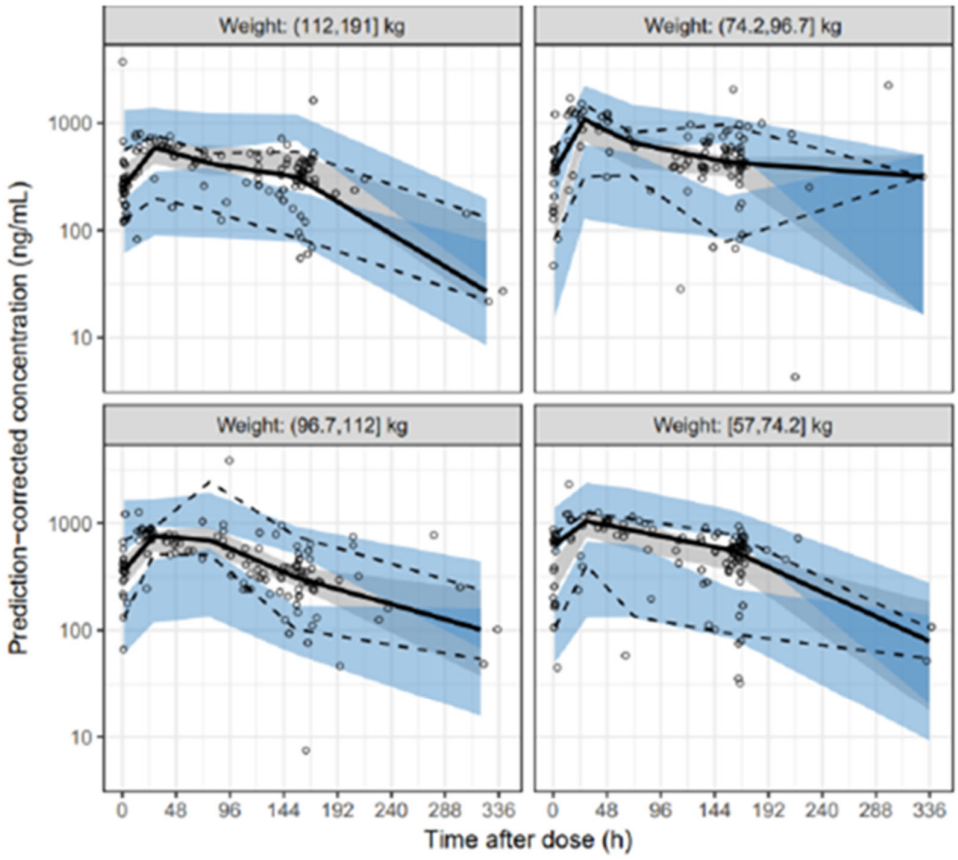


Source code: script/pk/pk-ema-qns.R
Source graphic: deliv/figure/pk/ema/pk-box-sim-age.pdf

Abbreviations: AUCss = area under the concentration-time curve over the dosing interval at steady state; Cmax,ss = maximum concentration in the dosing interval at steady state; IQR = interquartile range; QW = once weekly.
Median values are designated by a solid line in the centre of the box. Boxes indicate the IQR with whiskers extending to 1.5 * IQR. Post hoc estimates (for Cmax,ss and AUCss) for adults treated with tirzepatide 15 mg once weekly are represented by the grey region (fifth and 95th percentiles) and blue horizontal lines (medians). Ages 10, 15, and 17 years represent the minimum age allowed by the protocol, the median age, and the maximum age of participants, respectively.

Figure 9: Simulated exposures for tirzepatide once weekly in paediatric participants at different ages

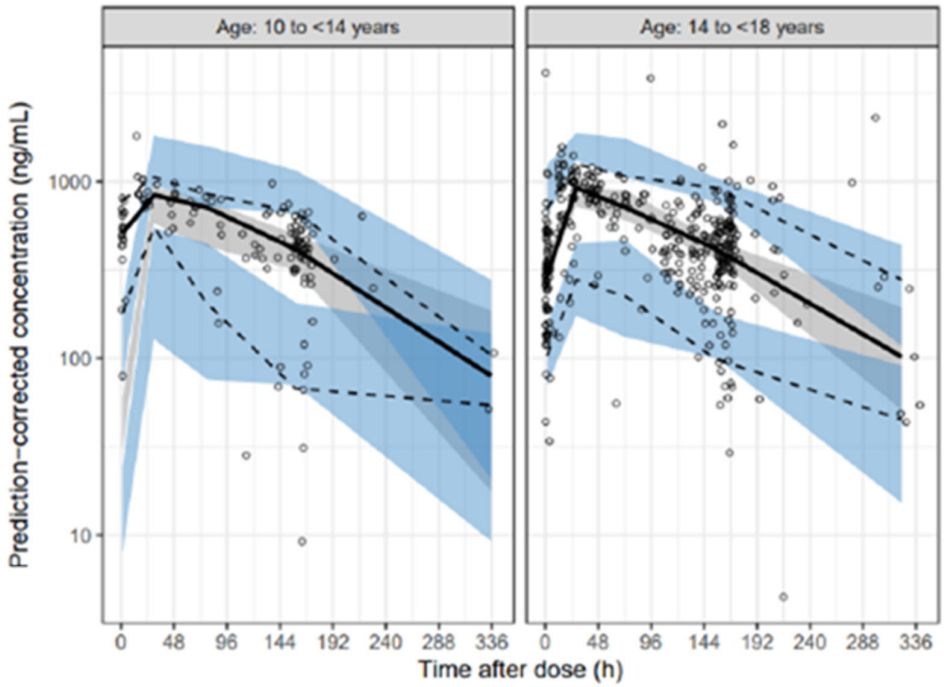
Figure 10 shows the prediction-corrected visual predictive check stratified by quartiles of baseline body weight. Prediction-corrected visual predictive checks stratified by age are shown in Figure 11: from 10 to less than 14 years of age, and from 14 to less than 18 years of age (evenly split across the age range allowed for the study), and Figure 12: from 10 to less than 16 years of age, and from 16 to less than 18 years of age (age groups with each representing approximately half of the participants with tirzepatide concentration measurements in the study). The prediction-corrected visual predictive checks, stratified by body weight and age, demonstrate that the paediatric population PK model adequately describes the paediatric data, as evidenced by the majority of observed paediatric concentrations falling within the model's prediction intervals. Therefore, the paediatric population PK model was not updated.



Source code: pk−vpc.R
Source graphic: deliv/figure/pk/vpc/217/pk−pcvpc−217−wtgrp.pdf

Observed values are indicated by black circles. Black lines represent the median (solid) or fifth and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (grey) or fifth and 95th percentiles (blue) of the simulated data.

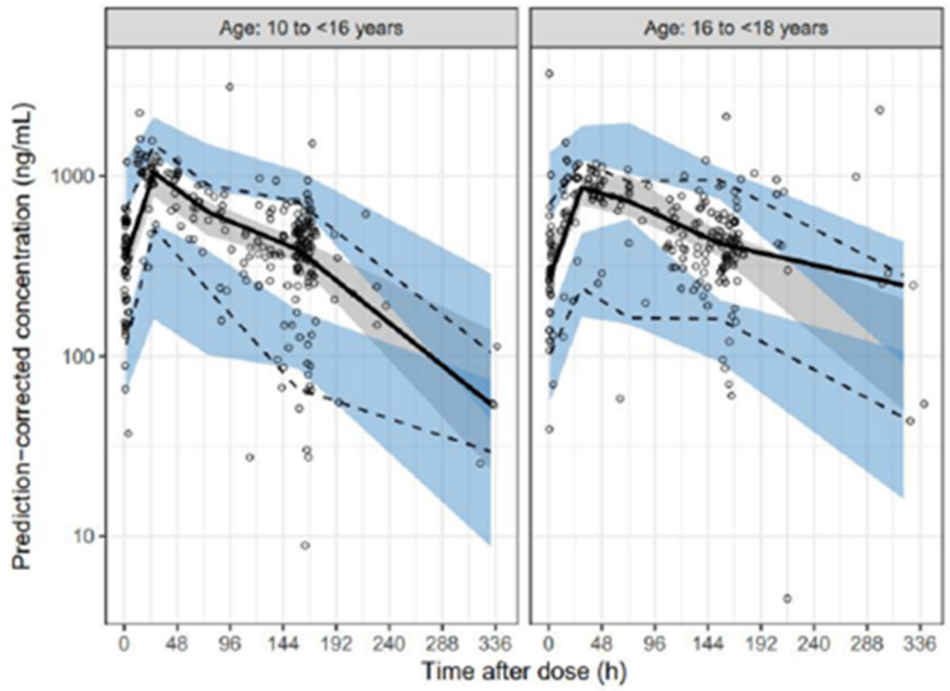
Figure 10: Prediction-corrected visual predictive check of tirzepatide concentrations versus time after dose stratified by baseline body weight



Source code: pk−vpc.R
Source graphic: deliv/figure/pk/vpc/217/pk−pcvpc−217−agegrp1.pdf

Observed values are indicated by black circles. Black lines represent the median (solid) or fifth and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (grey) or fifth and 95th percentiles (blue) of the simulated data.

Figure 11: Prediction-corrected visual predictive check of tirzepatide concentrations versus time after dose stratified by age (10 to <14 years of age and 14 to <18 years of age)



Source code: pk-vpc.R
Source graphic: deliv/figure/pk/vpc/217/pk-pcvpc-217-agegrp2.pdf

Observed values are indicated by black circles. Black lines represent the median (solid) or fifth and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (grey) or fifth and 95th percentiles (blue) of the simulated data.

Figure 12: Prediction-corrected visual predictive check of tirzepatide concentrations versus time after dose stratified by age (10 to <16 years of age and 16 to <18 years of age)

When evaluating covariate effects on tirzepatide AUC_{ss} and $C_{max,ss}$, AUC_{ss} and $C_{max,ss}$ decreased with increasing body weights and slightly increased with increasing age. The age range (11 to 17 years old) in the current paediatric dataset was limited. Age effects on tirzepatide steady-state exposures were small with effect sizes fully within the 80% - 125% range. Tirzepatide AUC_{ss} and $C_{max,ss}$ decreased approximately by 21% and 45% at weights of 120 kg and 190 kg (approximately 85th percentile and the maximum weight in the current dataset), respectively, compared to a 90 kg reference participant. Tirzepatide AUCss and Cmax,ss increased approximately by 60% at a weight of 50 kg (approximately the minimum weight in the current dataset), compared to a 90 kg reference participant (Figure 13 and Figure 14).

The reference participant was 90 kg and 15 years old. The gray shaded area is the reference range with a lower bound of 0.8 and an upper bound of 1.25. Solid diamonds outlined in black represent the median and the solid horizontal lines represent the 95% confidence interval. CI: confidence interval

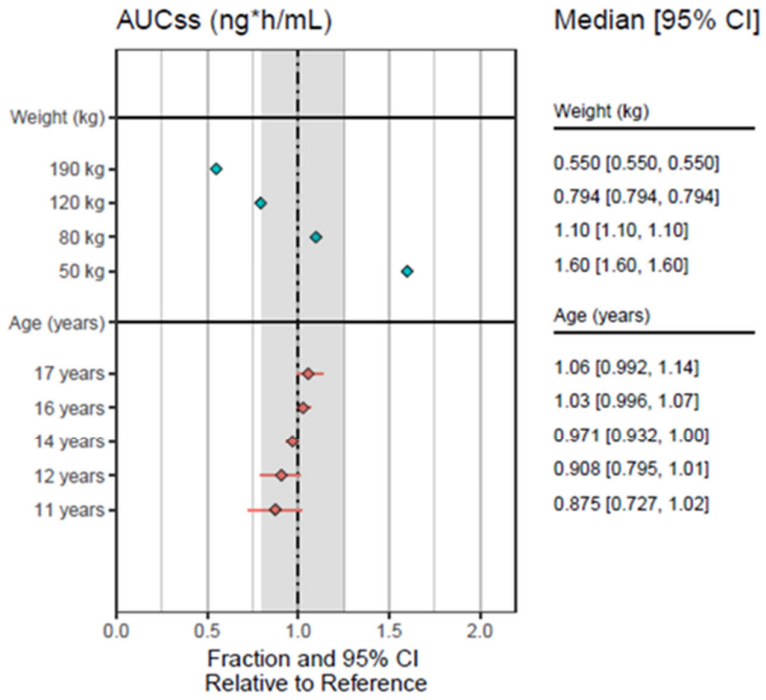


Figure 13: PK final model: covariate effects of body weight and age on the tirzepatide normalized area under the curve at steady-state (AUC_{ss})

The reference participant was 90 kg and 15 years old. The gray shaded area is the reference range with a lower bound of 0.8 and an upper bound of 1.25. Solid diamonds outlined in black represent the median and the solid horizontal lines represent the 95% confidence interval. CI: confidence interval

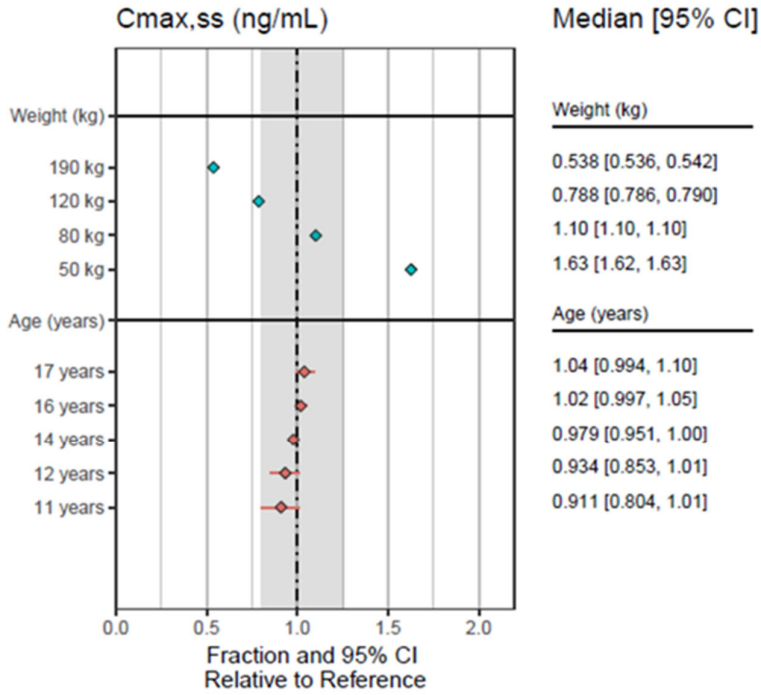


Figure 14: PK final model: covariate effects of body weight and age on the tirzepatide normalized maximum concentration at steady-state (Cmax,ss)

2.3.3. Pharmacodynamics

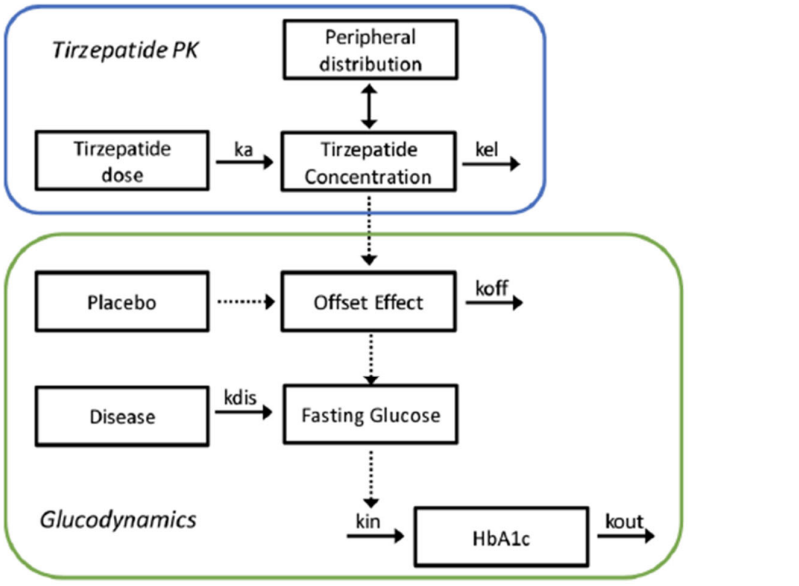
Not applicable

2.3.4. PK/PD modelling

The current analysis population included 93 participants contributing 898 fasting glucose (FG) and 896 HbA1c observations. Efficacy data (body weight, height, fasting serum glucose, HbA1c) were collected during nine visits (Week 0, 4, 8, 12, 16, 30, 42, 52, 56, or ET visit). Gastrointestinal (GI) adverse events (AEs) (nausea, vomiting, and diarrhoea) were reported by participants and entered by study personnel into the electronic case report format each study visit.

ER Analysis of Fasting Glucose and HbA1c

A previously developed ER base model in adult participants was re-used to characterize the effect of tirzepatide on FG and HbA1c in SURPASS-PEDS.



Abbreviations: HbA1c = hemoglobin A1c; ka = absorption rate constant; kdis = disease progression rate; kel = elimination rate constant; kin = input rate; kout = degradation rate constant; koff = offset rate constant; PK = pharmacokinetics.
Note: The solid arrows denote rates or rate constants. The dashed arrows denote an effect.

Figure 15: Fasting glucose/HbA1c base model

In this model, the time course of HbA1c response was driven by FG concentrations through a linked model that fitted both FG and HbA1c data jointly. A disease progression model that integrated an offset compartment, where tirzepatide and placebo effects were included, was utilized to describe FG response over time. The time course of HbA1c was described using an indirect response model dependent on FG. IIV (η) was included on the following model parameters: (1) baseline FG; (2) baseline HbA1c; (3) placebo effect; (4) rate constant for delay in treatment effect (Koff); (5) degradation rate for HbA1c (Kout); (6) rate of disease progression (Kdis); (7) lower limit for HbA1c (HLIM); and (8) concentration with half-maximal effect (EC50). Covariates screened for potential inclusion in the final model included sex, race, ethnicity, treatment group, ADA, age, BMI, body weight, waist circumference, eGFR, duration of diabetes, fasting glucose, HbA1c, metformin use, and insulin use. The previous final model detected a statistically significant relationship between fractional body weight change from baseline over time and EC50. With weight loss, EC50 was predicted to become lower, which suggested that tirzepatide becomes more potent when an individual's body weight had decreased from baseline. A 10% reduction in body weight was associated with a 50% reduction of EC50. A full covariate model (FCM) approach was followed where all relevant covariates were included simultaneously. The previously identified covariate, time-varying bodyweight, as well as any other covariates were considered whose η-covariate pairs plot suggested a covariate effect. The effects of continuous covariates were initially modeled using a normalized power model (on the log scale) while the effects of categorical covariates were described by an exponential model. Alternate functional forms were assessed as appropriate.

Effect-time curves are shown in Figure 16 and Figure 17.

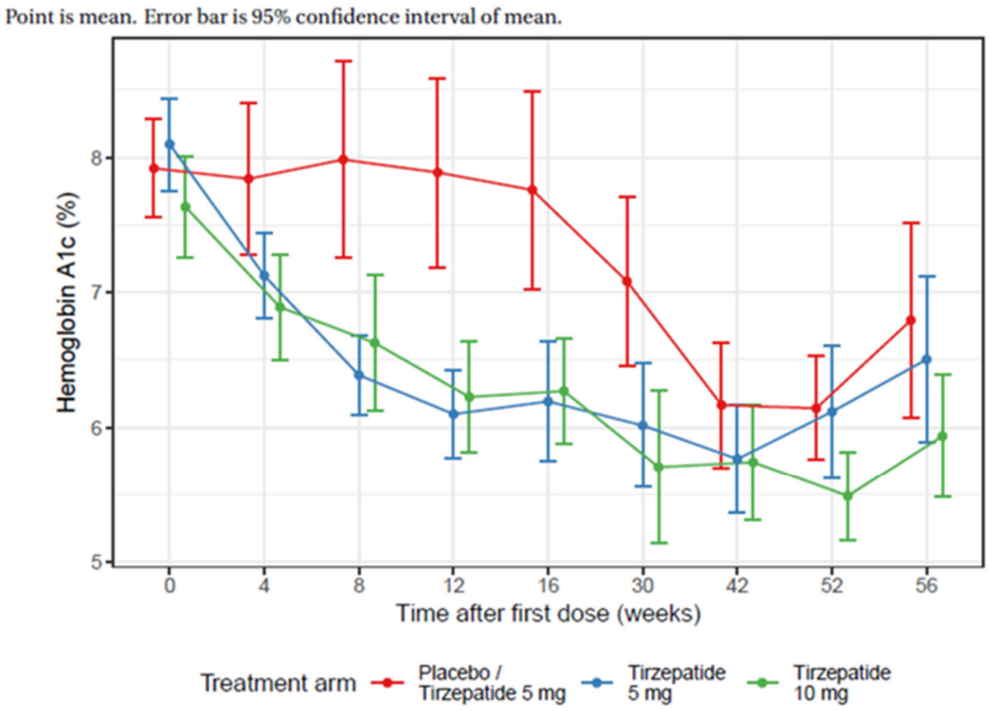


Figure 16: ER of fasting glucose and HbA1c: hemoglobin A1c versus time after first dose colored by treatment arm

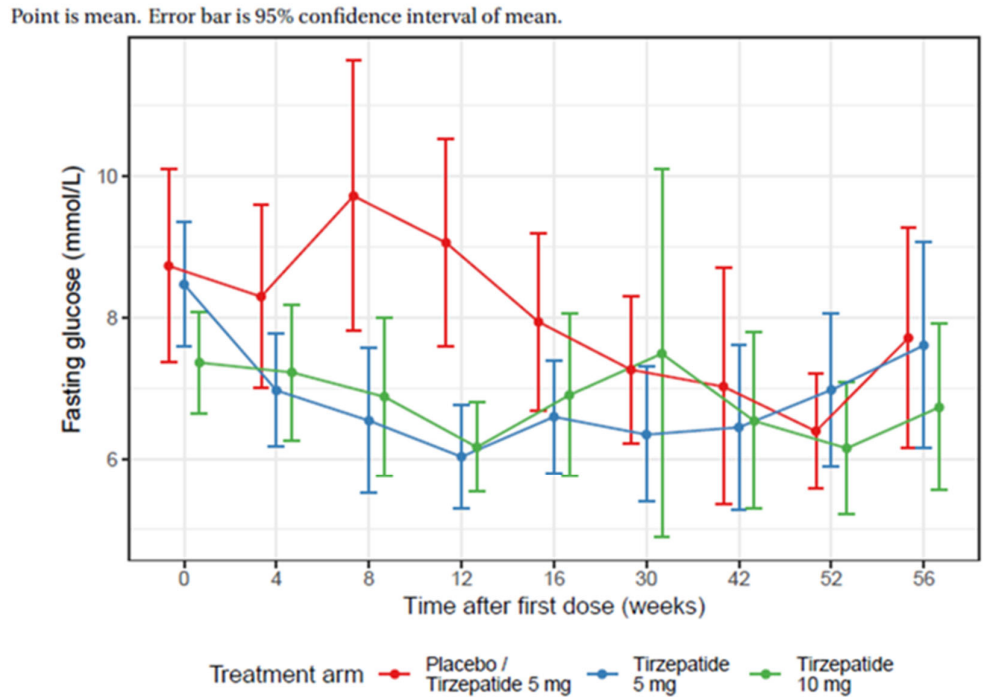


Figure 17: ER of fasting glucose and HbA1c: fasting glucose versus time after first dose colored by treatment arm

Even after starting treatment, participants who initially received placebo had slightly higher FG and HbA1c compared to participants who received active treatment, but all participants had comparable FG and HbA1c eventually.

PcVPCs for FG and HbA1c are presented in Figure 10 per treatment.

Black lines represent the median (solid) or 5th and 95th (dashed) percentiles of the observed data. Shaded areas represent the 95% prediction intervals for the median (gray) or 5th and 95th percentiles (blue) of the simulated data. All data and summaries have been prediction-corrected.

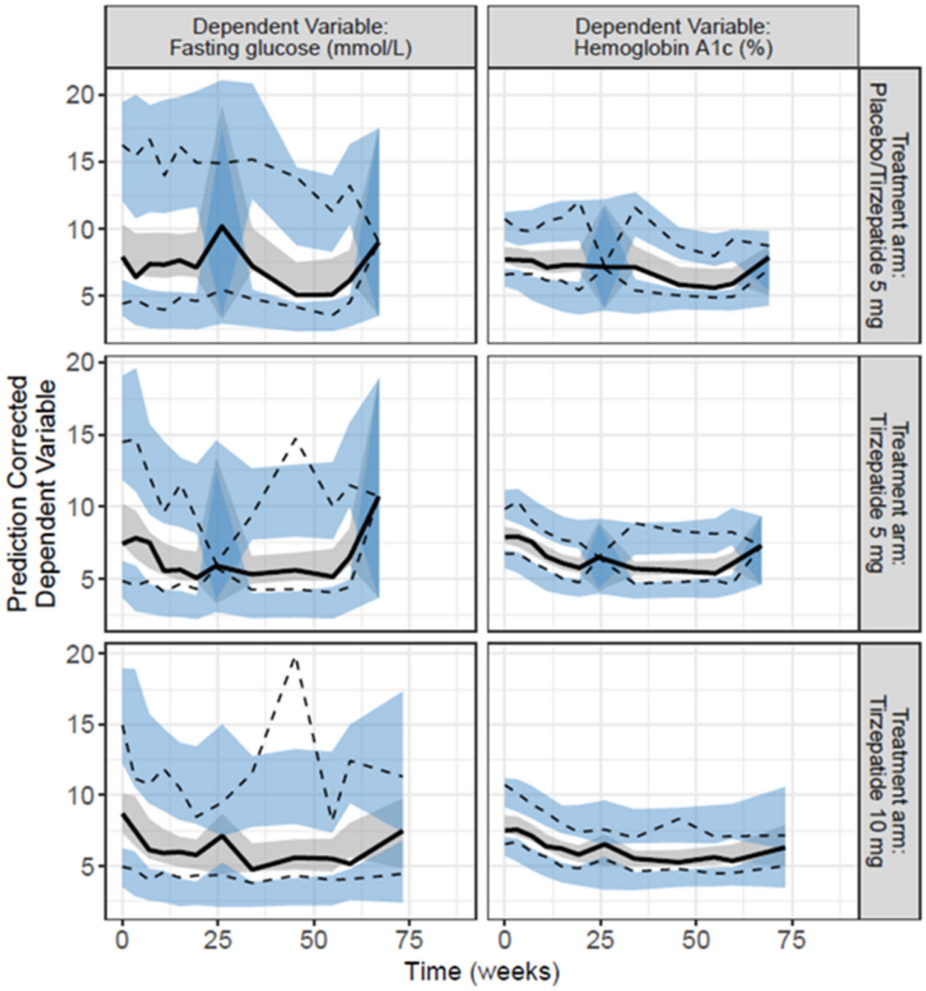
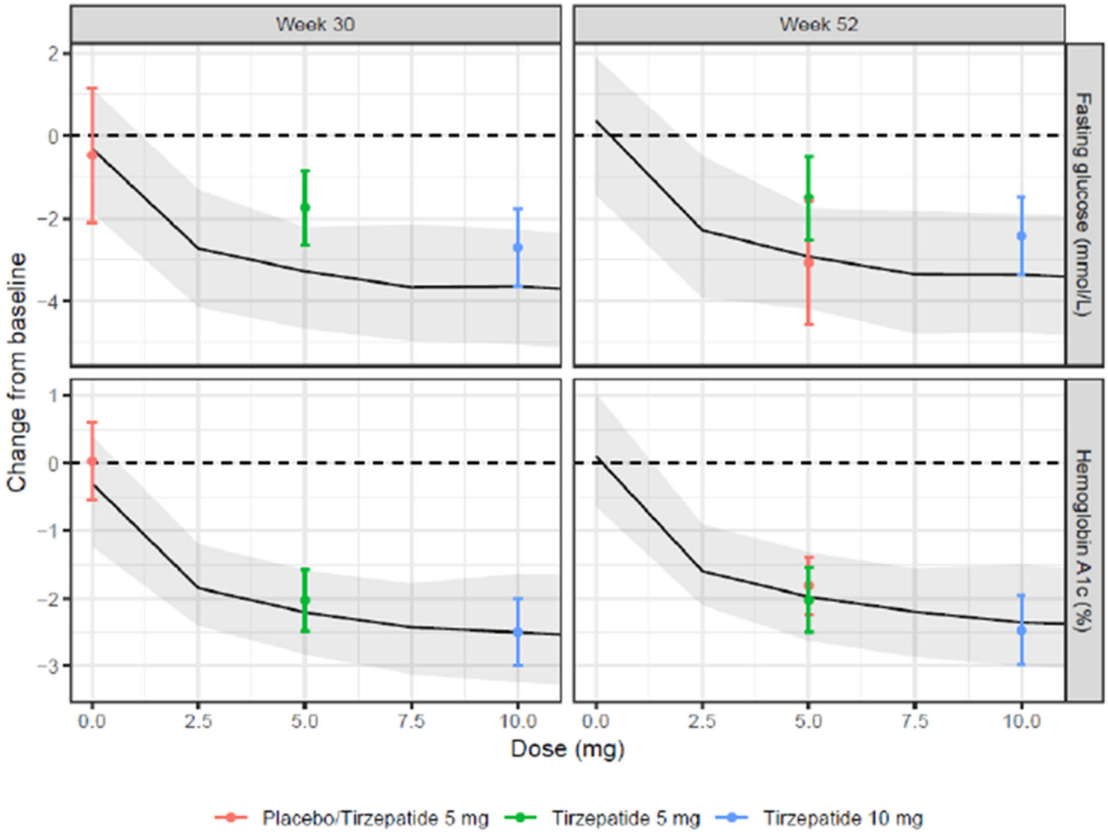


Figure 18: ER of fasting glucose and HbA1c final model: prediction corrected visual predictive check of fasting glucose and hemoglobin A1c versus time stratified by treatment arm



Abbreviations: HbA1c = glycated hemoglobin; PK/PD = pharmacokinetic/ pharmacodynamic; T2DM = type 2 diabetes mellitus.
Note: Solid black lines denote the mean of the simulations, and the shaded area denote the 95% confidence interval of the mean of the simulations. Colored symbols and error bars denote the mean and 95% confidence interval of observed data in Study GPGV.

Figure 19: PK/PD model-predicted and observed tirzepatide dose-response relationships for change from baseline fasting serum glucose (top) and HbA1c (bottom) at Week 30 (left) and Week 52 (right) in paediatric participants with T2DM

ER Analysis of Body Weight

A previously developed ER base model for weight loss in adults was re-used to characterize the effect of tirzepatide on body weight in SURPASS-PEDS. In this base model, body weight was subdivided into FFM and fat mass, which were calculated based on an individual's total body weight, height, and sex according to equation 1.

$$\begin{aligned} \text{FFM (male)} &= 9270 \cdot \text{BW}/(6680 + 216 \cdot \text{BMI}) \\ \text{FFM (female)} &= 9270 \cdot \text{BW}/(8780 + 244 \cdot \text{BMI}) \\ \text{Fat Mass} &= \text{BW} - \text{FFM} \end{aligned} \quad (1)$$

where: BMI = body mass index (kg/m^2), BW = body weight (kg), FFM = fat-free mass (kg).

Two indirect response models, one for FFM and one for fat mass, described their change over time in response to treatment with tirzepatide (Figure 20). Tirzepatide decreased the production of each of the two response variables, linearly with tirzepatide concentration and with a ceiling of one for the combined drug and placebo effects (corresponding to complete inhibition of production).

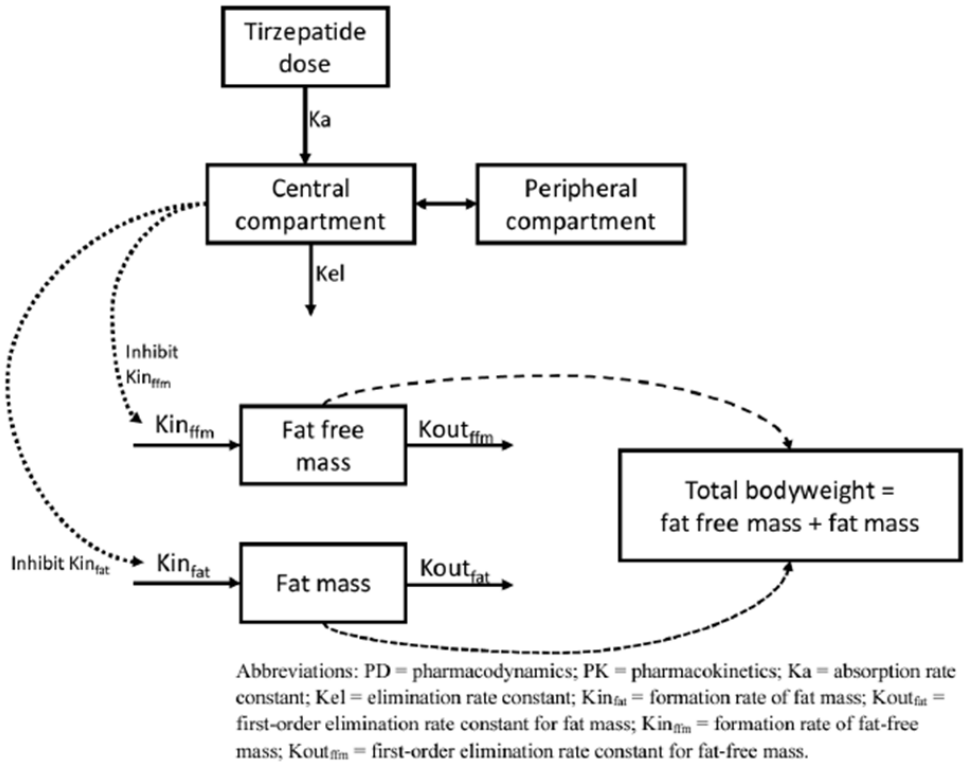


Figure 20: Body weight base model

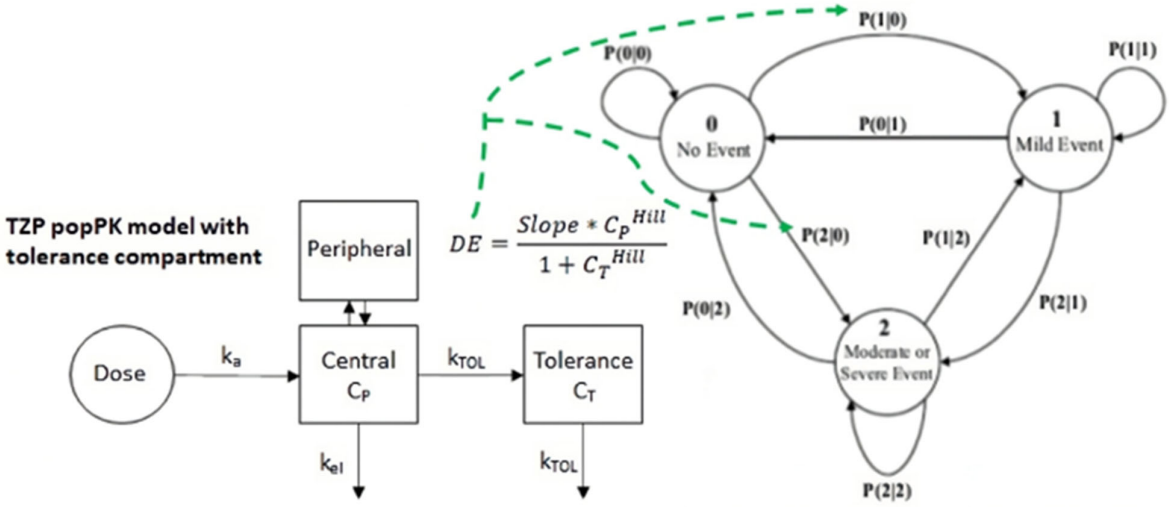
As the two subcomponents of total body weight were based on the same total bodyweight, a correlation between the residual errors for modeling each endpoint was included in the model. Parameters of this base model were estimated using the data from SURPASS-PEDS only. In the previous final model, statistically significant relationships were identified between sex and baseline FFM and fat mass (females having lower FFM and higher fat mass than males) and between Japanese race and baseline FFM/fat mass (Japanese participants having lower FFM and fat mass than non-Japanese participants). The modeling followed a sequential approach using the population PK final model *post hoc* parameters.

A comparison of model parameters in the paediatric and adult populations showed that baseline FFM and fat mass were very similar in both populations. The effect of sex on baseline FFM was similar in both populations, but the effect of sex on baseline fat mass in the paediatric population was about half that in the adult population, and its 95% CI included the null value. In both populations, the effect of treatment on body weight was primarily due to its effect on fat mass. Differences between the two populations included a statistically significant lower turnover rate constant for weight in the paediatric population compared to the adult population (corresponding to a longer "half-life" of weight loss of approximately 25 weeks versus 9 weeks, respectively) and a steeper slope for the linear exposure-response relationship in the paediatric population. In paediatric participants, the slope of the linear response for loss of fat mass was 2.78×10^{-4}/(ng/mL) (95% CI: 2.15 – 3.41 × 10−4/(ng/mL)), whereas it was 1.19×10^{-4}/(ng/mL) (95% CI: 1.16−1.26×10−4/(ng/mL)) in adults. The same trend was evident for the loss of FFM, although slopes were much shallower compared to the slopes for loss of fat mass. In paediatric participants, the slope for loss of FFM was 8.20×10−5/(ng/mL) (95% CI:

6.29−10.1×10−5/(ng/mL); Table S23), whereas it was 3.71×10−5/(ng/mL) (95% CI: 3.62−3.92×10−5/(ng/mL)) in adults.

Tolerability ER analysis

A previously developed Markov Chain model for adults was re-used to characterize the effect of tirzepatide on the incidence of nausea, vomiting, and diarrhoea events.



Abbreviations: AE = adverse event; ka = absorption rate constant; kel = elimination rate constant; C_P = drug concentration in central compartment; Hill = power model exponent; C_T = drug concentration in hypothetical tolerance compartment; DE = drug effect; K_{TOL} = tolerance rate constant; P(0|0) = probability of staying in the state of no AE; P(1|0) = probability of transition from the state of no AE to mild event; P(2|0) = probability of transition from the state of no AE to moderate/severe event; P(0|1) = probability of transition from the state of mild event to no AE; P(0|2) = probability of transition from the state of moderate/severe event to no AE; P(2|1) = probability of transition from state of mild to moderate/severe event; P(1|2) = probability of transition from state of moderate/severe to mild event; P(1|1) = probability of staying in the state of mild event; P(2|2) = probability of staying in the state of moderate/severe event; PopPK = population pharmacokinetics; TZP = tirzepatide.
Note: Green dotted lines indicate application of drug effect with tolerance on the transition probability from no AE to mild or moderate/severe events.

Figure 21: Base model for nausea, vomiting, and diarrhoea

Previously developed models for probabilities of diarrhoea, nausea, and vomiting over time in adults with T2DM treated with tirzepatide were also able to describe transitions into and out of AE states in a paediatric population with T2DM treated with tirzepatide. There were two main differences among the adult and paediatric models. For all tolerability endpoints, there were not enough moderate and severe events in the paediatric data to adequately model separate states for each AE severity. Therefore, the paediatric model was simplified to include only two states for each endpoint: experiencing no event or experiencing an event of any severity. The second difference applied only to the nausea and vomiting model. The adult model included an effect of the observed nausea state for each participant at each time on the probability of transitioning into one of the vomiting states. The paediatric model developed here

was unable to estimate that parameter with acceptable precision. Therefore, that parameter was removed from the paediatric model during model development.

The results suggested that paediatric patients had a lower sensitivity to tirzepatide treatment compared to adults for diarrhoea and nausea. Sensitivity of paediatric patients to tirzepatide treatment was similar to adults for vomiting. However, the paediatric model relied on limited data (93 participants) and was not able to distinguish AE severity states.

2.3.5. Discussion on clinical pharmacology

The PK of tirzepatide in paediatric patients aged 10 – 17 years was investigated via population PK analysis. The structural model was based on a model developed for adult T2DM patients including allometric scaling according to body weight for clearance (exponent 0.8) and volume (exponent 1) parameters and an additional age effect on clearance. Adult values were taken as priors since only sparse PK sampling was available in paediatrics. The final model parameters were comparable between adults and paediatrics; clearance was slightly faster in paediatric compared to adult patients (0.045 versus 0.036 L/h). PcVPCs showed an adequate model fit for the paediatric model. The applicant aimed at demonstrating that, with same doses, comparable exposures were achieved in children/adolescents as in adults. This comparison was done via model-based simulations. However, a comparison of the individual predictions of the exposure metrics is missing. The applicant was requested to present boxplots comparing exposure (AUC, Cmax and Cmin) between adults and paediatrics for the different doses (5 mg and 10 mg). Requested figures have been provided with individual predictions for AUC, Cmax and Cmin and observed Cmin in addition. Overall, exposure was comparable between adults and paediatrics with same doses (5 mg and 10 mg) with higher variability in the paediatric population, as expected. Median Cmax was higher in paediatric patients for both doses (5 mg and 10 mg) and upper 1.5 interquartile range (IQR) of Cmax was higher in paediatrics in the 5 mg dose group compared to adults given 5 mg. But variability was in a similar range comparing paediatrics and adults in the higher (10 mg) dose group.

In addition to that, standard figures according to following EMA Q&A were requested: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers. The reference interval should be based on the exposure observed at the recommended doses in adults, i.e. it should also include exposures at the higher dose of 15 mg QD which is recommended in adults but not suggested for paediatric patients. This should specifically include the lower weights (starting e.g. with the 5th weight percentile in 10-year-olds) as well as the higher weights (up to the maximum weight seen in the study) compared to adult predicted and observed exposures and to the therapeutic window of tirzepatide. Simulations should include doses 2.5 mg, 5 and 10 mg. Related to these results, the applicant was requested to discuss whether the warning requested to be included in section 4.4 should be further modified. Requested figures have been provided. Overall, exposure is comparable between adults and paediatrics in the same weight ranges. Most differences are obvious for Cmax, where maximal concentrations are predicted to be higher in children/adolescents compared to adults. This is especially critical in the two lower weight percentiles of paediatrics (mini mum up to fifth percentile: 47.5 kg to 50.3 kg and 5th up to 25th percentile: 50.3 kg to 63.1 kg) receiving the 10 mg dose. In these two weight percentiles, median Cmax in paediatrics (receiving 10 mg) is considerably above the median Cmax in adults receiving a 15 mg dose and more than 2-fold higher than in adult patients taking 10 mg in the two higher weight groups (75th to 95th and 95th to 100th percentile). This also means that around 30% of children with a body weight below the 25th weight percentile in this population will experience higher exposure than has been observed with the highest therapeutic

dose (15 mg) in the adult trials. Since Cmax is associated with safety risks, this is considered critical, especially in the lowest weight group. Therefore, a warning should be included in 4.2.:

"In children weighing < 60 kg, caution is advised when up-titrating to the 10 mg dose, since safety data are limited."

Furthermore, body weight was a covariate in the model, and the effect was included with fixed allometric exponents, although the patients in the study were overweight. Age is not regarded as a common covariate in a paediatric population ≥10 years of age, and the effect of age in the current model could potentially be compensating for the fact that PK in overweight paediatric patients may deviate from fixed allometric scaling. Nevertheless, the current model appears to describe the paediatric data; however, given that there are covariate effects of both body weight and age, additional pcVPCs were requested, stratified on body weight and age, respectively. The requested figures have been provided. PcVPCs show that the model adequately describes the observed data across patients' age and body weight.

ER models for FG and HbA1c, body weight and adverse events were presented. All models were based on the previously developed adult models with slight modifications to adapt for the paediatric population. The effect of tirzepatide on fasting glucose was overestimated, but HbA1c values were well captured by the model.

2.3.6. Conclusions on clinical pharmacology

The PK of tirzepatide in paediatric patients aged 10 – 17 years was investigated via population PK analysis. The parameters of the final model presented by the applicant were comparable between adults and paediatrics. The applicant has also presented models for FG and HbA1c, body weight and adverse events. Although the effect of tirzepatide on fasting glucose was overestimated, HbA1c values were well captured, and the model is therefore acceptable.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study with an Open-Label Extension Assessing the Efficacy, Safety, and Pharmacokinetics/Pharmacodynamics of Tirzepatide in Pediatric and Adolescent Participants with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin, or Basal Insulin, or Both (SURPASS-PEDS).

Methods

Design

Study GPGV was a randomized, double blind, placebo-controlled, 3-arm (tirzepatide 5 mg and 10 mg, and placebo), parallel group, multi-center study that evaluated tirzepatide in male or female participants ≥10 to<18 years of age with type 2 diabetes mellitus (T2DM). The double-blind part of the study lasted 30 weeks and was followed by a 22-week open-label extension.

The overall study duration was approximately 60 weeks across 4 required study periods and comprised the following parts:

- an approximate 4-week screening period,
- a 30-week double-blind placebo-controlled period,

- a 22-week open-label extension period on active treatment, and
- a 30-day post-treatment safety follow-up period.

The design is depicted in the Figure 22 below:

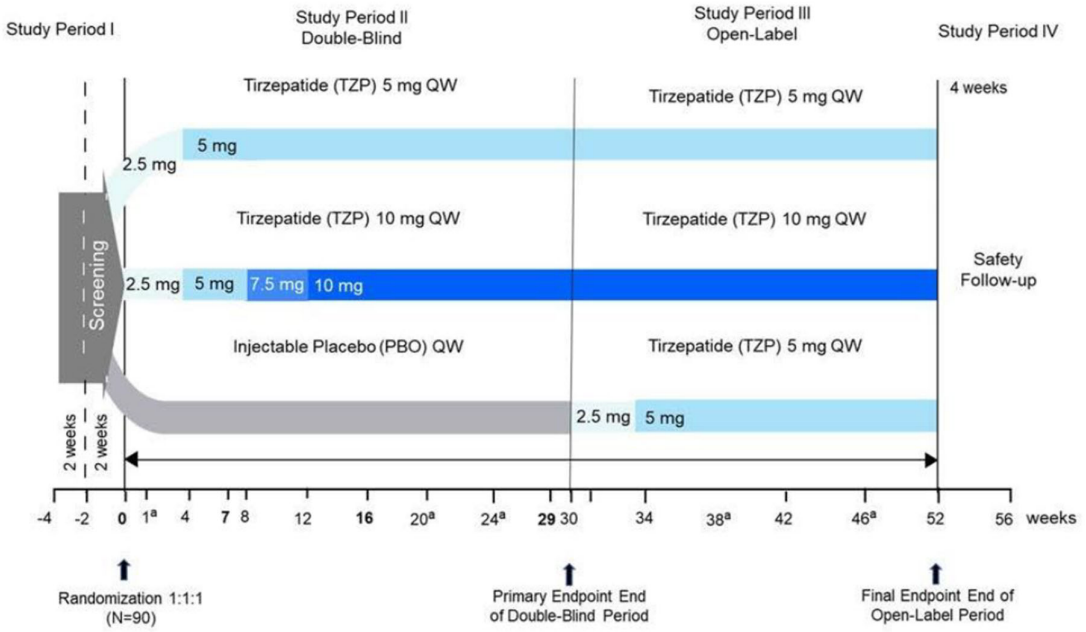


Figure 22: Design of Study GPGV (Abbreviations: N = number of participants in the analysis population; PBO = placebo; QW = once weekly; TZP = tirzepatide; [a]Phone visit. Visits indicated in bold fonts = pharmacokinetic assessments).

Study participants

Main inclusion criteria

Key inclusion criteria included the following:

- Male or female aged 10 to <18 years at the time of signing the informed consent/assent.
- Had T2DM treated at the time of randomization with lifestyle measures (standardized diet and exercise program) and
  - metformin,
  - basal insulin, or
  - both.
- If metformin was used, the dose was ≥1000 mg/day and not more than the locally approved dose.
  - Doses of metformin and basal insulin were stable (±15% for basal insulin) for ≥90 days prior to Visit 1 and until Visit 3.
- Had HbA1c >6.5% to ≤11% at the screening visit (determined by central laboratory).
- Body weight ≥50 kg and body mass index (BMI) >85th percentile of the general age- and gender-matched population for that country or region.

Main exclusion criteria

Key exclusion criteria included the following:

- Had type 1 diabetes mellitus.

- Had diabetes-associated autoantibodies (glutamic acid decarboxylase 65, islet cell antigen 2, or both), historically or at Visit 1.
- Have had at least 1 episode of severe hypoglycaemia and/or at least 1 episode of hypoglycaemic unawareness within the last 6 months.
- Had a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
- Had chronic or acute pancreatitis at any time prior to study entry (Visit 1).
- Female participants who were pregnant, breastfeeding, or intending to become pregnant.
- Had been treated with prescription drugs or over-the-counter medications that promote weight loss within 90 days prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3).

  Examples: Saxenda® (liraglutide 3.0 mg), Xenical® (orlistat), and phentermine.

Treatments

Study drug, dose, and mode of administration

Participants were randomly assigned to tirzepatide 5 mg, 10 mg, or placebo, administered subcutaneously once weekly via single-dose pen. Treatment with tirzepatide started at 2.5 mg followed by a dose escalation of 2.5 mg increments every 4 weeks to achieve the assigned maintenance dose. At the beginning of the open-label period, the placebo group is switched to tirzepatide and uptitrated to the 5 mg dose (labeled "placebo/TZP 5 mg" arm throughout this AR). The dosing scheme is detailed in Figure 23 below.

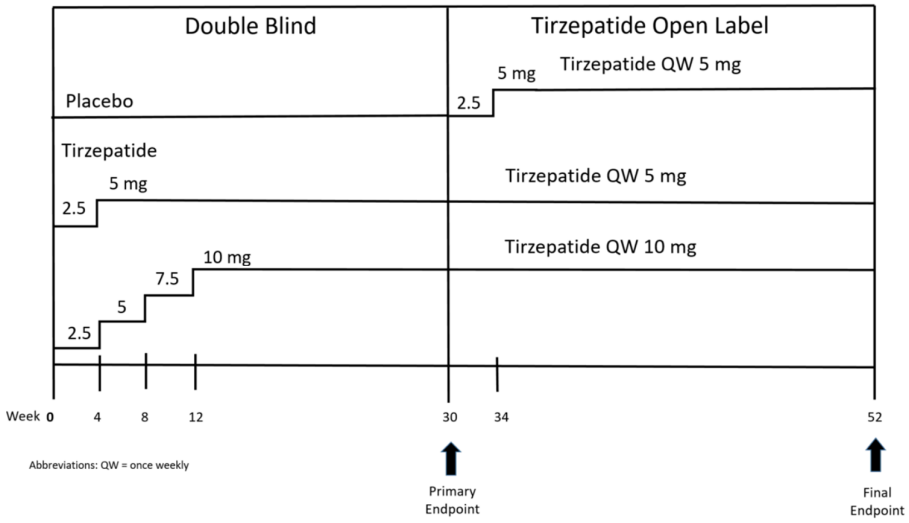


Figure 23: Tirzepatide dose escalation regimen in double blind and open label period of study GPGV (from study protocol).

Dose modification was not permitted. However, pre-defined measures were taken in case of gastrointestinal tolerability problems. The measures were escalated in 4 steps as follows (for details, see protocol p. 47):

- **STEP 1**: Advice for participants to adjust their eating behavior
- **STEP 2**: STEP 1 + anti-emetic or anti-diarrhoeal medication
- **STEP 3**: STEP 1 + STEP 2 + temporary interruption of tirzepatide; omission of 1 dose; participant will take 3 of 4 doses at that dose level.

- **STEP 4**: if STEPs 1-3 are ineffective at controlling GI symptoms, the participant may discontinue study intervention permanently. These participants will intensify insulin treatment and/or receive another glucose-lowering intervention and will continue participating in the study.

Background therapy

The background therapy consisted of diet and exercise, with metformin or basal insulin or both. Please see also inclusion criteria (above) and stratification criteria used at randomization (below).

Objectives

Table 2: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate that pooled 5 mg and 10 mg tirzepatide QW is superior to placebo at 30 weeks	• Change in HbA1c from baseline
Key Secondary (Controlled for Type I Error)	
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as separate treatment arms, is superior to placebo at 30 weeks	• Change in HbA1c from baseline
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, is superior to placebo at 30 weeks	• Incidence of HbA1c ≤6.5% • Change in BMI SDS (age- and sex-matched) from baseline • Change in FSG from baseline • % change in BMI from baseline
Additional Secondary (Not controlled for Type I Error)	
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, is superior to placebo at 30 weeks	• Incidence of HbA1c <7.0% and <5.7% • Change in daily average 6-point self-monitored blood glucose profiles from baseline
• To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 52 weeks	• Change in HbA1c from baseline • Incidence of HbA1c <7.0%, ≤6.5%, and <5.7% • Change in FSG from baseline
• To demonstrate that 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, is superior to placebo at 30 weeks	• Change in BMI from baseline • Incidence of BMI reduction ≥5%, ≥10%, and ≥15% • % change in body weight from baseline • Change in body weight from baseline • Change in waist circumference from baseline
• To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 52 weeks	• Change in BMI from baseline • % change in BMI from baseline • Change in BMI SDS (age- and sex-matched) from baseline • Incidence of BMI reduction ≥5%, ≥10%, and ≥15% • % change in body weight from baseline • Change in body weight from baseline • Change in waist circumference from baseline
• To compare 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks • To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 52 weeks	• Incidence of new or worsening of dyslipidaemia, hypertension, albuminuria, diabetic neuropathy, diabetic retinopathy or diabetic maculopathy in either eye
• To assess the safety of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 30 weeks and through the end of the safety follow-up period	• Treatment-emergent adverse events • Discontinuation of study intervention due to AEs • Adjudicated pancreatic AEs • Serum calcitonin

	• Incidence of allergic, hypersensitivity reactions, and injection site reactions • Incidence of treatment-emergent anti-drug antibodies to tirzepatide • % change from baseline for serum lipid levels • Change in systolic and diastolic blood pressure and heart rate from baseline • Occurrence of hypoglycemic events • Incidence of initiation of rescue therapy for severe persistent hyperglycemia
• To compare 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks • To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 52 weeks or end of the safety follow-up period	• Change from baseline for physical and developmental measures: o height o height SDS and weight SDS o height velocity o Tanner staging
• Characterize the pharmacokinetics and pharmacodynamic relationships of tirzepatide	• Relationship between tirzepatide exposure and key safety and efficacy measures
• To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, on PROs at 30 and 52 weeks	• Change from baseline for o PedsQL Generic Core Scales o PedsQL (3.2) Diabetic Module
Tertiary/Exploratory	
• To compare 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, to placebo at 30 weeks • To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, at 52 weeks	• Incidence of HbA1c ≤6.5% without clinically significant (blood glucose <54 mg/dL) or severe hypoglycemia • Incidence of HbA1c <7.0% without clinically significant (blood glucose <54 mg/dL) or severe hypoglycemia
• To assess the effect of 5 mg and 10 mg tirzepatide QW, analyzed as pooled and separate treatment arms, on PROs at 30 and 52 weeks	• Change from baseline for EQ-5D-Y
• To assess the effect of 5 mg and 10 mg tirzepatide QW, separately and pooled, at Weeks 8, 16, and 30 on additional metabolic measures	• Measures of insulin resistance, alpha cell and beta cell function, and serum adiponectin

Abbreviations: AE = adverse event; BMI = body mass index; FSG = fasting serum glucose; HbA1c = glycated hemoglobin A1c; PedsQL = Pediatric Quality of Life Inventory; PROs = patient-reported outcomes; QW = once weekly; SDS = standard deviation score.

Please note: To keep this AR short, from the above-listed endpoints only the primary endpoint and the key secondary endpoints (controlled for type I error) are going to be discussed in detail. For details on which endpoints are discussed in this AR, please see also comment at the beginning of the "Outcomes and estimation" subsection of the "Results" section.

Details on patient reported outcomes (PROs)

PedsQL Generic Core Scales

The PedsQL is a health-related quality-of-life measurement instrument that can be used in healthy children and adolescents and those with acute and chronic health conditions (Varni et al. 2019). The 23-item PedsQL 4.0 Generic Core Scales were designed to measure the core dimensions of health as delineated by the WHO (Varni et al. 2019) and role (school) functioning. The 2 versions used are for children (ages 8 to 12) and teenagers (ages 13 to 18) (Varni 2023).
Higher scores on this scale indicate better health-related quality of life. The PedsQL 4.0 Generic Core Scale dimensions and summary scores are shown in **Table 3**:

Table 3: PedsQL 4.0 Generic Core Scale dimensions and summary scores

Dimensions	Number of Items
Physical Functioning	**8**
Emotional Functioning	**5**
Social Functioning	**5**
School Functioning	**5**
Summary Scores	**Items per Summary Score**
Psychosocial (Emotional, Social, and School Functioning)	**15**
Physical Health (Physical Functioning)	**8**
Total	**23**

PedsQL (3.2) Diabetic Module

The PedsQL (3.2) Diabetes Module is a diabetes-specific health-related quality of life instrument that comprises 33 items with 5 dimensions for people aged 8 years and older. The 5 dimensions of the PedsQL (3.2) Diabetes Module are shown in **Table 4**:

Table 4: The five dimensions of the PedsQL (3.2) Diabetes Module

Dimensions	Number of Items
Diabetes Symptoms	15
Treatment I	5
Treatment II	6
Worry	3
Communication	4
Summary Scores	**Items per Summary Score**
Diabetes Symptoms (Diabetes symptoms)	15
Diabetes Management (Treatment I, Treatment II, Worry, and Communication)	18
Total	33

Scores are calculated for each dimension, and a total score is available. Scores are transformed on a scale from 0 to 100 with higher scores indicating better health-related quality of life and fewer problems or symptoms.

EQ-5D-Y

In 2024, the EQ-5D-Y was renamed the EQ-5D-Y-3L due to the release of a new variation of the instrument, the EQ-5D-Y-5L. However, the content of the instrument remains unchanged (EuroQol Research Foundation 2024). The youth-friendly EQ-5D-Y-3L version consists of 2 pages, the EQ-5D-Y-3L descriptive system and the EQ visual analogue scale (VAS) (EuroQol Research Foundation 2020).

The descriptive system comprises the same 5 dimensions as the EQ-5D 3 level (EQ-5D-3L) but uses youth-friendly wording. The 5 dimensions are

- mobility
- looking after myself
- doing usual activities
- having pain or discomfort, and
- feeling worried, sad, or unhappy.

Each dimension has 3 levels:

- no problems
- some problems, or
- a lot of problems.

The EQ-5D-Y-3L descriptive system was converted into a single index value by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index value is a

major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years that are used to inform economic evaluations of healthcare interventions. The Slovenian EQ-5D-Y-3L value set was used to calculate the index value for this analysis (Prevolnik et al. 2021).

Estimands

The "efficacy" and "treatment-regimen" estimands guided the primary, key secondary, and additional secondary efficacy analyses. The tertiary and exploratory efficacy endpoint analyses were conducted for the efficacy estimand.

Efficacy estimand: The clinical question of interest for the efficacy estimand was the treatment difference between tirzepatide and placebo after 30 weeks of intervention in paediatric and adolescent participants with type 2 diabetes mellitus (T2DM), prior to intervention discontinuation for any reason or initiation of rescue antihyperglycemic medication.

Treatment-regimen estimand: The clinical question of interest for the treatment-regimen estimand was the treatment difference between tirzepatide and placebo after 30 weeks of intervention in paediatric and adolescent participants with T2DM, regardless of intervention discontinuation for any reason or initiation of rescue antihyperglycemic intervention.

Safety estimand: The clinical interest for safety estimands was the safety assessment of individual treatment groups up to Week 30 and up to end of study in paediatric and adolescent participants with T2DM, regardless of adherence to the study drug or initiation of rescue antihyperglycemic medication.

Outcomes/endpoints

See **Table 2** above.

Sample size

Number of participants

The numbers of participants in the different stages of study GPGV are listed in **Table 5** below:

Table 5: Number of Participants (planned and analyzed)

	Number of Participants
Screened participants	146
Randomly assigned participants	99
Treated (at least 1 dose)	99
Modified intent-to-treat (mITT) population	99
Completed double-blind period	92
Completed open-label period	91
Completed the study (including safety follow-up)	90
Evaluable participants	88

Randomisation

All participants were centrally assigned to the randomized study drug using an interactive web response

system. Participants were randomly assigned in a 1:1:1 ratio to tirzepatide 5 mg QW, tirzepatide 10 mg QW, and placebo QW.

Participant stratification factors were

- age (≤14 years of age, >14 years of age), and
- baseline antihyperglycaemic medication use of
    - metformin only

- basal insulin only, or
- metformin and basal insulin.

Blinding (masking)

Double-blind period: Investigators, site staff, clinical monitors, and participants will remain blinded to the treatment assignments until the double-blind period of the study is complete. Emergency unblinding for AEs may be performed through the IWRS, but ONLY if the participant's well-being requires knowledge of treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS. In case of an emergency, the investigator has the sole responsibility for determining if unblinding is warranted, the decision and rationale of which must be promptly documented and reported to the MAH. In case of unblinding, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor medical monitor.

Open-label period: The study intervention will be assigned using an IWRS.

Statistical methods

Analysis Populations and Data Sets

Table 6: Analysis Populations and Data Sets

Analysis Population	Description
Screened population	All participants who signed the ICF.
Randomized population	All participants who were randomly assigned to an intervention arm.
Modified intent-to-treat (mITT) population	All randomly assigned participants who were exposed to at least 1 dose of study drug (that is tirzepatide or placebo).

Analysis Sets	Study Periods (Weeks)	Data Obtained from mITT Population Excluded/Included
Efficacy Analysis Set 1 (EAS1)	double-blind period (up to Week 30)	Data excluded if obtained after - initiating rescue therapy, or - discontinuing from study drug.
Efficacy Analysis Set 2 (EAS2)	double-blind period and the open-label period (up to Week 52)	
Full Analysis Set (FAS)	double-blind period (up to Week 30)	Data included regardless of - initiation of rescue therapy, or - adherence to study drug.
Full Analysis Set 2 (FAS2)	double-blind period and the open-label period (up to Week 52)	
Safety Analysis Set 1 (SS1)	double-blind period (up to Week 30)	
Safety Analysis Set 2 (SS2)	double-blind period, open-label period, and safety follow-up period (up to Week 56)	

Abbreviation: ICF = informed consent form.

Unless otherwise specified:

for analyses guided by the treatment-regimen estimand, FAS and FAS2 were used
for analyses guided by the efficacy estimand, EAS1 and EAS2 were used, and
for safety analyses, SS1 and SS2 were used.

Efficacy Analyses

When evaluating primary, key secondary and additional efficacy objectives, analyses were conducted relative to 2 estimands, including the treatment-regimen estimand and the efficacy estimand.

Continuous Endpoints Analysis

Efficacy Estimand Analyses

For analysis aligned to the efficacy estimand, MMRMs were used to analyze continuous measurements for mean comparisons over time among treatments. The response variable of the MMRM model was the change from baseline. Unless specifically provided, the terms in the model included treatment, visit, treatment-by-visit interaction, baseline age group, baseline antihyperglycemic medication, and baseline of the dependent variable.
Restricted maximum likelihood was used to obtain model parameter estimates and the Kenward-Roger option was used to estimate denominator degrees of freedom. A linear contrast, averaging estimates from the individual tirzepatide doses at the Week 30 visit, was used to estimate the treatment effect of the pooled tirzepatide compared with placebo. An unstructured covariance matrix was used to model the within-patient errors.
For analyses aligned to the efficacy estimand, missing data were considered missing at random and an MMRM model, which impute the missing values implicitly under the MAR assumption, was used.

Treatment-Regimen Estimand Analyses

For the treatment-regimen estimand, analyses of continuous endpoints used an ANCOVA model with missing data imputed. The response variable was the change from baseline. The terms of the model included treatment, baseline age group, baseline antihyperglycemic medication, and baseline of the dependent variable.
For efficacy analyses relative to the treatment-regimen estimand, the missing or invalid data were

handled as outlined in the following table.

Table 7: Missing or invalid data

Missing/Invalid Data	Strategy to Handle Missing/Invalid Data	Assumptions for Missing Values	Methods to Handle Missing Values
Data missing at baseline, invalid data collected or missing data after treatment DC due to the leading to invalid measurements ascertained while on treatment, missing data from participants completing the treatment period on the study drug intervention, or missing data after study DC due to inadvertent enrollment.	Hypothetical	MAR	Multiple imputation assuming MAR
Missing data due to any other reason (for example, study DC due to any reason other than inadvertent enrollment).	Treatment policy	MNAR	Jump to Reference at Week 30 and return to baseline at Week 52

Abbreviations: DC = discontinuation; MAR = missing at random; MNAR = missing not at random.

Binary Endpoints Analysis

For binary endpoints derived from a continuous variable and for both treatment-regimen and efficacy estimands, a logistic regression model was used. The model included treatment, baseline age group, baseline antihyperglycemic medication, and baseline of the dependent variable.
The unconditional treatment group effect was assessed by risk difference based on the delta method using a formula provided in Ye et al. (2023) (supported by Steingrimsson et al. 2017).
For missing data imputation, the missing value in the underlying continuous variable was imputed first under each estimand. The imputed values were then dichotomized into binary outcomes based on cutoff values.

Subgroup analysis

Analyses were guided by the treatment-regimen estimand in FAS for the primary endpoint at Week 30. A primary multiple imputation method was used to impute missing data, consistent with the primary analysis model. The 2-way interaction of treatment-by-subgroup was evaluated to assess an interaction in the treatment effect with the subgroup levels. Significance was evaluated at a 2-sided alpha of 0.1.

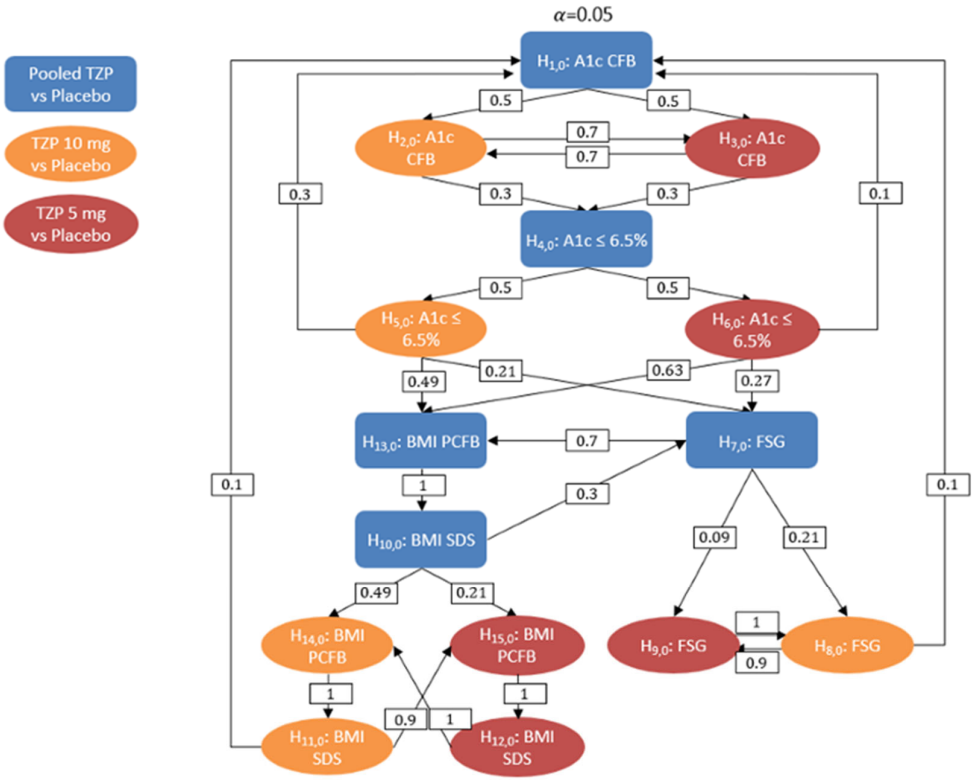
Sensitivity Analyses

A 2-way tipping point analysis was utilized for evaluating the primary endpoint for the treatment-regimen estimand. It was conducted to assess the impact of missing data on the robustness of the primary endpoint outcome measures.

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

The following figure shows the type I error control strategy for evaluating the primary and key secondary efficacy objectives relative to each estimand using the graphical approach to strongly

control the type I error at a 2-sided significance level of 0.05.



Abbreviations: A1c = glycated hemoglobin; BMI = body mass index; CFB = change from baseline; FSG = fasting serum glucose; PCFB = percent change from baseline; SDS = standard deviation score; TZP = tirzepatide; vs = versus.

Figure 24: Type I Error Rate Control Strategy for Primary and Key Secondary Efficacy Analyses

Changes in Planned Analyses Prior to Unblinding or Database Lock

In addition to planned analyses outlined in the approved SAP Version 3, the following additional analyses on the treatment-regimen estimand at Week 52 were added to the planned analyses prior to unblinding or database lock:

change from baseline in weight and waist circumference
percent change from baseline in weight, and
proportion of participants achieving HbA1c and BMI thresholds.

Changes Following Study Unblinding/Database Lock and Post Hoc Analyses

The following additional analyses were made after unblinding or database lock:

change in basal insulin from baseline to Week 30 using FAS and from baseline to Week 52 using FAS2
subgroup analysis on growth parameters height velocity and height velocity SDS by tanner stage at baseline for baseline to Week 30 and from baseline to Week 52, and
summary of injection site reaction for double-blind based on SS1 and for overall periods using SS2.

Due to the lack of available data, the planned analysis as indicated in SAP for change in daily average 6-point SMBG profiles at Week 30 endpoint was not performed. Only a summary of SMBG by visit and

time point from baseline to Week 30 using SS1 is provided.

Results

Participant flow

Disposition of participants

Out of 146 screened subjects, 99 were eventually randomized. Reasons for non-randomization of the other 47 subjects were screening failure (n=42) and withdrawal by subject (n=5). All of the 99 randomized participants were exposed to at least 1 dose of study drug, and 92 of these continued into the open-label period of the study.

Only double-blind period

A total of 92 randomly assigned participants (92.9%) completed the Week 30 primary endpoint visit (placebo: N=34; TZP 5 mg: N=29, and TZP 10 mg: N=29). A total of 90 randomly assigned participants (90.9%) completed the Week 30 primary endpoint visit on treatment (placebo: N=32; TZP 5 mg: N=29, and TZP 10 mg: N=29). No significant differences were observed across treatment groups in the proportion of participants discontinuing the study or treatment during the double-blind period.

Double-blind and open-label period

A total of 91 randomly assigned participants (91.9%) completed the Week 52 visit (placebo à TZP 5 mg: N=33; TZP 5 mg: N=29; TZP 10 mg: N=29). A total of 90 randomly assigned participants (90.9%) completed the Week 52 visit on treatment (placebo à TZP 5 mg: N=32; TZP 5 mg: N=29; TZP 10 mg: N=29). One participant discontinued during the safety follow-up period. A total of 90 participants completed the study. See also **Table 8** and **Figure 25** below.

Reasons for Discontinuation

The most common reason for discontinuation from the study was "Withdrawal by Subject" for participants randomly assigned to

- placebo (1 participant; 2.9%)
- tirzepatide 5 mg (1 participant; 3.1%), and
- tirzepatide 10 mg (2 participants; 6.1%).

The most common reason for discontinuation from treatment was "Withdrawal by Subject" for participants randomly assigned to

- placebo (2 participants; 5.9%)
- tirzepatide 5 mg (1 participant; 3.1%), and
- tirzepatide 10 mg (2 participants; 6.1%).

See also **Table 8** and **Figure 25** below.

Table 8: Summary of Study and Treatment Disposition - All Randomized Participants- I8F-MC-GPGV - Double-Blind, Open-Label, and Follow-up Periods

Disposition Event	Plc/TZP 5 mg (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)	TZP_ALL (N=65)	Total (N=99)
	n (%)				
Randomized	34 (100.0)	32 (100.0)	33 (100.0)	65 (100.0)	99 (100.0)

Safety Population	34 (100.0)	32 (100.0)	33 (100.0)	65 (100.0)	99 (100.0)
Modified Intent-to-Treat Population	34 (100.0)	32 (100.0)	33 (100.0)	65 (100.0)	99 (100.0)
Completed Study	32 (94.1)	29 (90.6)	29 (87.9)	58 (89.2)	90 (90.9)
Double-Blind Period					
Completed 30-Week Treatment	32 (94.1)	29 (90.6)	29 (87.9)	58 (89.2)	90 (90.9)
Discontinued 30-Week Treatment	2 (5.9)	3 (9.4)	4 (12.1)	7 (10.8)	9 (9.1)
Adverse Event	0 (0.0)	2 (6.3)	0 (0.0)	2 (3.1)	2 (2.0)
Withdrawal by Subject	2 (5.9)	1 (3.1)	2 (6.1)	3 (4.6)	5 (5.1)
Other	0 (0.0)	0 (0.0)	2 (6.1)	2 (3.1)	2 (2.0)
Completed 30-Week Treatment Period	34 (100.0)	29 (90.6)	29 (87.9)	58 (89.2)	92 (92.9)
Discontinued 30-Week Treatment Period	0 (0.0)	3 (9.4)	4 (12.1)	7 (10.8)	7 (7.1)
Adverse Event	0 (0.0)	2 (6.3)	0 (0.0)	2 (3.1)	2 (2.0)
Withdrawal by Subject	0 (0.0)	1 (3.1)	2 (6.1)	3 (4.6)	3 (3.0)
Other	0 (0.0)	0 (0.0)	2 (6.1)	2 (3.1)	2 (2.0)
Double-Blind and Open-Label Periods					
Completed 52-Week Treatment	32 (94.1)	29 (90.6)	29 (87.9)	58 (89.2)	90 (90.9)
Discontinued 52-Week Treatment	2 (5.9)	3 (9.4)	4 (12.1)	7 (10.8)	9 (9.1)
Adverse Event	0 (0.0)	2 (6.3)	0 (0.0)	2 (3.1)	2 (2.0)
Withdrawal by Subject	2 (5.9)	1 (3.1)	2 (6.1)	3 (4.6)	5 (5.1)
Other	0 (0.0)	0 (0.0)	2 (6.1)	2 (3.1)	2 (2.0)
Completed 52-Week Treatment Period	33 (97.1)	29 (90.6)	29 (87.9)	58 (89.2)	91 (91.9)
Discontinued 52-Week Treatment Period	1 (2.9)	3 (9.4)	4 (12.1)	7 (10.8)	8 (8.1)
Adverse Event	0 (0.0)	2 (6.3)	0 (0.0)	2 (3.1)	2 (2.0)
Withdrawal by Subject	1 (2.9)	1 (3.1)	2 (6.1)	3 (4.6)	4 (4.0)
Other	0 (0.0)	0 (0.0)	2 (6.1)	2 (3.1)	2 (2.0)
Discontinued Study	2 (5.9)	3 (9.4)	4 (12.1)	7 (10.8)	9 (9.1)
Reason for Study Discontinuation					
Adverse Event	0 (0.0)	2 (6.3)	0 (0.0)	2 (3.1)	2 (2.0)
Lost to Follow Up	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Withdrawal by Subject	1 (2.9)	1 (3.1)	2 (6.1)	3 (4.6)	4 (4.0)
Withdrawal due to Caregiver	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.5)	1 (1.0)
Circumstances					
Other	0 (0.0)	0 (0.0)	1 (3.0)	1 (1.5)	1 (1.0)

Abbreviations: NC = Not Calculable; N = number of participants in the analysis population; n = number of participants in the specified category; Plc = placebo; TZP = tirzepatide.

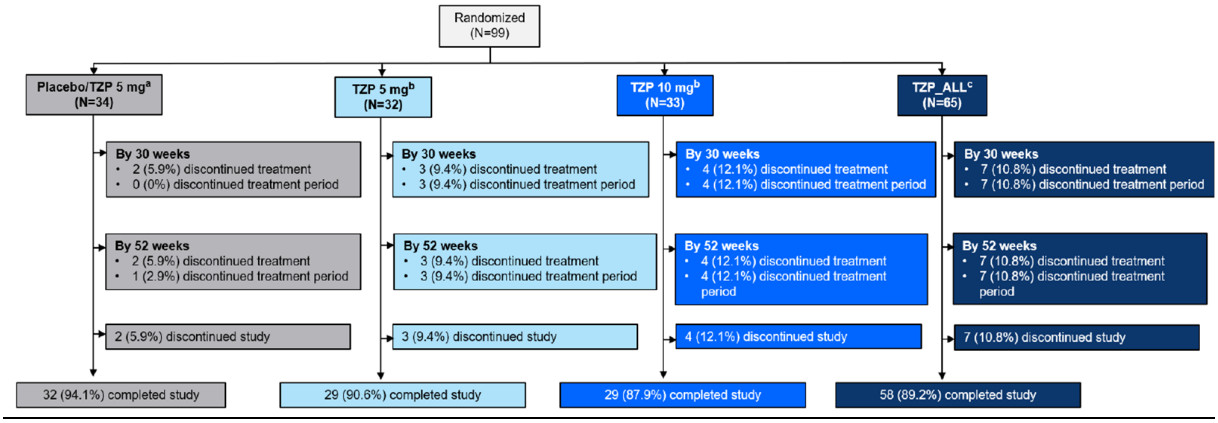


Figure 25: Participant disposition from randomization to safety follow-up

Conduct of the study

Changes in conduct – study amendments

Study GPGV had no protocol amendments. Protocol GPGV was approved on 14 Dec 2021. The first participant visit occurred on 13 April 2022. The last participant visit occurred on 28 January 2025. A protocol addendum was submitted on 16 Dec 2021 (new language was added to the exclusion criteria for compliance with Brazil and Lilly requirements).

Protocol deviations

After completion and approval of the final study report for Study GPGV, it turned out that at Site 59290, three (3) additional participants had important protocol deviations related to informed consent (no reconsent during the study). In the following, the updated information on important protocol deviations (from clinical study report addendum) is discussed.

Until the end of the open label period, the total number of subjects with at least one important protocol deviation period was 22 (Plc/TZP 5 mg: 4 [11.8%]; TZP 5 mg: 12 [37.5%]; TZP 10 mg: 6 [18.2%]; TZP_ALL: 18 [27.7%]). The most common deviations were related to informed consent (15.2%) and laboratory procedure compliance (8.1%). Of the 15 participants with important protocol deviations related to informed consent, 12 participants were eventually reconsented during the study and the 3 aforementioned participants were not.

One participant was inadvertently enrolled in Study GPGV and assigned to TZP 10 mg, when using a bolus insulin as background medication at baseline, i.e., the inclusion criteria were violated. After detection of this deviation, the participant was discontinued from treatment and treatment period at Visit 5. The participant attended the safety follow-up visit at the end of the study and was included in analyses under the subgroup basal insulin only.

Four (4) protocol deviations occurred in the open-label phase, two of which belonged to the category "Investigational Medicinal Product and/or Investigational Device".

See **Table 9** for an overview of important protocol deviations from randomization to end of open-label phase.

Table 9: Important Protocol Deviations - Randomized Participants - I8F-MC-GPGV - Double-Blind and Open-Label Periods

Protocol Deviation Category	Plc/TZP 5 mg (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)	TZP_ALL (N=65)	Total (N=99)
	n (%)				
Subjects with ≥1 Important Protocol Deviation	4 (11.8)	12 (37.5)	6 (18.2)	18 (27.7)	22 (22.2)
Protocol Deviation	4 (11.8)	12 (37.5)	6 (18.2)	18 (27.7)	22 (22.2)
Informed Consent	2 (5.9)	9 (28.1)	4 (12.1)	13 (20.0)	15 (15.2)
Laboratory Procedure Compliance	2 (5.9)	5 (15.6)	1 (3.0)	6 (9.2)	8 (8.1)
Study Procedure Compliance	2 (5.9)	1 (3.1)	1 (3.0)	2 (3.1)	4 (4.0)
Investigational Medicinal Product and/or Investigational Device	1 (2.9)	0	1 (3.0)	1 (1.5)	2 (2.0)
Eligibility Criteria	0	0	1 (3.0)	1 (1.5)	1 (1.0)
Study Procedure Compliance - Other	0	0	1 (3.0)	1 (1.5)	1 (1.0)
Treatment Assignment/Randomization	0	0	1 (3.0)	1 (1.5)	1 (1.0)

Abbreviations: N = number of participants in the analysis population; n = number of participants in the specified category; TZP = tirzepatide. The percentages are calculated based on the number of subjects in the analysis population.
Note: Plc/TZP 5 mg represents placebo treatment in double-blind period and TZP 5 mg in open-label period. TZP 5 mg and TZP 10mg represent TZP 5 mg/5 mg and TZP 10 mg/10 mg respectively in both double-blind and open-label periods. TZP_ALL represents pooled arms of TZP 5mg/5mg and TZP 10 mg/10 mg.

Treatment compliance

The treatment compliance was defined as taking ≥75% of the required doses of the study drug. Overall compliance across all study groups was 98% (97 out of 99). A total of 2 participants (5.9%) in the placebo group were non-compliant. All participants in the tirzepatide groups were compliant.
A total of 5 (5.1%) participants (placebo: 3 [8.8%]; TZP 5 mg: 2 [6.3%]) missed 3 or more consecutive study drug doses during the study.

Baseline data

Demographics and baseline disease characteristics

Table 10 below summarizes baseline demographics and clinical characteristics.

Table 10: Participant Demographic and Baseline Disease Characteristics - Randomized Participants - I8F-MC-GPGV

Demographic Parameter		Placebo/ TZP 5 mg	TZP 5 mg	TZP 10 mg	TZP_ALL	Total
		N=34	N=32	N=33	N=65	N=99
Sex, n (%)	n[a]	34	32	33	65	99
	F	21 (61.8)	21 (65.6)	18 (54.5)	39 (60.0)	60 (60.6)
	M	13 (38.2)	11 (34.4)	15 (45.5)	26 (40.0)	39 (39.4)
Age (years)	n[a]	34	32	33	65	99
	Mean	14.6	15.0	14.6	14.8	14.7
	Std. Dev.	1.8	1.9	1.8	1.9	1.8
Age categories, n (%)	n[a]	34	32	33	65	99
	≤14 years	16 (47.1)	13 (40.6)	15 (45.5)	28 (43.1)	44 (44.4)
	>14 years	18 (52.9)	19 (59.4)	18 (54.5)	37 (56.9)	55 (55.6)
Ethnicity, n (%)	n[a]	34	32	33	65	99
	Hispanic or Latino	24 (70.6)	24 (75.0)	17 (51.5)	41 (63.1)	65 (65.7)
	Not Hispanic or Latino	9 (26.5)	8 (25.0)	16 (48.5)	24 (36.9)	33 (33.3)
	Not Reported	1 (2.9)	0	0	0	1 (1.0)
Race, n (%)	n[a]	34	32	33	65	99
	American Indian or Alaska Native	8 (23.5)	7 (21.9)	5 (15.2)	12 (18.5)	20 (20.2)
	Asian	3 (8.8)	1 (3.1)	2 (6.1)	3 (4.6)	6 (6.1)
	Black or African American	2 (5.9)	5 (15.6)	4 (12.1)	9 (13.8)	11 (11.1)
	Native Hawaiian or Other Pacific Islander	0	1 (3.1)	2 (6.1)	3 (4.6)	3 (3.0)
	White	21 (61.8)	17 (53.1)	19 (57.6)	36 (55.4)	57 (57.6)

	Multiple	0	1 (3.1)	1 (3.0)	2 (3.1)	2 (2.0)
Country/region, n (%)	n[a]	34	32	33	65	99
	Australia	0	1 (3.1)	1 (3.0)	2 (3.1)	2 (2.0)
	Brazil	3 (8.8)	8 (25.0)	5 (15.2)	13 (20.0)	16 (16.2)
	India	3 (8.8)	1 (3.1)	2 (6.1)	3 (4.6)	6 (6.1)
	Israel	3 (8.8)	1 (3.1)	4 (12.1)	5 (7.7)	8 (8.1)
	Italy	1 (2.9)	0	2 (6.1)	2 (3.1)	3 (3.0)
	Mexico	13 (38.2)	10 (31.3)	8 (24.2)	18 (27.7)	31 (31.3)
	United Kingdom	1 (2.9)	0	0	0	1 (1.0)
	United States	10 (29.4)	11 (34.4)	11 (33.3)	22 (33.8)	32 (32.3)
Weight (kg)	n[a]	34	32	33	65	99
	Mean	93.5	93.2	103.2	98.3	96.6
	Std. Dev.	25.69	27.05	29.55	28.57	27.58
BMI (kg/m²)	n[a]	34	32	33	65	99
	Mean	34.7	33.9	37.7	35.8	35.4
	Std. Dev.	7.693	7.166	8.432	8.002	7.874
BMI SDS	n[a]	34	32	33	65	99
	Mean	2.99	2.86	3.48	3.17	3.11
	Std. Dev.	1.18	1.01	1.23	1.16	1.17
BMI percentile	n[a]	34	32	33	65	99
	Mean	98.0	98.3	99.3	98.8	98.6
	Std. Dev.	3.36	3.02	1.27	2.34	2.75
Antihyperglycemic medications use, n (%)	n[a]	34	32	33	65	99
	Basal Insulin Only	2 (5.9)	3 (9.4)	3 (9.1)	6 (9.2)	8 (8.1)
	Metformin + Basal Insulin	8 (23.5)	7 (21.9)	8 (24.2)	15 (23.1)	23 (23.2)
	Metformin Only	24 (70.6)	22 (68.8)	22 (66.7)	44 (67.7)	68 (68.7)
Basal insulin[b], n (%)	n[a]	34	32	33	65	99
	N	24 (70.6)	22 (68.8)	22 (66.7)	44 (67.7)	68 (68.7)
	Y	10 (29.4)	10 (31.3)	11 (33.3)	21 (32.3)	31 (31.3)
HbA1c (%)	n[a]	34	32	33	65	99
	Mean	8.02	8.22	7.89	8.05	8.04
	Std. Dev.	1.30	1.17	1.22	1.20	1.23
HbA1c (mmol/mol)	n[a]	34	32	33	65	99
	Mean	64.17	66.33	62.75	64.51	64.39
	Std. Dev.	14.18	12.81	13.37	13.12	13.42
HbA1c group, n (%)	n[a]	34	32	33	65	99
	≤8.0%	20 (58.8)	17 (53.1)	21 (63.6)	38 (58.5)	58 (58.6)
	>8.0%	14 (41.2)	15 (46.9)	12 (36.4)	27 (41.5)	41 (41.4)
Fasting glucose (mg/dL)	n[a]	32	28	32	60	92
	Mean	156.1	147.8	151.6	149.8	152.0
	Std. Dev.	77.83	52.34	68.31	60.90	66.91
	MISSING	2	4	1	5	7
Fasting glucose (mmol/L)	n[a]	32	28	32	60	92
	Mean	8.66	8.20	8.42	8.32	8.44
	Std. Dev.	4.32	2.91	3.79	3.38	3.71
	MISSING	2	4	1	5	7
Duration of T2DM (years)	n[a]	34	32	33	65	99
	Mean	2.65	2.54	1.93	2.23	2.37
	Std. Dev.	2.27	1.63	1.33	1.50	1.80
Tanner stage for boy genital, n (%)	n[a]	13	11	15	26	39
	G5	7 (53.8)	7 (63.6)	8 (53.3)	15 (57.7)	22 (56.4)
Tanner stage for girl breast, n (%)	n[a]	21	21	18	39	60
	B5	13 (61.9)	16 (76.2)	11 (61.1)	27 (69.2)	40 (66.7)

Abbreviations: B5 = Tanner stage B5 (breast, for girl) is the final stage of sexual maturity rating; BMI = body mass index; F = female; G5 = Tanner stage G5 (genital, for boy) is the final stage of sexual maturity rating; HbA1c = glycated hemoglobin A1c; M = male; n = number of participants within the category; N = number of participants in the analysis population; Std. Dev. = standard deviation; SDS = standard deviation score; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

a Number of participants with non-missing data.
b "Basal Insulin only" subgroup includes one participant, who was inadvertently enrolled with background medication of insulin aspart only at the time of randomization.

Note: Placebo/TZP 5 mg represents placebo intervention in double-blind period and TZP 5 mg in open-label period. TZP 5 mg and TZP 10 mg represent TZP 5 mg/5 mg and TZP 10 mg/10 mg, respectively, in both double-blind and open-label periods. TZP_ALL represents pooled arms of TZP 5 mg/5 mg and TZP 10 mg/10 mg.

Regarding medical history and preexisting conditions, the most frequently reported conditions were T2DM (n=99), obesity (n=29), and hyperlipidaemia (n=9).

Concomitant Therapies

One or more concomitant medications were administered to all the participants. Concomitant medications to manage BP and lipids as well as GI symptoms were allowed during the study, and details on their use are shown below in **Table 11**.

Antihyperglycemic medications

At **baseline**, the following antidiabetic medications were used:

- metformin: 68 (68.7%) participants
- basal insulin: 8 (8.1%) participants
- metformin and basal insulin: 23 (23.2%) participants.

Antihyperglycaemic **rescue therapy** was defined in the protocol as follows:

Patients who had not previously received rescue therapy, and receiving study drug at baseline ***plus***

- metformin: increased dose of ≥500 mg metformin and/or insulin at any dose for >2 weeks
- metformin + basal insulin: increased dose of ≥500 mg metformin and/or any increased dose of basal insulin >15% and/or adding another type of insulin at any dose for >2 weeks
- basal insulin: any increased dose of basal insulin >15% and/or adding another type of insulin at any dose for >2 weeks, or initiation of new antihyperglycemic therapy at any dose for >2 weeks

In the double-blind period, 6 (6.1%) participants in the placebo group and no participants in tirzepatide groups initiated rescue therapy. No participants initiated rescue therapy during the open-label period.

Further concomitant medications

Antihypertensive and lipid-lowering medications are shown in **Table 11** below.

Table 11: Concomitant antihypertensive and lipid-lowering medications in different parts of study GPGV

Medication - study part	**Plc/TZP 5 mg N=34 n (%)**	**TZP 5 mg N=32 n (%)**	**TZP 10 mg N=33 n (%)**	**Total N=99 n (%)**
Antihypertensive medication				
- baseline	4 (11.8)	2 (6.2)	2 (6.1)	8 (8.1)
- postbaseline	no new participant started an antihypertensive medication postbaseline			
Lipid-lowering medication				
- baseline	1 (2.9)	4 (12.5)	3 (9.1)	8 (8.1)
- postbaseline	3 (8.8)	6 (18.8)	3 (9.1)	12 (12.1)

In the double-blind period, 1 (1.0%) participant in the TZP 5 mg group initiated at least 1 antidiarrhoeal medication after baseline and 6 (6.1%) participants initiated at least 1 antiemetic medication after baseline (plc: 1 [2.9%]; TZP 5 mg: 2 [6.2%], TZP 10 mg: 3 [9.1%]).

Numbers analysed

See above, section on Sample size as well as section on Participant flow/study disposition.

Outcomes and estimation

Introductory comment:
To keep this AR short, from the endpoints listed above in the "Objectives" section, only the primary endpoint and the key secondary endpoints (controlled for type I error) are going to be discussed in detail (treatment regimen and efficacy estimand) in the "Results" section.

Out of the uncontrolled additional secondary endpoints, only the following selection is going to be shown (only treatment-regimen estimand):

- Change in HbA1c from baseline until week 52
- Change in daily average 6-point self-monitored blood glucose profiles from baseline
- Change in BMI SDS from baseline
- Patient-reported outcomes: PedsQL Generic Core Scales and PedsQL (3.2) Diabetic Module

The other additional secondary endpoints are considered confirmative for the primary and key secondary endpoints, but they are not shown in this AR to avoid too much redundancy. For the safety-related endpoints (including change from baseline for physical and developmental measures) it is referred to the safety section.

The tertiary/exploratory endpoints will only shortly be mentioned without showing details.

Primary efficacy endpoint

Mean Change in HbA1c at Week 30

For both the treatment-regimen and efficacy estimands, pooled tirzepatide 5 and 10 mg achieved superiority compared with placebo for mean change in HbA1c from baseline to Week 30 (**Table 12**). For the sake of brevity, the HbA1c data in mmol/mol were omitted from the table.

Table 12. Change from Baseline in HbA1c (%) in study GPGV; Treatment-Regimen Estimand (upper part) and Efficacy Estimand (lower part); Double-Blind Period

Treatment-Regimen Estimand (ANCOVA with Primary Multiple Imputation by Treatment for Missing Data at Week 30; mITT - Full Analysis Set)				
Parameters	**Placebo**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	34	32	33	65
Mean	8.02	8.22	7.89	8.05
Week 30 (Visit 13): n	32	29	27	56
Change from Baseline[a]				
Least-squares mean	-0.23	-1.90	-2.16	-2.03
Within-treatment p-value	0.310	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-1.67 (-2.31, -1.02)	-1.93 (-2.57, -1.29)	-1.80 (-2.35, -1.25)
Between-treatment p-value	NA	<0.001	<0.001	<0.001
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; n = number of subjects at the specified time point; NA = not applicable; TZP = tirzepatide. **Note 1:** Descriptive statistics are based on observed values; **Note 2:** Statistical inference and summary for baseline uses observed values; **Note 3:** Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets; **Note 4:** Missing values imputed based on primary multiple imputation, refer to SAP for missing data imputation; **Note 5:** Imputed missing data 100 times; **Note 6:** TZP_ALL represents pooled arms of TZP 5mg and TZP 10mg. a - ANCOVA model for endpoint measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment (Type III sum of squares).				
Efficacy Estimand (MMRM by Treatment and Visit from Baseline to Week 30; mITT - Efficacy Analysis Set 1)				
Baseline: n	34	32	32	64
Mean	8.02	8.22	7.92	8.07
Week 30 (Visit 13): n	26	29	27	56
Change from Baseline[b]				
Least-squares mean	0.049	-2.16	-2.30	-2.23
Within-treatment p-value	0.843	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-2.21 (-2.89, -1.53)	-2.35 (-3.03, -1.66)	-2.28 (-2.87, -1.69)

Between-treatment p-value	NA	<0.001	<0.001	<0.001

Abbreviations: CI = confidence interval; MMRM = mixed model repeated measures; n = number of subjects in the population with non-missing value at the specified time point; NA = not applicable; TZP = tirzepatide.

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:** TZP_ALL represents pooled arms of TZP 5mg and TZP 10mg.

b -MMRM model for post-baseline measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment + Time + Treatment*Time(Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.

Mean change in HbA1c over time

Figure 26 presents the mean change in HbA1c over time. For the efficacy estimand, participants in the tirzepatide 5 mg, tirzepatide 10 mg, and pooled treatment groups had significant reductions in HbA1c from baseline compared with placebo starting at Week 4 until week 30:

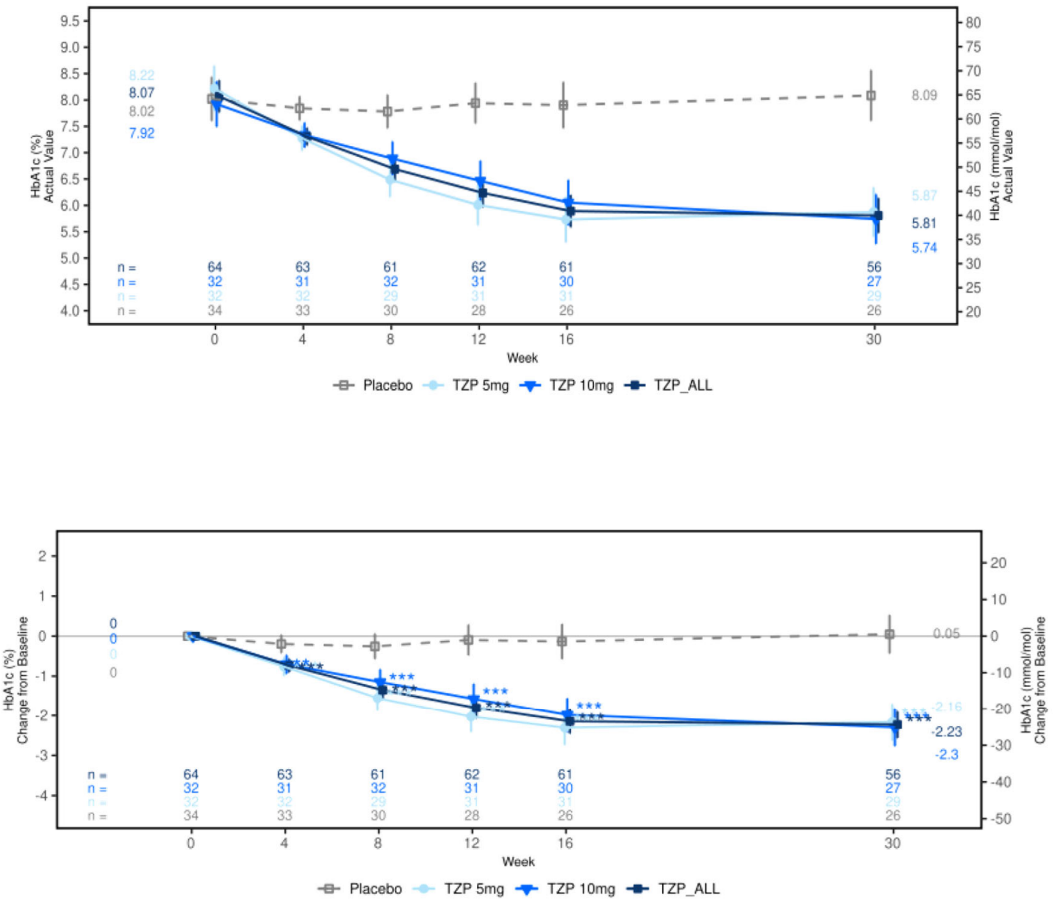


Figure 26: Development of absolute HbA1c values over time (upper figure) and change from baseline in HbA1c (lower figure) – HbA1c values shown as % (left axis) and mmol/mol (right axis); MMRM by treatment and visit from baseline to Week 30; mITT - efficacy analysis Set 1 - efficacy estimand; double-blind period

Sensitivity Analysis for Mean Change in HbA1c: Tipping point analyses

A 2-way tipping point analysis was conducted to evaluate the primary endpoint for the treatment-regimen

estimand. The impact of the missing data imputation method on the robustness of the primary endpoint outcome measures was assessed. The analysis supports the robustness of the conclusions to the imputation of missing data with clinically plausible extreme values based on the change in HbA1c

from baseline to Week 30 for pooled tirzepatide 5 and 10 mg (no details shown in the AR).

Key secondary endpoints

Individual Dose Mean Change in HbA1c at Week 30

As shown in **Table 9** above, for both the treatment-regimen and efficacy estimands, tirzepatide 5 and 10 mg individually achieved superiority compared with placebo for the mean change in HbA1c from baseline to Week 30. Mean reduction in HbA1c was numerically larger with the 10-mg dose of tirzepatide than with the 5 mg dose at Week 30.

Proportion of Participants with HbA1c ≤6.5% at Week 30

For both the treatment-regimen and efficacy estimands, tirzepatide 5 and 10 mg, individually and pooled, achieved superiority compared with placebo for the proportion of participants with HbA1c ≤6.5% at Week 30 (see **Figure 27** below).

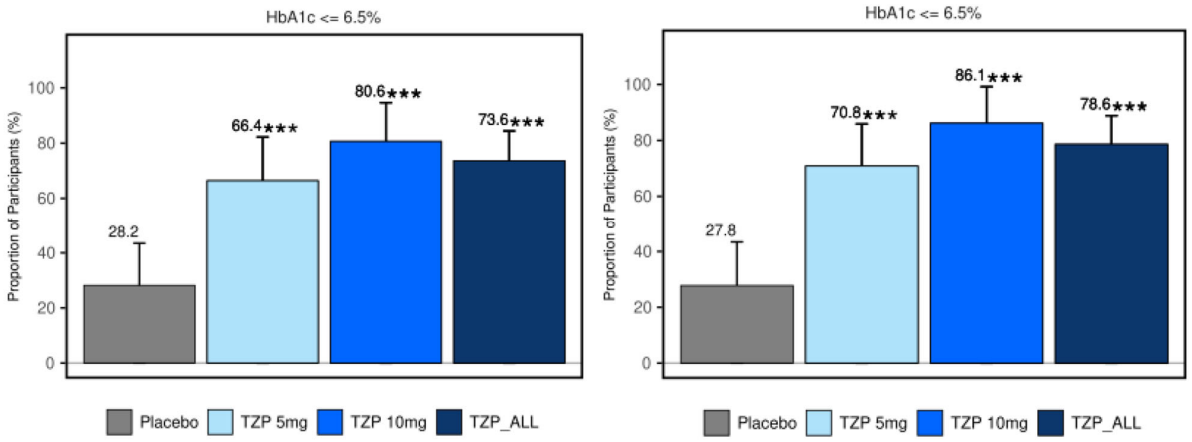


Figure 27: Plot of proportion of participants achieving HbA1c thresholds; double-blind period. Left side: Treatment-regimen estimand; Right side: Efficacy estimand.

Mean Change in FSG at Week 30

For both the treatment-regimen and efficacy estimands, tirzepatide 5 and 10 mg, individually and pooled, achieved superiority compared with placebo for the mean change in FSG from baseline to Week 30 – see **Table 13** below. For the sake of brevity, the FSG data in mmol/L were omitted from the table.

Table 13: Change from Baseline in Fasting Serum Glucose FSG (mg/dL) in study GPGV; Treatment-Regimen Estimand (upper part) and Efficacy Estimand (lower part); Double-Blind Period

Fasting SERUM Glucose (mg/dL)				
Treatment-Regimen Estimand (ANCOVA with Primary Multiple Imputation by Treatment for Missing Data at Week 30; mITT - Full Analysis Set)				
Parameters	**Placebo**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	32	28	32	60
Mean	156.1	147.8	151.6	149.8
Week 30 (Visit 13): n	33	28	28	56
Change from Baseline[a]				
Least-squares mean	-6.58	-35.5	-50.6	-43.0
Within-treatment p-value	0.371	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-28.9 (-49.7, -8.05)	-44.0 (-64.3, -23.6)	-36.4 (-54.2, -18.6)
Between-treatment p-value	NA	0.007	<0.001	<0.001

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; n = number of subjects in the population with baseline and post-baseline value at the specified time point; NA = not applicable; TZP = tirzepatide.

Note 1: Descriptive statistics are based on observed values; **Note 2:** Statistical inference and summary for baseline uses observed values; **Note 3**: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets; **Note 4:** Missing values are imputed based on primary multiple imputation, refer to SAP for missing data imputation; **Note 5:** Imputed missing data 100 times; **Note 6:** TZP_ALL represents pooled arms of TZP 5mg and TZP 10mg.

a - ANCOVA model for endpoint measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment (Type III sum of squares).

Efficacy Estimand (MMRM by Treatment and Visit from Baseline to Week 30; mITT - Efficacy Analysis Set 1)

Parameters	**Placebo**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	29	27	31	58
Mean	153.3	148.6	154.2	151.6
Week 30 (Visit 13): n	25	25	28	53
Change from Baseline[a]				
Least-squares mean	-7.93	-35.0	-53.5	-44.2
Within-treatment p-value	0.306	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-27.0 (-48.9, -5.21)	-45.6 (-66.7, -24.5)	-36.3 (-55.0, -17.6)
Between-treatment p-value	NA	0.016	<0.001	<0.001

Abbreviations: CI = confidence interval; NA = not applicable; MMRM = mixed model repeated measures; n = number of subjects in the population with non-missing value at the specified time point; SD = standard deviation; SE = standard error; TZP = tirzepatide.

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:** TZP_ALL represents pooled arms of TZP 5 mg and TZP 10 mg.

a - MMRM model for post-baseline measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment + Time + Treatment*Time(Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.

Change in FSG over time

Figure 28 presents the mean change from baseline in FSG in mg/dL. For the efficacy estimand, participants treated with tirzepatide, individually and pooled, had significantly greater reductions in FSG from baseline compared with placebo starting at Week 8 for the 5-mg treatment and Week 16 for the 10-mg and pooled treatments, until Week 30.

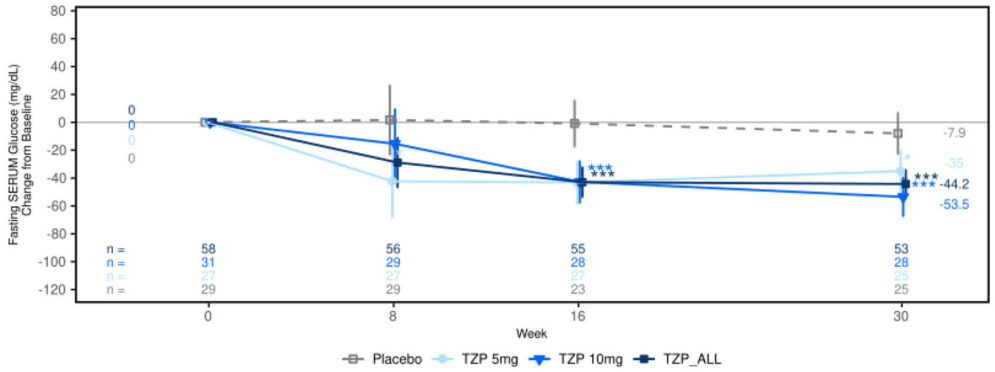


Figure 28: Change from baseline in fasting serum glucose (mg/dL); MMRM by treatment and visit from baseline to week; mITT - efficacy analysis set 1 - efficacy estimand; I8F-MC-GPGV - double-blind period

Mean Change in BMI-SDS at Week 30

For both the treatment-regimen and efficacy estimands, tirzepatide 5 and 10 mg, individually and pooled, achieved superiority compared with placebo for the change in BMI-SDS (age- and sex-matched) from baseline at Week 30 (see **Table 14** below).

Table 14: Change from Baseline in BMI SDS (Age- and Sex-Matched) in study GPGV; Treatment-Regimen Estimand (upper part) and Efficacy Estimand (lower part); Double-Blind Period

Change from Baseline in BMI SDS (Age- and Sex-Matched)
Treatment-Regimen Estimand (ANCOVA with Primary Multiple Imputation by Treatment for Missing Data at

Week 30; mITT - Full Analysis Set)				
Parameters	**Placebo**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	34	32	33	65
Mean	2.99	2.86	3.48	3.17
Week 30 (Visit 13): n	34	29	29	58
Change from Baseline[a]				
Least-squares mean	-0.092	-0.45	-0.76	-0.60
Within-treatment p-value	0.183	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-0.36 (-0.55, -0.16)	-0.66 (-0.86, -0.47)	-0.51 (-0.68, -0.34)
Between-treatment p-value	NA	<0.001	<0.001	<0.001
Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; n = number of subjects at the specified time point; NA = not applicable; SDS = standard deviation score; TZP = tirzepatide.				
Note 1: Descriptive statistics are based on observed values; **Note 2:** Statistical inference and summary for baseline uses observed values; **Note 3:** Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets; **Note 4:** Missing values are imputed based on primary multiple imputation, refer to SAP for missing data imputation; **Note 5:** Imputed missing data 100 times; **Note 6:** TZP_ALL represents pooled arms of TZP 5mg and TZP 10mg.				
a - ANCOVA model for endpoint measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment (Type III sum of squares).				
Efficacy Estimand (MMRM by Treatment and Visit from Baseline to Week 30; mITT - Efficacy Analysis Set 1)				
Parameters	**Placebo**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	34	32	32	64
Mean	2.99	2.86	3.41	3.14
Week 30 (Visit 13): n	27	29	29	58
Change from Baseline[b]				
Least-squares mean	-0.091	-0.50	-0.76	-0.63
Within-treatment p-value	0.242	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-0.41 (-0.62, -0.19)	-0.67 (-0.88, -0.45)	-0.54 (-0.72, -0.35)
Between-treatment p-value	NA	<0.001	<0.001	<0.001
Abbreviations: BMI = body mass index; CI = confidence interval; MMRM = mixed model repeated measures; n = number of subjects in the population with non-missing value at the specified time point; NA = not applicable; SDS = standard deviation score; TZP = tirzepatide.				
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:** TZP_ALL represents pooled arms of TZP 5mg and TZP 10mg.				
b - MMRM model for post-baseline measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment + Time + Treatment*Time (Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.				

Change in BMI-SDS over time

Figure 29 below presents the change from baseline in BMI-SDS. For the efficacy estimand, participants treated with tirzepatide 5 and 10 mg, individually and pooled, had significantly greater reductions in BMI-SDS from baseline compared with placebo starting at Week 4 until Week 30.

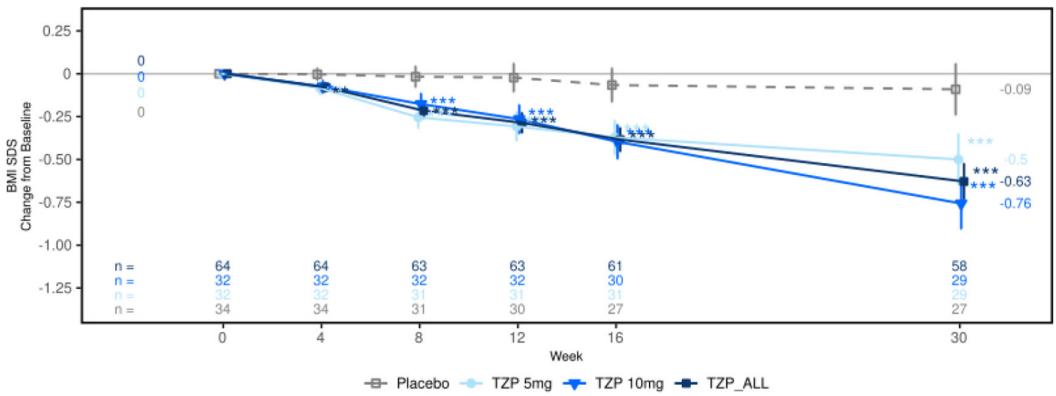


Figure 29: Change from baseline in BMI SDS (age- and sex-matched); MMRM by treatment and visit from baseline to Week 30: mITT - efficacy analysis Set 1 - efficacy estimand; I8F-MC-GPGV - double-blind period.

Percent Change in BMI at Week 30

For both the treatment-regimen and efficacy estimands, tirzepatide 5 and 10 mg, individually and pooled, achieved superiority compared with placebo for the mean percent change in BMI from baseline

to Week 30 (**Table 15** below).

Table 15: Change from Baseline in BMI in study GPGV; Treatment-Regimen Estimand (upper part) and Efficacy Estimand (lower part); Double-Blind Period

Percent change from baseline in BMI				
Treatment-Regimen Estimand (ANCOVA with Primary Multiple Imputation by Treatment for Missing Data at Week 30; mITT - Full Analysis Set)				
Parameters	**Placebo**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	34	32	33	65
Mean	34.7	33.9	37.7	35.8
Week 30 (Visit 13): n	34	29	29	58
Percent Change from Baseline[a]				
Least-squares mean	-0.55	-6.73	-11.07	-8.90
Within-treatment p-value	0.621	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-6.18 (-9.31, -3.05)	-10.52 (-13.67, -7.38)	-8.35 (-11.05, -5.66)
Between-treatment p-value	NA	<0.001	<0.001	<0.001
Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; n = number of subjects in the population with baseline and post-baseline value at the specified time point; NA = not applicable; TZP = tirzepatide. **Note 1:** Descriptive statistics are based on observed values; **Note 2:** Statistical inference and summary for baseline uses observed values; **Note 3:** Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets; **Note 4:** Missing values are imputed based on primary multiple imputation, refer to SAP for missing data imputation; **Note 5:** Imputed missing data 100 times; **Note 6:** TZP_ALL represents pooled arms of TZP 5mg and TZP 10mg. a - ANCOVA model for endpoint measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment (Type III sum of squares).				
Efficacy Estimand (MMRM by Treatment and Visit from Baseline to Week 30; mITT - Efficacy Analysis Set 1)				
Parameters	**Placebo**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	34	32	32	64
Mean	34.7	33.9	37.3	35.6
Week 30 (Visit 13): n	27	29	29	58
Percent Change from Baseline[b]				
Least-squares mean	-0.37	-7.41	-11.20	-9.30
Within-treatment p-value	0.762	<0.001	<0.001	<0.001
Difference from Placebo (95% CI)	NA	-7.04 (-10.48, -3.60)	-10.82 (-14.25, -7.39)	-8.93 (-11.91, -5.95)
Between-treatment p-value	NA	<0.001	<0.001	<0.001
Abbreviations: CI = confidence interval; MMRM = mixed model repeated measures; n = number of subjects in the population with non-missing value at the specified time point; NA = not applicable; TZP = tirzepatide. **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:** TZP_ALL represents pooled arms of TZP 5mg and TZP 10mg. b - MMRM model for post-baseline measures: Variable = Baseline + Baseline Age group + Baseline Antihyperglycemic medication + Treatment + Time + Treatment*Time(Type III sum of squares). Variance-Covariance structure (Percent Change from Baseline) = Unstructured.				

Percent Change in BMI over time

Figure 30 presents the mean percent change in BMI over time. For the efficacy estimand, participants treated with tirzepatide, individually and pooled, had significantly greater reductions in BMI from baseline compared with placebo starting at Week 4 until Week 30.

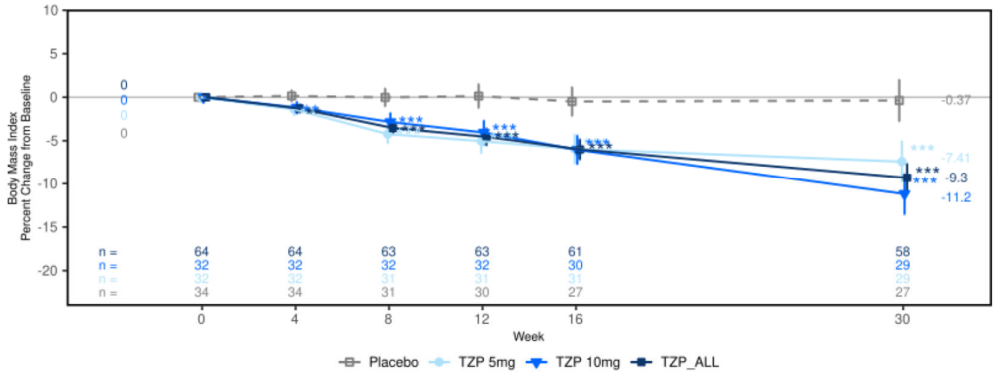


Figure 30: Percent change from baseline in BMI; MMRM by treatment and visit from baseline to Week 30 mITT - Efficacy Analysis Set 1 - efficacy estimand I8F-MC-GPGV - double-blind period.

Additional Secondary Efficacy Endpoints

Of the additional secondary efficacy endpoints, only the following selection is going to be shown in this AR (if available, the treatment-regimen estimand will be preferred):

- Change in HbA1c from baseline until week 52
- Change in daily average 6-point self-monitored blood glucose profiles from baseline
- Change in BMI SDS from baseline until week 52
- Patient-reported outcomes: PedsQL Generic Core Scales and PedsQL (3.2) Diabetic Module

The other additional secondary endpoints are considered confirmative for the primary and key secondary endpoints, but they are not shown in this AR to avoid too much redundancy. The safety-related endpoints (incl. physical and developmental measures) are discussed below in the safety section.

Change in HbA1c from baseline until week 52

The mean change from baseline in HbA1c to Week 52 is presented in Table **16** for the treatment-regimen estimand.

Table 16: Change from Baseline in HbA1c (%);Treatment-Regimen Estimand; I8F-MC-GPGV - Double-Blind and Open-Label Periods

Change from Baseline in HbA1c (%)				
Treatment-Regimen Estimand (ANCOVA with Primary Multiple Imputation by Treatment for Missing Data at Week 52; mITT - Full Analysis Set 2)				
Parameters	**Placebo/ TZP 5 mg**	**TZP 5 mg**	**TZP 10 mg**	**TZP_ALL**
Baseline: n	34	32	33	65
Mean	8.02	8.22	7.89	8.05
Week 52 (Visit 19): n	31	29	29	58
Change from Baseline[a]				
Least-squares mean	-1.83	-1.84	-2.17	-2.01
Within-treatment p-value	<0.001	<0.001	<0.001	<0.001

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; n = number of subjects at the specified time point; TZP = tirzepatide.

Note 1: Descriptive statistics are based on observed values; **Note 2:** Statistical inference and summary for baseline uses observed values; **Note 3:** Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets; **Note 4:** Missing values are imputed based on primary multiple imputation, refer to SAP for missing data imputation; **Note 5:** Imputed missing data 100 times; **Note 6:** Placebo/TZP 5 mg represents placebo treatment in double-blind period and TZP 5mg in open-label period. TZP 5 mg and TZP 10 mg represent TZP 5 mg/5 mg and TZP 10 mg/10 mg respectively in both double-blind and open-label periods. TZP_ALL represents pooled arms of TZP 5 mg/5 mg and TZP 10 mg/10 mg.

a - ANCOVA model for endpoint measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment (Type III sum of squares).

Change in daily average 6-point self-monitored blood glucose profiles from baseline

A total of 9 participants (1 in the placebo group) had a complete 6-point SMBG profile at baseline and week 30. Due to the lack of available data, which was caused by participant non-compliance, the planned analysis on this endpoint was not performed as originally indicated in the statistical analysis plan. Although most of the participants collected the required BG measurements for the 6-point SMBG profiles, many participants did not associate each BG measurement with a corresponding time point in the diary, resulting in insufficient data for analysis.

Change in BMI SDS from baseline at week 52

The mean change in BMI-SDS (age- and sex-matched) from baseline to Week 52 is presented in **Table 17** below for the treatment-regimen estimand. In all three groups, a significant effect was observed, which was lowest in the placebo/TZP 5 mg arm and highest in the TZP 10 mg arm.

Table 17: Change in BMI-SDS (Age- and Sex-Matched) ANCOVA with Primary Multiple Imputation by Treatment for Missing Data at Week 52; mITT - Full Analysis Set 2 - Treatment-Regimen Estimand I8F-MC-GPGV - Double-Blind and Open-Label Periods

Change from Baseline in BMI SDS (Age- and Sex-Matched)				
Parameters	Placebo/ TZP 5 mg	TZP 5 mg	TZP 10 mg	TZP_ALL
Baseline: n	34	32	33	65
Mean	2.99	2.86	3.48	3.17
Week 52 (Visit 19): n	33	29	29	58
Change from Baseline[a]				
Least-squares mean	-0.38	-0.60	-1.06	-0.83
Within-treatment p-value	<0.001	<0.001	<0.001	<0.001

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; n = number of subjects at the specified time point; SDS = standard deviation score; TZP = tirzepatide.

Note 1: Descriptive statistics are based on observed values; **Note 2:** Statistical inference and summary for baseline uses observed values; **Note 3:** Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets; **Note 4:** Missing values are imputed based on primary multiple imputation, refer to SAP for missing data imputation; **Note 5:** Imputed missing data 100 times; **Note 6:** Placebo/TZP 5mg represents placebo treatment in double-blind period and TZP 5mg in open-label period. TZP 5mg and TZP 10mg represent TZP 5mg/5mg and TZP 10mg/10mg respectively in both double-blind and open-label periods.

TZP_ALL represents pooled arms of TZP 5mg/5mg and TZP 10mg/10mg.
a - ANCOVA model for endpoint measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment (Type III sum of squares).

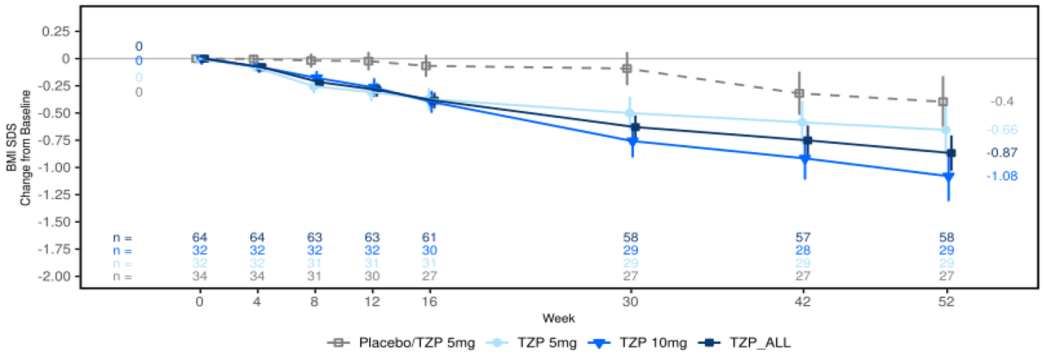


Figure 31: Change from baseline in BMI SDS (age- and sex-matched); MMRM by treatment and visit from baseline to Week 52 in study GPGV (i.e., double-blind and open-label period); mITT - Efficacy Analysis Set 2 - efficacy estimand

Patient-reported outcomes: PedsQL Generic Core Scales and PedsQL (3.2) Diabetic Module

For an explanation of the PedsQL score, please see above, section on "Objectives".

PedsQL Generic Core Scales

Table 18 shows the change from baseline to Weeks 30 and 52 in PedsQL generic core scales (analyzed using transformed scores). No statistically significant or clinically meaningful differences in change from baseline to Week 30 for any dimension were observed in the tirzepatide groups compared with placebo group. However, at Week 30, there was a positive change from baseline in all the summary scores for the Peds-QL Generic Core Scales across the tirzepatide and placebo groups.

Table 18: Change from Baseline in PEDS-QL Generic Scale Scores MMRM by Treatment and Visit from Baseline to Week 52; mITT - Efficacy Analysis Set 2 - Efficacy Estimand; I8F-MC-GPGV - Double-Blind and Open-Label Periods

Parameters	Placebo/ TZP 5 mg	TZP 5 mg	TZP 10 mg	TZP_ALL
PedsQL - Physical Functioning Score				
Baseline: n	26	29	27	56

Mean	82.1	77.4	82.5	79.9
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	5.77	1.46	1.44	1.45
Within-treatment p-value	0.010	0.478	0.496	0.325
Difference from Placebo/TZP 5 mg (95% CI)	NA	-4.31 (-10.33, 1.71)	-4.33 (-10.38, 1.72)	-4.32 (-9.60, 0.95)
Between-treatment p-value	NA	0.158	0.158	0.107
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	5.03	4.26	3.06	3.66
Within-treatment p-value	0.022	0.040	0.148	0.014
PedsQL - Emotional Functioning Score				
Baseline: n	26	29	27	56
Mean	74.2	64.3	69.1	66.6
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	3.44	2.97	3.37	3.17
Within-treatment p-value	0.307	0.342	0.293	0.158
Difference from Placebo/TZP 5 mg (95% CI)	NA	-0.47 (-9.67, 8.74)	-0.070 (-9.27, 9.13)	-0.27 (-8.34, 7.81)
Between-treatment p-value	NA	0.920	0.988	0.948
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	6.78	4.35	4.11	4.23
Within-treatment p-value	0.071	0.219	0.258	0.097
PedsQL - Social Functioning Score				
Baseline: n	26	29	27	56
Mean	83.5	76.6	83.3	79.8
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	0.75	3.30	0.97	2.13
Within-treatment p-value	0.793	0.217	0.723	0.264
Difference from Placebo/TZP 5 mg (95% CI)	NA	2.55 (-5.27, 10.37)	0.22 (-7.61, 8.05)	1.38 (-5.46, 8.23)
Between-treatment p-value	NA	0.518	0.955	0.688
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	4.54	4.16	3.00	3.58
Within-treatment p-value	0.104	0.118	0.269	0.060
PedsQL - School Functioning Score				
Baseline: n	26	29	27	56
Mean	70.4	56.0	68.1	61.9
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	7.48	6.06	0.73	3.40

Within-treatment p-value	0.027	0.055	0.818	0.128
Difference from Placebo/TZP 5 mg (95% CI)	NA	-1.42 (-10.62, 7.79)	-6.74 (-15.9, 2.37)	-4.08 (-12.09, 3.93)
Between-treatment p-value	NA	0.760	0.145	0.314
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	12.03	13.30	0.18	6.74
Within-treatment p-value	<0.001	<0.001	0.955	0.003
PedsQL - Psychosocial Health Summary Score				
Baseline: n	26	29	27	56
Mean	76.0	65.6	73.5	69.4
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	3.46	4.66	1.46	3.06
Within-treatment p-value	0.179	0.054	0.549	0.075
Difference from Placebo/TZP 5 mg (95% CI)	NA	1.20 (-5.86, 8.26)	-2.00 (-9.00, 5.01)	-0.40 (-6.55, 5.76)
Between-treatment p-value	NA	0.735	0.572	0.898
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	7.47	7.82	2.20	5.01
Within-treatment p-value	0.005	0.002	0.387	0.006
PedsQL - Physical Health Summary Score				
Baseline: n	26	29	27	56
Mean	82.1	77.4	82.5	79.9
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	5.77	1.46	1.44	1.45
Within-treatment p-value	0.010	0.478	0.496	0.325
Difference from Placebo/TZP 5 mg (95% CI)	NA	-4.31 (-10.33, 1.71)	-4.33 (-10.38, 1.72)	-4.32 (-9.60, 0.95)
Between-treatment p-value	NA	0.158	0.158	0.107
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	5.03	4.26	3.06	3.66
Within-treatment p-value	0.022	0.040	0.148	0.014
PedsQL - Total Score				
Baseline: n	26	29	27	56
Mean	78.1	69.7	76.7	73.1
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	4.27	3.62	1.40	2.51
Within-treatment p-value	0.053	0.079	0.502	0.087
Difference from Placebo/TZP 5 mg (95% CI)	NA	-0.66 (-6.66, 5.35)	-2.87 (-8.85, 3.10)	-1.77 (-7.01, 3.47)
Between-treatment p-value	NA	0.828	0.341	0.504

Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	6.61	6.65	2.45	4.55
Within-treatment p-value	0.004	0.002	0.262	0.003

Abbreviations: CI = confidence interval; MMRM = mixed model repeated measures; n = number of subjects in the population with non-missing value at the specified time point; NA = not applicable; TZP = tirzepatide.

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/TZP 5 mg represents placebo treatment in double-blind period and TZP 5mg in open-label period. TZP 5 mg and TZP 10 mg represent TZP 5 mg/5 mg and TZP 10 mg/10 mg respectively in both double-blind and open-label periods. TZP_ALL represents pooled arms of TZP 5 mg/5 mg and TZP 10 mg/10 mg.

a - MMRM model for post-baseline measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment + Time + Treatment*Time(Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.

In **Figure 32**, the PEDS-QL Generic Scale Scores (change from baseline, least-squares means) with the most prominent differences between TZP 10 mg and placebo were converted to bar diagrams (TZP_ALL column removed) by the assessor to better illustrate the treatment effects on these different scores:

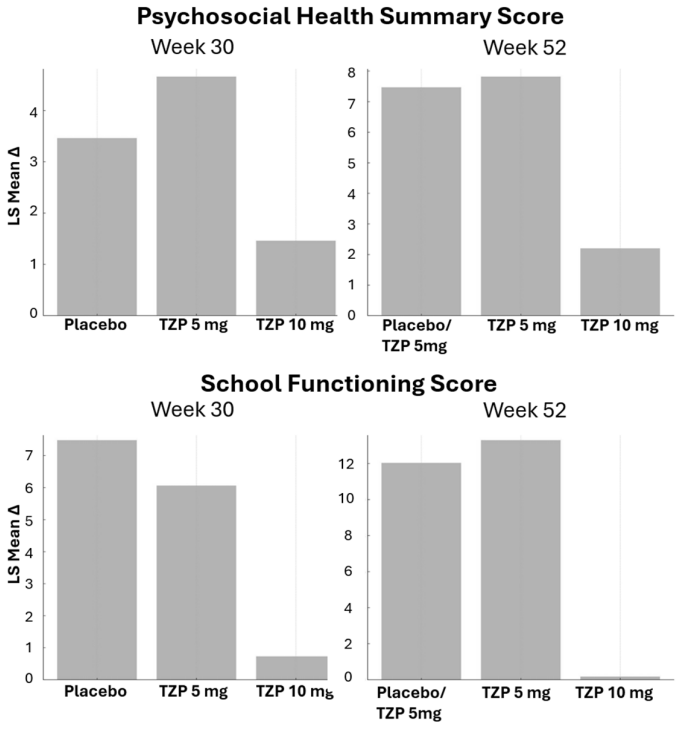


Figure 32: Effect of tirzepatide in comparison to placebo on the "Psychosocial Health Summary Score" and the "School Functioning Score" after 30 weeks (double-blind period) and 52 weeks (end of open-label period). Change from Baseline, Least-squares means. Diagram generated by assessor.

PedsQL (3.2) Diabetes Module Change from Baseline to Weeks 30 and 52

The changes from baseline to Weeks 30 and 52 in PedsQL (3.2) Diabetic Module and total scores are presented in **Table 19**. No statistically significant or clinically meaningful differences in change from baseline to Week 30 for any dimension were observed in the tirzepatide groups compared with placebo group. However, at Week 30, there was a positive change from baseline in all the summary scores for the Peds-QL Diabetes Module 3.2 across the tirzepatide and placebo groups, except for the Communications subscale score for the tirzepatide 5 mg group.

Table 19: Change from Baseline in PEDS-QL Diabetes [3.2] Scores by Domain; MMRM by Treatment and Visit from Baseline to Week 52; mITT - Efficacy Analysis Set 2 - Efficacy Estimand; I8F-MC-GPGV - Double-Blind and Open-Label Periods

Parameters	Placebo/ TZP 5 mg	TZP 5 mg	TZP 10 mg	TZP_ALL
PedsQL DM - Diabetes Symptoms Score				
Baseline: n	25	29	27	56
Mean	69.5	63.5	65.2	64.3
Week 30 (Visit 13): n	24	29	27	56
Change from Baseline[a]				
Least-squares mean	4.61	7.12	4.22	5.67
Within-treatment p-value	0.072	0.003	0.078	<0.001
Difference from Placebo/TZP 5 mg (95% CI)	NA	2.51 (-4.34, 9.36)	-0.39 (-7.29, 6.51)	1.06 (-4.99, 7.11)
Between-treatment p-value	NA	0.468	0.910	0.729
Week 52 (Visit 19): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	7.50	10.17	8.91	9.54
Within-treatment p-value	0.004	<0.001	<0.001	<0.001
PedsQL DM - Treatment I Score				
Baseline: n	25	29	27	56
Mean	79.6	68.6	73.1	70.8
Week 30 (Visit 13): n	24	29	27	56
Change from Baseline[a]				
Least-squares mean	2.89	0.12	3.50	1.81
Within-treatment p-value	0.375	0.968	0.248	0.393
Difference from Placebo/TZP 5 mg (95% CI)	NA	-2.77 (-11.64, 6.10)	0.60 (-8.22, 9.43)	-1.08 (-8.88, 6.71)
Between-treatment p-value	NA	0.535	0.892	0.782
Week 52 (Visit 19): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	4.91	2.53	9.24	5.89
Within-treatment p-value	0.150	0.420	0.005	0.010
PedsQL DM - Treatment II Score				
Baseline: n	25	29	27	56
Mean	77.8	71.7	77.2	74.3
Week 30 (Visit 13): n	24	29	27	56
Change from Baseline[a]				
Least-squares mean	4.74	1.68	5.57	3.62
Within-treatment p-value	0.105	0.527	0.043	0.059
Difference from Placebo/TZP 5 mg (95% CI)	NA	-3.07 (-10.95, 4.82)	0.82 (-7.06, 8.71)	-1.12 (-8.05, 5.81)
Between-treatment p-value	NA	0.441	0.836	0.748
Week 52 (Visit 19): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	5.97	6.13	6.19	6.16

Within-treatment p-value	0.087	0.059	0.064	0.009
PedsQL DM - Worry Score				
Baseline: n	25	29	27	56
Mean	59.7	54.6	57.4	56.0
Week 30 (Visit 13): n	24	29	27	56
Change from Baseline[a]				
Least-squares mean	8.61	7.29	9.90	8.60
Within-treatment p-value	0.077	0.100	0.031	0.008
Difference from Placebo/TZP 5 mg (95% CI)	NA	-1.32 (-14.35, 11.71)	1.29 (-11.83, 14.42)	-0.012 (-11.50, 11.48)
Between-treatment p-value	NA	0.841	0.845	0.998
Week 52 (Visit 19): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	11.92	12.75	12.99	12.87
Within-treatment p-value	0.026	0.010	0.011	<0.001
PedsQL DM - Communication Score				
Baseline: n	25	29	27	56
Mean	85.3	64.4	77.1	70.5
Week 30 (Visit 13): n	24	29	27	56
Change from Baseline[a]				
Least-squares mean	3.49	-4.53	6.16	0.81
Within-treatment p-value	0.281	0.127	0.040	0.696
Difference from Placebo/TZP 5 mg (95% CI)	NA	-8.03 (-17.0, 0.90)	2.67 (-6.00, 11.33)	-2.68 (-10.43, 5.07)
Between-treatment p-value	NA	0.077	0.542	0.493
Week 52 (Visit 19): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	2.56	7.53	8.71	8.12
Within-treatment p-value	0.545	0.058	0.032	0.005
PedsQL DM - Diabetes Management Summary Score				
Baseline: n	25	29	27	56
Mean	76.9	66.4	72.7	69.4
Week 30 (Visit 13): n	24	29	27	56
Change from Baseline[a]				
Least-squares mean	3.92	1.46	5.72	3.59
Within-treatment p-value	0.087	0.480	0.008	0.017
Difference from Placebo/TZP 5 mg (95% CI)	NA	-2.46 (-8.67, 3.76)	1.80 (-4.33, 7.92)	-0.33 (-5.76, 5.10)
Between-treatment p-value	NA	0.433	0.561	0.904
Week 52 (Visit 19): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	5.25	7.21	8.60	7.90
Within-treatment p-value	0.072	0.008	0.002	<0.001
PedsQL DM - Total Score				
Baseline: n	25	29	27	56
Mean	73.5	65.1	69.3	67.1

Week 30 (Visit 13): n	24	29	27	56
Change from Baseline[a]				
Least-squares mean	3.99	4.27	5.03	4.65
Within-treatment p-value	0.044	0.018	0.007	<0.001
Difference from Placebo/TZP 5 mg (95% CI)	NA	0.28 (-5.05, 5.61)	1.04 (-4.25, 6.34)	0.66 (-4.02, 5.34)
Between-treatment p-value	NA	0.917	0.696	0.779
Week 52 (Visit 19): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	6.03	8.79	8.74	8.76
Within-treatment p-value	0.018	<0.001	<0.001	<0.001

Abbreviations: CI = confidence interval; MMRM = mixed model repeated measures; n = number of subjects in the population with non-missing value at the specified time point; NA = not applicable; TZP = tirzepatide.

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/TZP 5 mg represents placebo treatment in double-blind period and TZP 5mg in open-label period. TZP 5 mg and TZP 10 mg represent TZP 5 mg/5 mg and TZP 10 mg/10 mg respectively in both double-blind and open-label periods. TZP_ALL represents pooled arms of TZP 5 mg/5 mg and TZP 10 mg/10 mg.

a - MMRM model for post-baseline measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment + Time + Treatment*Time(Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.

The applicant has also provided subgroup analyses of the change in PedsQL (3.2) Diabetic Module as well as summary and total scores for participants aged ≥10 to ≤14 years and ≥15 to <18 years. However, due to the small size of the subgroups, these data are not considered very robust and therefore not discussed in the AR.

Tertiary and Exploratory Efficacy Endpoints

To keep the AR short, in the following, only a summary of the significant effects of tirzepatide on tertiary and exploratory endpoint parameters at the end of the double-blind period (at week 30) is provided.

Proportion of Participants with HbA1c <7.0% or ≤6.5% without Clinically Significant (Blood Glucose <54 mg/dL) or Severe Hypoglycaemia

Data on clinically significant or severe hypoglycaemia are shown below in the safety section. There were no severe hypoglycaemic episodes in the study. Tirzepatide 5 and 10 mg, individually and pooled, resulted in statistically significantly greater proportions of participants with HbA1c <7.0% and ≤6.5% without clinically significant (BG <54 mg/dL) or severe hypoglycaemia compared with placebo at Week 30.

Change in Measures of Insulin Resistance, Beta Cell Function, and Serum Adiponectin at Week 30

At week 30, compared with placebo, tirzepatide 5 and 10 mg, individually and pooled, had statistically significant

- decreases in intact proinsulin compared with placebo ($p<0.05$ for all comparisons)
- increases in HOMA-B (C-peptide) ($p<0.01$ or $p<0.001$), and
- increases in HOMA-B (insulin) ($p<0.05$ or $p<0.01$)

Additionally, compared with placebo at Week 30, there were statistically significant

- increases in adiponectin with tirzepatide 5 mg ($p<0.05$), and
- decreases in HOMA-IR (insulin) with tirzepatide 10 mg ($p<0.05$).

No statistically significant differences compared with placebo at Week 30 were observed with other measures.

EQ-5D-Y-3L and EQ VAS Scores Change from Baseline to Weeks 30 and 52

Table 20 presents change from baseline to Weeks 30 and 52 in EQ-5D-Y-3L index and EQ VAS scores, which was also included as tertiary/exploratory endpoint.

Table 20: Change from Baseline in EQ-5D-Y Index and EQ VAS Scores; MMRM by Treatment and Visit from Baseline to Week 52; mITT - Efficacy Analysis Set 2 - Efficacy Estimand; I8F-MC-GPGV - Double-Blind and Open-Label Periods

Parameters	Plc/ TZP 5 mg	TZP 5 mg	TZP 10 mg	TZP_ALL
EQ-5D-Y-3L Health State Index (Slovenia)				
Baseline: n	26	29	27	56
Mean	0.90	0.85	0.84	0.85
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	0.005	0.011	0.013	0.012
Within-treatment p-value	0.862	0.658	0.618	0.506
Difference from Placebo/TZP 5 mg (95% CI)	NA	0.007 (-0.070, 0.083)	0.008 (-0.069, 0.086)	0.008 (-0.060, 0.075)
Between-treatment p-value	NA	0.864	0.828	0.825
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	0.006	0.032	0.019	0.026
Within-treatment p-value	0.832	0.220	0.484	0.177
EQ5DY- EQ VAS Score				
Baseline: n	26	29	27	56
Mean	76.8	76.3	75.3	75.8
Week 30 (Visit 13): n	25	29	27	56
Change from Baseline[a]				
Least-squares mean	8.72	5.36	4.12	4.74
Within-treatment p-value	0.002	0.040	0.124	0.012
Difference from Placebo/TZP 5 mg (95% CI)	NA	-3.35 (-10.91, 4.20)	-4.60 (- 12.24, 3.05)	-3.97 (-10.63, 2.68)
Between-treatment p-value	NA	0.380	0.235	0.238
Week 52 (Visit 19): n	26	29	27	56
Change from Baseline[a]				
Least-squares mean	7.70	4.26	3.38	3.82
Within-treatment p-value	0.008	0.115	0.225	0.051

Abbreviations: CI = confidence interval; MMRM = mixed model repeated measures; n = number of subjects in the population with non-missing value at the specified time point; NA = not applicable; TZP = tirzepatide.

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/TZP 5 mg represents placebo treatment in double-blind period and TZP 5mg in open-label period. TZP 5 mg and TZP 10 mg represent TZP 5 mg/5 mg and TZP 10 mg/10 mg respectively in both double-blind and open-label periods. TZP_ALL represents pooled arms of TZP 5 mg/5 mg and TZP 10 mg/10 mg.

a - MMRM model for post-baseline measures: Variable = Baseline + Baseline Antihyperglycemic medication + Baseline Age group + Treatment + Time + Treatment*Time(Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.

Ancillary analyses

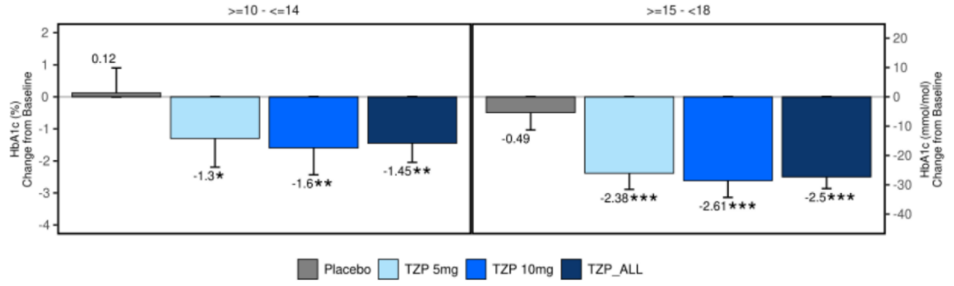
Subgroup analyses of the primary endpoint:

Subgroup analyses were conducted to assess treatment interaction with important factors potentially affecting the change in HbA1c for the mITT population for the treatment-regimen estimand.

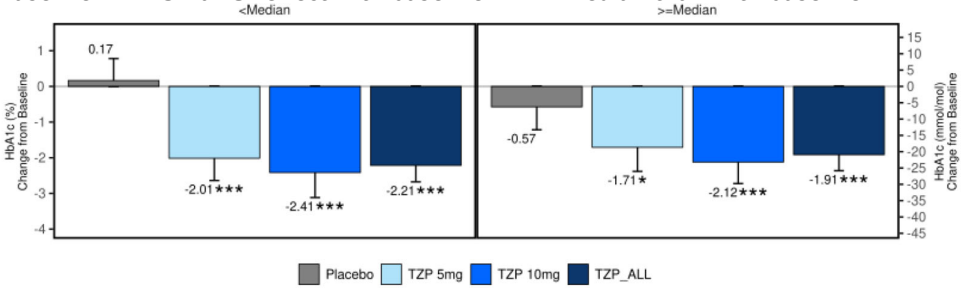
The results of the treatment-by-subgroup interactions were tested at a 2-sided alpha level of 0.1. All subgroups showed a significantly greater reduction in HbA1c in the tirzepatide groups than in the placebo group (treatment p-values <0.001). The treatment-by-subgroup interaction was statistically significant for baseline body weight (p = 0.046) and a similar tendency, albeit not significant, was seen for baseline BMI (p = 0.200).

In **Figure 33,** the effect size (% change in HbA1c from baseline) is depicted for the individual subgroup analyses:

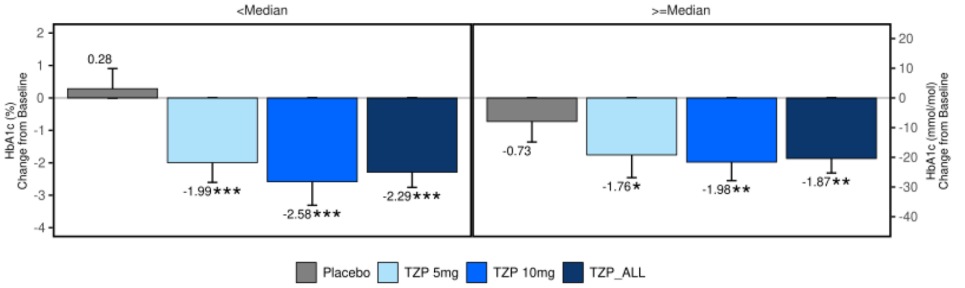
Age group: **larger** effect in participants aged ≥15 - <18 than in those aged ≥10 - ≤14



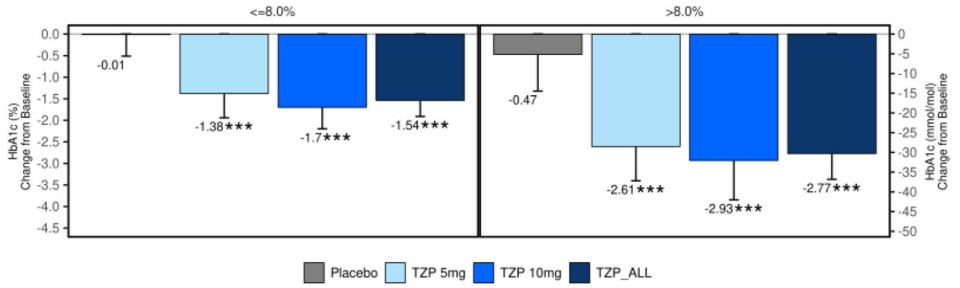
Baseline BMI: **smaller** effect with baseline BMI ≥median than with baseline BMI <median



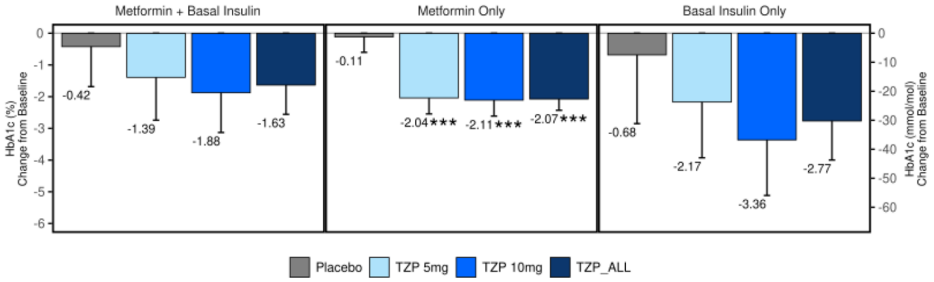
Baseline body weight: **smaller** effect with body weight ≥median than with body weight <median



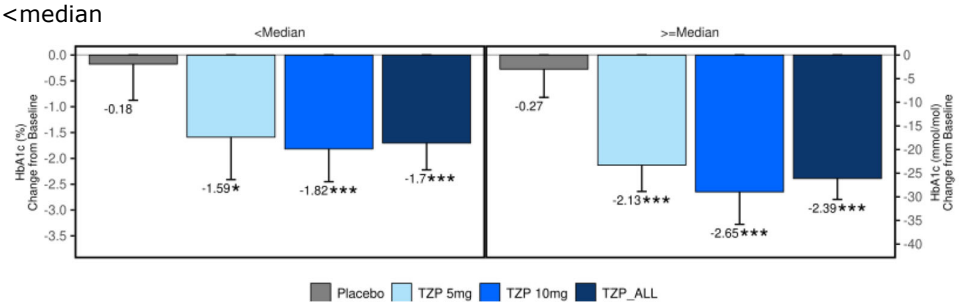
Baseline HbA1c: **larger** effect with baseline HbA1c >8.0% than with baseline HbA1c ≤8.0%



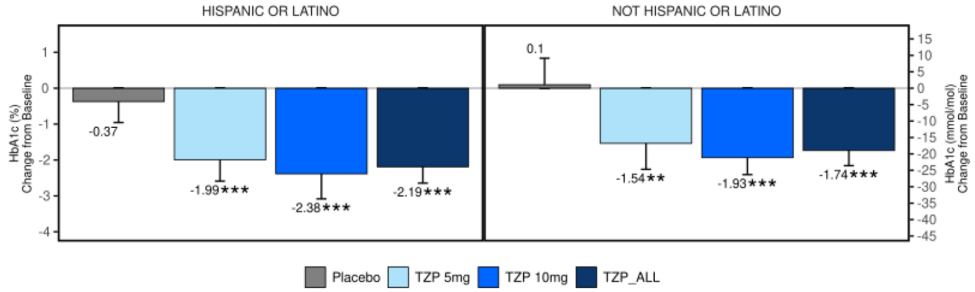
Baseline antihyperglycaemic medication: **larger** effect with metformin only as compared to metformin + basal insulin; basal insulin only group very small (n=8) → not interpreteable



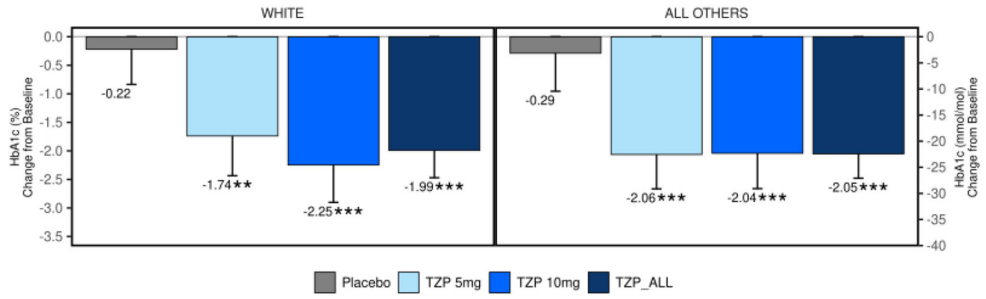
Duration of diabetes: **larger** effect with diabetes duration ≥median than with diabetes duration <median



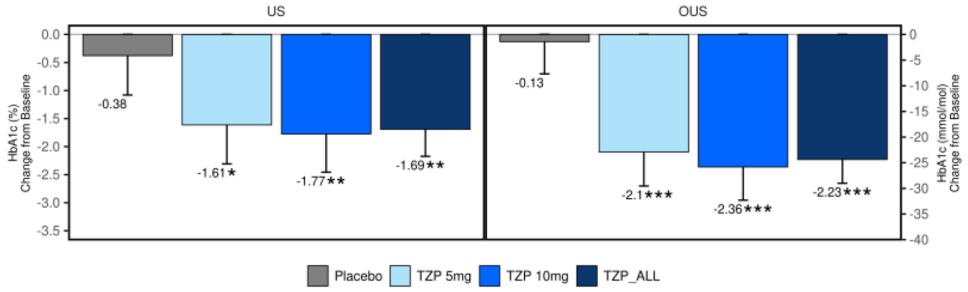
Ethnicity: **smaller** effect in *not Hispanic or Latino* than in *Hispanic or Latino* participants



Race: no consistent differences.



Region: **larger** effect in non-US as compared to US participants



Sex: **smaller** effect in male than in female participants

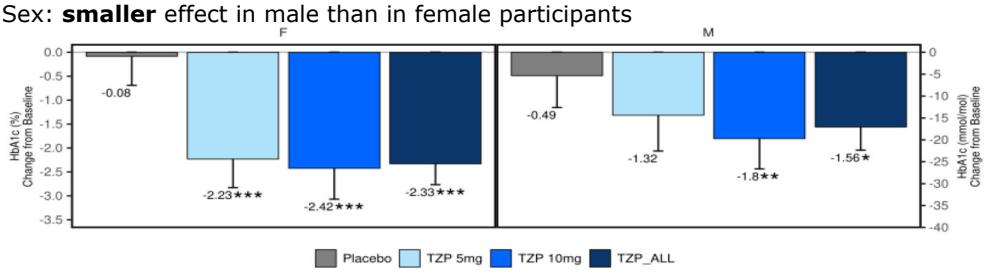


Figure 33: Effect size (% change in HbA1c from baseline) in individual subgroups

Summary of main study

See effects table in section 3.6.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study I8F-MC-GPGV (SURPASS-PEDS) was a randomized, double-blind, placebo-controlled, phase 3 study with an open-label extension assessing the efficacy, safety, and pharmacokinetics/pharmacodynamics of tirzepatide in paediatric and adolescent participants with Type 2 Diabetes Mellitus (T2DM) inadequately controlled with metformin, or basal insulin, or both.

The 52-week treatment phase consisted of a 30-week double-blind treatment period, followed by a 22-week open label extension. The primary objective was to demonstrate the superiority of tirzepatide 5 mg and 10 mg vs. placebo regarding HbA1c reduction from baseline at week 30 (end of double-blind

period). The study design is adequate and in line with the recommendations of the EU guideline on medicinal products for treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev.2).

Studied population

Out of 146 screened subjects, 99 were randomized to once weekly placebo (n=34), tirzepatide 5 mg (n=32) or tirzepatide 10 mg(n=33), with stratified randomization according to age (≤14 and >14 years of age) as well as baseline antihyperglycaemic medication (metformin only, basal insulin only, metformin and basal insulin). This approach is endorsed, as it ensures sufficient coverage of the entire target age range. The background therapy (metformin and/or basal insulin) corresponds to the current ADA recommendations for juvenile T2DM [*Diabetes Care* (2025) 48(1 Suppl 1):S283-S305]. It is noted that the current ADA recommendations also include SGLT2 inhibitors and GLP1 agonists as treatment options. It is acceptable to exclude GLP1 agonists as background therapy, due to potential interference with the mechanism of action of tirzepatide. However, dapagliflozin was authorized for use in the paediatric population on 15 Nov 2021 (EC decision date), i.e., prior to the approval of the study protocol on 14 Dec 2021. Thus, it would have been possible to include this therapy option. The distribution of anti-diabetic background treatments was balanced across the treatment groups. Most patients used metformin only (~69%), followed by metformin *plus* basal insulin (~23%) and basal insulin only (~8%).

The majority of participants was female (60.6%), which reflects the distribution of paediatric T2DM patients reported in the literature (e.g., Pinhas-Hamiel O (2023)). Most of the participants (58.6%) were in the lower HbA1c category of ≤8.0%. The vast majority of patients appeared to be overweight/obese, which was a consequence of the inclusion criterion which selected children and adolescents above the 85th percentile for BMI. This may hamper the evaluation of a weight-loss independent action of TZP on HbA1c. However, as the direct antihyperglycemic mechanism of action of TZP (increase of glucose-dependent insulin secretion) is well known, inclusion of a mostly overweight/obese population is not considered a shortcoming. Nevertheless, the resulting lack of experience with normal-weight children is reflected in SmPC sections 4.2 and 5.1.

The study was conducted at 39 centres in the US, Mexico, Australia, Brazil, India, Israel, Italy, and the United Kingdom. Only 4% of participants were from Europe (Italy, UK). Nevertheless, the study results are considered transferable to a European population, since the proportion of participants from the US is relatively large and US participants can be considered sufficiently similar (~30%).

Demographic and baseline characteristics were largely comparable across treatment groups. However, it is noted that the 10 mg group, in comparison to the other two treatment groups, exhibits a higher body weight (by ~10 kg), a more than 20% higher percentage of "Not Hispanic/Latino" participants and a shorter T2DM mean duration (TZP 10 mg: 1.93 years; placebo: 2.65 years; 5 mg TZP: 2.54 years). Moreover, the 5 mg TZP arm contained more participants in the G5/B5 Tanner stage as compared to the other two study arms (by ~10% more for boys and 14-15% more for girls). However, it is difficult to say, to which extent such imbalances eventually influence the efficacy results.

Statistical methods

The applicant used both the treatment-regimen and the efficacy estimand to analyse the treatment effect. While the treatment-regimen estimand addresses the treatment effect regardless of intervention discontinuation for any reason or initiation of rescue antihyperglycemic intervention, the efficacy estimand analyses the treatment effect prior to intervention discontinuation for any reason or initiation of rescue antihyperglycemic medication. The treatment-regimen estimand is preferred in this assessment, since it reflects the actual therapeutic effect to be expected in later clinical reality.

Overall, the statistical methods are considered appropriate.

Participant flow and Study conduct

90.9% of all participants completed the week 30 primary endpoint visit (end of double-blind period) as well as the week 52 visit (end of open-label period) on treatment. No significant differences were observed across treatment groups. Thus, the participant retention rate can be considered sufficiently high to yield reliable results. The most common reason for discontinuation was "withdrawal by subject". It is considered reassuring that only 2 discontinuations (both in TZP 5 mg arm) occurred due to adverse events.

Results

Primary endpoint

For the treatment-regimen estimand, the least squares (LS) mean difference of the HbA1c change from baseline for pooled tirzepatide *vs.* placebo at week 30 was -1.80 (95% CI: -2.35, -1.25; p<0.001), which indicated clinically relevant anti-hyperglycaemic efficacy and significant superiority of tirzepatide over placebo. The treatment effect showed a trend indicating some dose dependency [Difference from placebo (95% CI): tirzepatide 5 mg: 1.67 (-2.31, -1.02); tirzepatide 10 mg: -1.93 (-2.57, -1.29)]. The robustness of the results was confirmed by a 2-way tipping point analysis.

The treatment effect was somewhat more pronounced than the effect observed at the same doses in the placebo-controlled monotherapy study SURPASS-1 in adults. However, similar as in the studies with adults in the SURPASS programme, most of the treatment effect was already reached after 16 weeks.

The treatment-by-subgroup interaction was significant for baseline body weight (p=0.046). All other trends were not significant, e.g., an *increased* effect of tirzepatide (% HbA1c change from baseline at 30 weeks) with higher age, higher baseline HbA1c, or longer diabetes duration at baseline. By contrast the effect of tirzepatide was reduced in male vs. female participants, non-US vs. US participants, or not Hispanic/Latino vs. Hispanic/Latino participants.

Key secondary endpoints

The blood glucose-related key secondary endpoints (Individual Dose Mean Change in HbA1c at Week 30, Proportion of Participants with HbA1c ≤6.5% at Week 30 and mean change from baseline in fasting serum glucose at week 30) all confirm the primary endpoint result and show that tirzepatide at any dose level is significantly superior in comparison to placebo. Like the primary endpoint, these key secondary endpoints also suggest dose dependency of the tirzepatide effect. Tirzepatide also demonstrated superiority vs. placebo with regard to body weight reduction after 30 weeks, either expressed as BMI or - more appropriate for a paediatric population - as BMI-SDS. The weight-reducing effect of tirzepatide is well known and important for reversing the metabolic changes associated with T2DM.

Additional secondary endpoints and exploratory endpoints

For the sake of brevity only a small part of the secondary endpoints was discussed in this AR. The mean HbA1c reduction from baseline at week 52 was less pronounced than after 30 weeks, but still highly significant and clinically relevant. Thus, it was demonstrated that the antihyperglycaemic effect of tirzepatide is maintained during long-term treatment. The body weight-related additional secondary endpoints show that, during the open label period, the weight reduction continued in the TZP 5 mg and 10 mg group. The placebo group was switched to 5 mg of TZP at the beginning of the open-label period and also showed a significant weight reduction. However, due to the later onset of tirzepatide therapy, the weight reduction in the placebo/5 mg TZP arm did not reach the same extent as in the 5 mg TZP arm at week 52.

The applicant had also intended to analyse 6-point SMBG profiles, which would have been important to assess the ability of tirzepatide to reduce postprandial glucose peaks. However, only a very limited number of 9 participants (only 1 in the placebo arm) has correctly entered the BG values into their diary. Thus, a meaningful analysis of these data was not possible.

The additional secondary endpoints also included PROs (PedsQL (3.2) Diabetic Module, PedsQL Generic Core Scales as well as EQ-5D-Y-3L and EQ VAS Scores). No statistically significant effect of tirzepatide was observed in the EQ-5D-Y-3L Health index or the EQ VAS score. Similarly, change from Baseline in PedsQL (3.2) Diabetic Module shows no meaningful effects of tirzepatide vs. placebo. However, the PedsQL Generic Core Scales show a pronounced improvement in the placebo group, but tirzepatide, especially at the 10 mg dose, causes considerably less improvement in quality of life than placebo, specifically in the school functioning score and the psychosocial health summary score. This is possibly due to the increased incidence of gastrointestinal adverse events, which is considered acceptable given the positive long-term health benefits of tirzepatide treatment. It is reassuring that none of the PedsQL Generic Core Scales worsened with tirzepatide vs. baseline.

Several measures of insulin resistance and β-cell function (HOMA-B, HOMA-IR, intact proinsulin) as well as serum adiponectin were determined as exploratory endpoints. The results suggest that tirzepatide improves pancreatic β-cell function and insulin sensitivity in a paediatric population with T2DM.

2.4.3. Conclusions on the clinical efficacy

In children from 10 to <18 years of age with T2DM, tirzepatide (5 mg and 10 mg) causes a significant and clinically relevant decrease in HbA1c compared to placebo. This effect was confirmed by various blood glucose-related secondary endpoints. As to be expected for a GLP-1/GIP dual agonist, tirzepatide also caused a pronounced weight reduction. In conclusion, tirzepatide at the 5 mg and 10 mg dose is considered efficacious at improving blood glucose control in children and adolescents with T2DM. The proposed extension of indication to a population aged ≥10 to <18 years is considered sufficiently justified from the efficacy perspective.

2.5. Clinical safety

Introduction

Safety analyses were conducted on the mITT population using the analysis sets SS1 and SS2. SS1 encompasses the data collected during the double-blind period, i.e. up to Week 30. SS2 covers the whole study duration including safety follow-up, i.e. up to Week 56.

In the following, presentation of safety data will mainly focus on SS1 unless otherwise indicated because the open-label period is less informative due to the lack of a control group.

Patient exposure

Since this safety analysis encompasses one study only, patient exposure can be derived from the patient flow data provided in the efficacy section.

Adverse events

An overview of the adverse events (AEs) observed in Study GPGV is provided in the table below. AEs (of any type) were clearly increased with TZP compared to plc (67.7% TZP combined vs. 44.1% plc). A marked difference between plc and TZP was also observed for AEs considered related to the study drug

by the investigator (38.5% TZP combined vs. 8.8% plc). Reassuringly, serious AEs were rare and were balanced between the treatment groups. Events of discontinuation due to AE were also infrequent.

Table 21: Overview of Adverse Events mITT - Safety Analysis Set 1 I8F-MC-GPGV - Double-Blind Period

	Placebo (N=34)	TZP 5mg (N=32)	TZP 10mg (N=33)	TZP_ALL (N=65)	Total (N=99)
Event Type*a	n (%)	n (%)	n (%)	n (%)	n (%)
AE leading to death*b	0	0	0	0	0
Serious Adverse Events	1 (2.9)	1 (3.1)	1 (3.0)	2 (3.1)	3 (3.0)
Discontinuations from Study due to an Adverse Event	0	2 (6.2)	0	2 (3.1)	2 (2.0)
Discontinuations from Study Treatment due to an Adverse Event	0	2 (6.2)	0	2 (3.1)	2 (2.0)
Treatment-emergent Adverse Events	15 (44.1)	21 (65.6)	23 (69.7)	44 (67.7)	59 (59.6)
Treatment-emergent Adverse Events Related to Study Treatment*c	3 (8.8)	13 (40.6)	12 (36.4)	25 (38.5)	28 (28.3)

*a – Subjects may be counted in more than one category.
*b – Deaths are also included as serious adverse events and discontinuations due to adverse events.
*c – Includes events that were considered related to study treatment as judged by the investigator.

AEs per SOC and PT

Most of the reported AEs (expressed as Preferred Terms, PT) were related to gastrointestinal (GI) symptoms, see table below. Besides GI events, a dose-dependent increase with TZP was observed for headache.

Table 22: Summary of Treatment-Emergent Adverse Events Occurring in ≥5% of Participants in Any Group MedDRA Preferred Term by Decreasing Frequency mITT - Safety Analysis Set 1 I8F-MC-GPGV - Double-Blind Period

	n (%)			
	Placebo (N=34)	**TZP 5 mg** (N=32)	**TZP 10 mg** (N=33)	**TZP_ALL** (N=65)
Participants with ≥1 TEAE	15 (44.1)	21 (65.6)	23 (69.7)	44 (67.7)
Diarrhoea	2 (5.9)	8 (25.0)	8 (24.2)	16 (24.6)
Nausea	3 (8.8)	7 (21.9)	6 (18.2)	13 (20.0)
Vomiting	1 (2.9)	5 (15.6)	4 (12.1)	9 (13.8)
Abdominal pain upper	3 (8.8)	2 (6.2)	4 (12.1)	6 (9.2)
Abdominal pain	1 (2.9)	5 (15.6)	1 (3.0)	6 (9.2)
Dyspepsia	0	2 (6.2)	4 (12.1)	6 (9.2)
Headache	1 (2.9)	2 (6.2)	3 (9.1)	5 (7.7)
Oropharyngeal pain	2 (5.9)	3 (9.4)	1 (3.0)	4 (6.2)
Cough	1 (2.9)	3 (9.4)	1 (3.0)	4 (6.2)
Hyperglycaemia	5 (14.7)	0	0	0
Nasopharyngitis	2 (5.9)	1 (3.1)	2 (6.1)	3 (4.6)
Decreased appetite	0	0	4 (12.1)	4 (6.2)
Anxiety	0	1 (3.1)	2 (6.1)	3 (4.6)
Gastroenteritis	2 (5.9)	0	0	0
Injection site reaction	0	0	2 (6.1)	2 (3.1)
Tonsillitis	0	2 (6.2)	0	2 (3.1)

It can also be derived from the above table that anxiety was more frequent in the TZP groups than in the plc group. For a complete picture, the SOC Psychiatric disorders was retrieved from Table 23, see below. Anxiety was numerically more frequent with TZP than with plc. Reassuringly, suicidal ideation balanced across the groups, not indicating a contribution of TZP.

Table 23: Treatment-Emergent Adverse Events MedDRA Preferred Term by Decreasing Frequency within System Organ Class Modified Intent-to-Treat - Safety Analysis Set 1 PDPM I8F-MC-GPGV - Double-Blind Period

	Placebo (N=34)	TZP 5mg (N=32)	TZP 10mg (N=33)	TZP_ALL (N=65)	Total (N=99)
Psychiatric disorders	1 (2.9)	3 (9.4)	2 (6.1)	5 (7.7)	6 (6.1)
Anxiety	0	1 (3.1)	2 (6.1)	3 (4.6)	3 (3.0)
Suicidal ideation	1 (2.9)	1 (3.1)	1 (3.0)	2 (3.1)	3 (3.0)
Anxiety disorder	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Borderline personality disorder	1 (2.9)	0	0	0	1 (1.0)
Depression	0	0	1 (3.0)	1 (1.5)	1 (1.0)
Insomnia	1 (2.9)	0	0	0	1 (1.0)
Mood altered	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Suicide attempt	1 (2.9)	0	0	0	1 (1.0)

The AE analysis per SOC, see table below, also clearly shows a predominance of GI events. Metabolism and nutrition disorders were less frequent with TZP. This probably is mainly due to a reduced number of hyperglycaemia events as suggested by the PT table above.

Table 24: Summary of Treatment-Emergent Adverse Events SOCs with Most Frequently Reported TEAEs mITT - Safety Analysis Set 1 I8F-MC-GPGV - Double-Blind Period

System Organ Class	n (%)			
	Placebo (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)	TZP_ALL (N=65)
Gastrointestinal disorders	4 (11.8)	15 (46.9)	15 (45.5)	30 (46.2)
Infections and infestations	6 (17.6)	10 (31.2)	7 (21.2)	17 (26.2)
Metabolism and nutrition disorders	7 (20.6)	1 (3.1)	4 (12.1)	5 (7.7)

It can be derived from the above table that infections were numerically more frequent in the TZP groups than in the plc group. For further clarification, the respective part of Table GPGV.8.74 is shown below, providing the kinds (PTs) of the infection events. The types of infections were heterogenous; no individual entities could be identified that drove the numerical increase in infections.

Table 25: Treatment-Emergent Adverse Events MedDRA Preferred Term by Decreasing Frequency within System Organ Class Modified Intent-to-Treat - Safety Analysis Set 1 PDPM I8F-MC-GPGV - Double-Blind Period

	Placebo (N=34)	TZP 5mg (N=32)	TZP 10mg (N=33)	TZP_ALL (N=65)	Total (N=99)
Infections and infestations	6 (17.6)	10 (31.2)	7 (21.2)	17 (26.2)	23 (23.2)
Nasopharyngitis	2 (5.9)	1 (3.1)	2 (6.1)	3 (4.6)	5 (5.1)
Influenza	1 (2.9)	1 (3.1)	1 (3.0)	2 (3.1)	3 (3.0)
Ear infection	0	1 (3.1)	1 (3.0)	2 (3.1)	2 (2.0)
Gastroenteritis	2 (5.9)	0	0	0	2 (2.0)
Pharyngitis	1 (2.9)	0	1 (3.0)	1 (1.5)	2 (2.0)
Rhinitis	0	1 (3.1)	1 (3.0)	2 (3.1)	2 (2.0)
Tonsillitis	0	2 (6.2)	0	2 (3.1)	2 (2.0)
Abscess jaw	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Appendicitis	0	1 (3.1)	0	1 (1.5)	1 (1.0)
COVID-19	0	0	1 (3.0)	1 (1.5)	1 (1.0)
Candida infection	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Cellulitis	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Gastrointestinal viral infection	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Mastoiditis	0	0	1 (3.0)	1 (1.5)	1 (1.0)
Otitis externa	0	0	1 (3.0)	1 (1.5)	1 (1.0)
Suspected COVID-19	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Upper respiratory tract infection	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Viral infection	0	1 (3.1)	0	1 (1.5)	1 (1.0)

Severity

In most cases the severity of the AEs was mild. Severe events were infrequent (in 1 to 2 individuals per group) with no dose-dependency.

AEs of special interest (AESI)

Hypoglycaemia

There were no severe hypoglycaemic events (Level 3) in the study. The Level 2 events are analysed in more detail in the following tables, separated by events with blood glucose (BG) <70 mg/dL vs. <54 mg/dL and separated for concomitant use of basal insulin. As expected, episodes with BC<70 were more frequent that ones with BG<54. TZP clearly caused an increase in frequency of hypoglycaemia event, e.g. from 0.15 events per year (plc) to 0.81 (TZP all) for the events with BG<54. However, dose-dependency was not observed. Most events were observed in the 5 mg TZP group.

Regarding concomitant insulin use, it can be derived from the respective tables that in the insulin population the hypoglycaemia rates (i.e. events per year) were markedly higher in all groups (including plc) than in the total study population, e.g. 1.98 events (BG<54) per year with insulin vs. 0.81 events per year overall in the combined TZP group. However, when regarding the absolute number of episodes, it becomes clear that there were also hypoglycaemia events in subjects not treated with insulin. E.g., 29 events of BG<54 were observed in total in the TZP all group and 22 events with insulin, meaning that 7 events occurred without insulin.

Table 26: Incidence and Rate of Hypoglycaemia with Blood Glucose **<54 mg/dL** or Severe Hypoglycaemia Exclude Hypoglycaemic Events Occurring after Initiation of a New Antihyperglycemic Therapy Modified Intent-to-Treat - Safety Analysis Set 1 I8F-MC-GPGV - Double-Blind Period

0<=wk<=30	N	n (%)	Number of Episodes	Group Mean (SE)	Total Exposure (Years)	Aggregated Rate per Year	Group Mean (SE)
Placebo	34	2 (5.9)	3	0.07 (0.05)	20	0.15	0.09 (0.06)
TZP 5mg	32	5 (15.6)	20	0.16 (0.10)	18	1.11	1.37 (0.82)
TZP 10mg	33	5 (15.2)	9	0.17 (0.10)	18	0.51	0.62 (0.31)
TZP_ALL	65	10 (15.4)	29	0.16 (0.07)	36	0.81	0.99 (0.45)

Table 27: Incidence and Rate of Hypoglycaemia with Blood Glucose **<70 mg/dL** Exclude Hypoglycaemic Events Occurring after Initiation of a New Antihyperglycemic Therapy. Modified Intent-to-Treat - Safety Analysis Set I8F-MC-GPGV - Double-Blind Period. Variable Analysed: All Documented Hypoglycaemia Incidence with Glucose < 70 mg/dL (Adjusted for Year)

0<=wk<=30	N	n (%)	Number of Episodes	Group Mean (SE)	Total Exposure (Years)	Aggregated Rate per Year	Group Mean (SE)
Placebo	34	6 (17.6)	10	0.17 (0.10)	20	0.51	0.40 (0.16)
TZP 5mg	32	12 (37.5)	43	0.37 (0.23)	18	2.39	1.96 (0.59)
TZP 10mg	33	10 (30.3)	33	0.32 (0.20)	18	1.86	2.58 (1.01)
TZP_ALL	65	22 (33.8)	76	0.34 (0.15)	36	2.13	2.27 (0.59)

Table 28: Incidence and Rate of Hypoglycemia with Blood Glucose **<54 mg/dL** or Severe Hypoglycemia Exclude Hypoglycemic Events Occurring after Initiation of a New Antihyperglycemic Therapy Modified Intent-to-Treat - Safety Analysis Set 1 - Participants with **Baseline Basal Insulin Use** I8F-MC-GPGV - Double-Blind Period

0<=wk<=30	N	n (%)	Number of Episodes	Group Mean (SE)	Total Exposure (Years)	Aggregated Rate per Year	Group Mean (SE)
Placebo	10	1 (10.0)	2	0.14 (0.15)	6	0.35	0.14 (0.12)

TZP 5mg	10	3 (30.0)	16	0.31 (0.31)	6	2.79	4.20 (2.89)
TZP 10mg	11	3 (27.3)	6	0.30 (0.29)	5	1.12	1.58 (1.01)
TZP_ALL	21	6 (28.6)	22	0.30 (0.21)	11	1.98	2.85 (1.61)

Table 29: Incidence and Rate of Hypoglycaemia with Blood Glucose **<70 mg/dL** Exclude Hypoglycaemic Events Occurring after Initiation of a New Antihyperglycemic Therapy Modified Intent-to-Treat - Safety Analysis Set 1 - Participants with **Baseline Basal Insulin Use** I8F-MC-GPGV - Double-Blind Period

0<=wk<=30	N	n (%)	Number of Episodes	Group Mean (SE)	Total Exposure (Years)	Aggregated Rate per Year	Group Mean (SE)
Placebo	10	2 (20.0)	5	0.22 (0.22)	6	0.87	0.55 (0.33)
TZP 5mg	10	5 (50.0)	26	0.48 (0.61)	6	4.54	2.99 (1.28)
TZP 10mg	11	3 (27.3)	17	0.31 (0.32)	5	3.17	6.33 (4.21)
TZP_ALL	21	8 (38.1)	43	0.39 (0.30)	11	3.88	4.67 (1.96)

Pancreas events

No pancreatitis events were sent for adjudication.

As expected for a GLP-1RA, serum lipase and pancreatic amylase increased with treatment as shown in the following figures (expressed as percent change from baseline; taken from Figure GPGV.5.17 of Study Report).

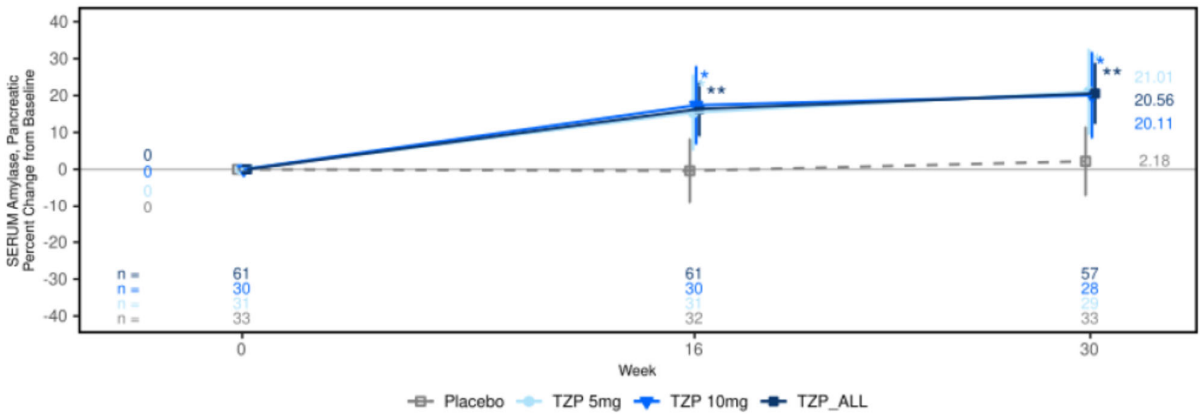


Figure 34: Percent Change from Baseline of SERUM Amylase, Pancreatic (U/L)

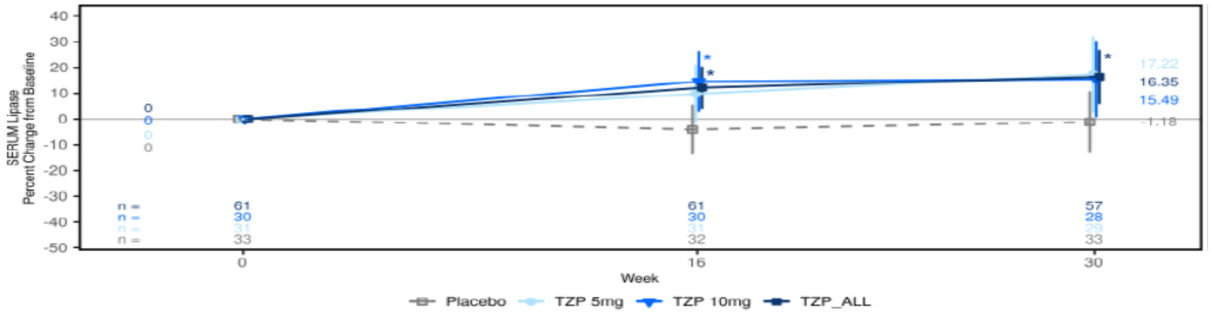


Figure 35: Percent Change from Baseline of SERUM Lipase (U/L)

Thyroid events

No participants reported TEAEs of thyroid malignancy.

As expected for TZP, serum calcitonin increased with treatment as shown in the figure below (expressed as percent change from baseline).

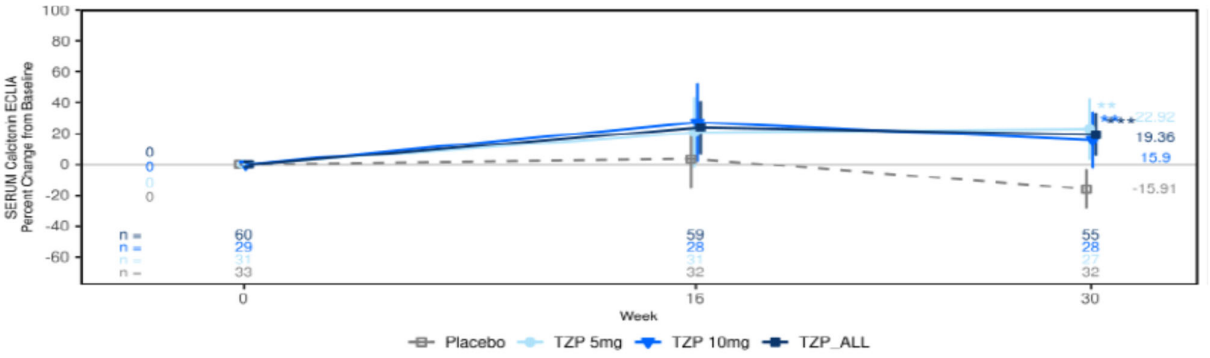


Figure 36: Percent Change from Baseline of SERUM Calcitonin ECLIA (ng/L)

Gallbladder events

According to Listing GPGV.8.13 of the Study Report, one event of cholelithiasis with cholecystitis was reported in the open-label extension period (the subject received 5 mg TZP in the double-blind period).

Hepatic events

Seum chemistry parameters for liver disease as measured in Study GPGV are graphically summarised in the figure below. In all cases, bilirubin was in the normal range or only slightly above ULN (upper limit of normal). For the transaminases (ALT, AST), many subjects had values above ULN, mainly up to 3xULN. This was true for the TZP as well as for the plc group so that relationship of an increased transaminase value to TZP is unlikely. More likely, it was due to the underlying disease (diabetes, obesity).

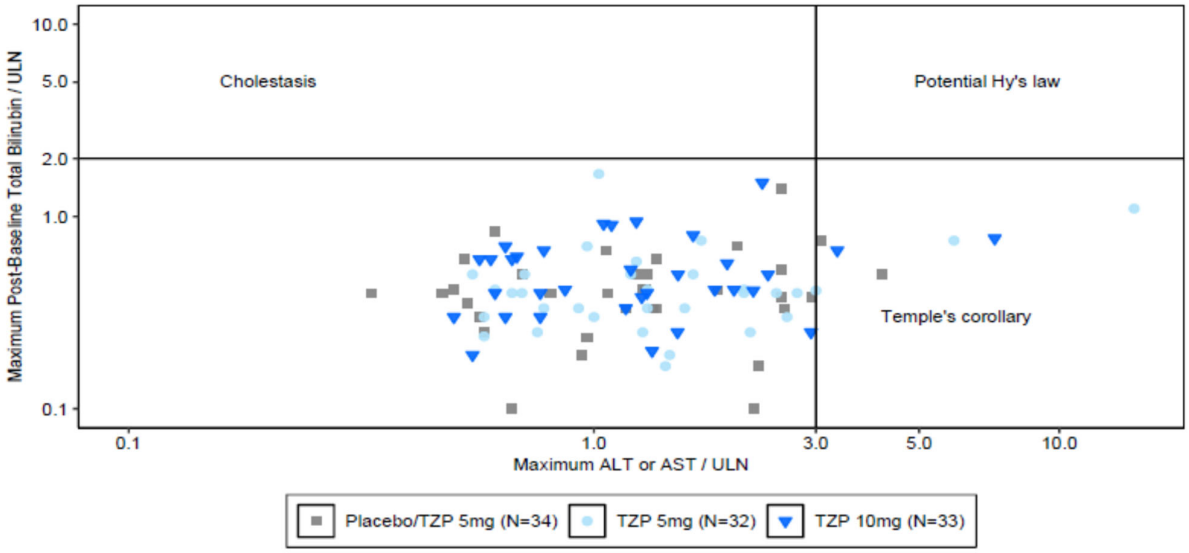


Figure 37: Hepatocellular drug-induced liver injury screening plot: maximum total bilirubin vs maximum ALT or maximum AST All postbaseline blood samples mITT - Safety Analysis Set 2 I8F-MC-GPGV - double-blind, open-label, and safety follow-up periods.

GI events

As already mentioned in the section on general AEs, most adverse events were related to the GI tract. The table below provides a complete listing of the different GI events observed. Most frequent AEs were diarrhoea, nausea, vomiting and abdominal pain. This is in line with findings in adults.

Table 30: Summary of TEAEs in the GI Disorders System Organ Class, Occurring in ≥1% of Participants in Any Treatment Group, by Preferred Term; mITT Population - Safety Analysis Set 1; I8F-MC-GPGV - Double-Blind Period; n (%)

System Organ Class Preferred Term	Placebo (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)	TZP_ALL (N=65)
Participants with ≥1 TEAE, Gastrointestinal disorders	4 (11.8)	15 (46.9)	15 (45.5)	30 (46.2)
Diarrhoea	2 (5.9)	8 (25.0)	8 (24.2)	16 (24.6)
Nausea	3 (8.8)	7 (21.9)	6 (18.2)	13 (20.0)
Vomiting	1 (2.9)	5 (15.6)	4 (12.1)	9 (13.8)
Abdominal pain upper	3 (8.8)	2 (6.2)	4 (12.1)	6 (9.2)
Abdominal pain	1 (2.9)	5 (15.6)	1 (3.0)	6 (9.2)
Dyspepsia	0	2 (6.2)	4 (12.1)	6 (9.2)
Abdominal discomfort	0	1 (3.1)	1 (3.0)	2 (3.1)
Constipation	0	0	1 (3.0)	1 (1.5)

Eructation	0	1 (3.1)	0	1 (1.5)
Flatulence	0	1 (3.1)	0	1 (1.5)
Gastritis	0	1 (3.1)	0	1 (1.5)
Gastrooesophageal reflux disease	0	0	1 (3.0)	1 (1.5)
Malabsorption	0	0	1 (3.0)	1 (1.5)
Oesophagitis	0	1 (3.1)	0	1 (1.5)
Rectal haemorrhage	0	1 (3.1)	0	1 (1.5)

Most GI events were mild; no severe events were observed.

The prevalence of GI symptoms decreased over time, see table and figure below. This is known from GLP-1RA use in adults. Incidence was highest in the first 4 weeks of treatment. After around 14 weeks, virtually no new occurrence of GI events (nausea, vomiting, diarrhoea) was observed.

Table 31: Prevalence of Treatment-Emergent Nausea, Vomiting, and Diarrhoea by Treatment over Time; mITT Population - Safety Analysis Set 1; I8F-MC-GPGV - Double-Blind Period

Nausea/Vomiting/Diarrhoea Time Point	Placebo (N=34)	TZP 5 mg (N=32)	TZP 10 mg (N=33)	TZP_ALL (N=65)
0 < Weeks ≤ 4	2 (5.88)	9 (28.12)	7 (21.21)	16 (24.62)
4 < Weeks ≤ 8	2 (5.88)	5 (15.62)	6 (18.18)	11 (16.92)
8 < Weeks ≤ 12	1 (2.94)	4 (12.50)	5 (15.15)	9 (13.85)
12 < Weeks ≤ 16	0	2 (6.25)	4 (12.50)	6 (9.38)
16 < Weeks ≤ 20	1 (2.94)	0	3 (9.68)	3 (4.84)
20 < Weeks ≤ 24	1 (2.94)	3 (9.68)	3 (10.00)	6 (9.84)
24 < Weeks ≤ 30	2 (5.88)	2 (6.45)	0	2 (3.28)
After the first dose	4 (11.76)	12 (37.50)	13 (39.39)	25 (38.46)

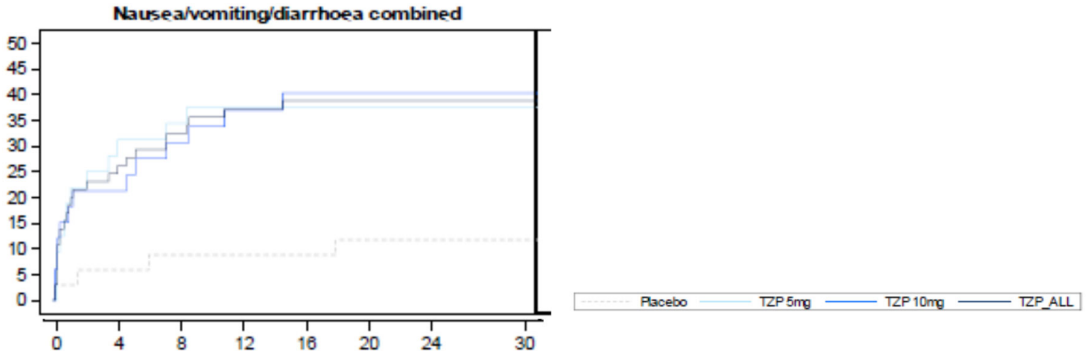


Figure 38: Plot of time to first onset (weeks) of nausea, vomiting, and diarrhoea; mITT - Safety Analysis Set 1; I8F-MC-GPGV - double-blind period.

Renal function

eGFR

After treatment start with TZP, eGFR initially declined and then remined constant from Week 8 to Week 30, Thereafter, it slightly increased again for unknown reasons. In the plc group, eGFR remained nearly constant up to Week 30. At Week 30, plc subjects were switched to 5 mg TZP. This again resulted in a decline of eGFR, see figure below.

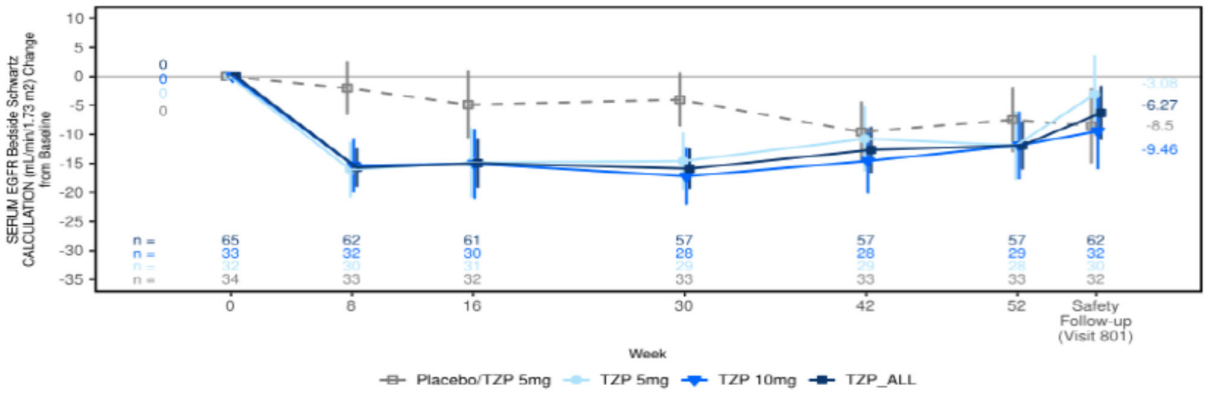


Figure 39: Change from baseline in eGFR using standard units; MMRM by treatment and visit from baseline to safety follow-up; mITT - Safety Analysis Set 2; I8F-MC-GPGV - double-blind, open-label, and follow-up periods.

The applicant presented an evaluation separating eGFR data by the absence of presence of glomerular hyperfiltration at baseline. Hyperfiltration was defined as eGFR >128.6 mL/min/1.73 m^2.

The mechanisms leading to hyperfiltration in diabetic patients are not fully clear, but it is assumed that hyperglycaemia plays a role. Hyperglycaemia leads to increased glomerular filtration of glucose. Glucose becomes reabsorbed in the renal tubules (as far as possible). This is accompanied by increased reabsorption of sodium since reabsorption of glucose is achieved by a sodium-glucose co-transporter. Thereby, the amount of sodium reaching the macula densa is reduced. This, in turn, leads to an increase in intra-glomerular pressure and thereby increased GFR.

Hence, a reduction in blood glucose level, e.g. by TZP, can reduce GFR in subjects with hyperfiltration. The applicant's evaluation indeed revealed that eGFR decrease with TZP was markedly more pronounced in subjects with baseline hyperfiltration than without. With hyperfiltration, plc-corrected eGFR decrease was **28.0** mL/min/1.73m², whereas it was **7.7** mL/min/1.73m² without hyperfiltration (TZP groups combined). For further details, see the two following tables.

Table 32: Change from Baseline in eGFR with Zappitelli Equation; MMRM by Treatment and Visit from Baseline to Week 30; mITT - Safety Analysis Set 1 - Participants **with Glomerular Hyperfiltration** at Baseline; I8F-MC-GPGV - Double-Blind Period

Parameters	Placebo	TZP 5mg	TZP 10mg	TZP_ALL
Baseline: n	5	5	5	10
Mean	141.6	140.7	144.2	142.4
Week 30 (Visit 13): n	5	5	4	9
Change from Baseline				
Least-squares mean	7.80	-24.4	-16.0	-20.2
Difference from Placebo (95% CI)	NA	**-32.2** (-56.5, -7.96)	**-23.8** (-53.5,5.92)	**-28.0** (-50.5, -5.50)

Table 33. Change from Baseline in eGFR with Zappitelli Equation; MMRM by Treatment and Visit from Baseline to Week 30; mITT - Safety Analysis Set 1 - Participants **without Glomerular Hyperfiltration** at Baseline; I8F-MC-GPGV - Double-Blind Period

Parameters	Placebo	TZP 5mg	TZP 10mg	TZP_ALL
Baseline: n	26	22	25	47
Mean	104.0	104.7	104.3	104.5
Week 30 (Visit 13): n	26	20	24	44
Change from Baseline				
Least-squares mean	-0.69	-6.57	-10.25	-8.41

Difference from Placebo (95% CI)	NA	**-5.88** (-13.56,1.79)	**-9.56** (-16.9,-2.20)	**-7.72** (-14.15,-1.29)

Urine albumin excretion

Albumin excretion in urine was measured as UACR (urine albumin creatinine ratio). Mean UACR was in the normal range at baseline in all groups; it was between 12 mg/g and 19 mg/g. From baseline to Week 30, UACR decreased in each group, by 20% to 40%, most pronounced in the plc group. The relevance of this finding is unclear.

Immunogenicity

Hypersensitivity reactions

There were no potential immediate hypersensitivity reactions, occurring within 24 hours of the end of the study drug administration.

A total of 2 (2.0%) participants experienced at least 1 AE of potential, nonimmediate hypersensitivity reactions more than 24 hours following study drug administration. These participants were in the tirzepatide 5 mg group. The PTs reported were urticaria of moderate severity and bronchospasm of mild severity. Neither were SAEs.

Injection site reactions

There were more participants in the tirzepatide groups who experienced injection site reaction TEAEs (n=3 [**4.6%**]) compared with the placebo group (n=1 [**2.9%**]):

- injection site pain: placebo group: n=1 (2.9%) and tirzepatide 5 mg: n=1 (3.1%)
- injection site reaction: tirzepatide 10 mg: n=2 (6.1%) (Table GPGV.8.112).

All events were mild in severity except for 1 participant in the 10 mg tirzepatide group, with 1 TEAE of injection site reaction, which was moderate in severity. No events were serious or severe.

Anti-drug antibodies (ADA)

ADA were determined using an assay that was developed for previous studies in adults. The evaluation focused on treatment-emergent (TE-) ADA, which were defined as in table 34 footnote b. The results are summarised in the table below. The most salient finding is that 49.2% of participants treated with TZP developed TE-ADA. This is in line with findings from previous studies in adults and is probably related to the fact that TZP contains amino acid sequences from the non-human peptide exenatide.

Table 34: Summary of TE Tirzepatide ADA. mITT - Immunogenicity Analysis Set 1. I8F-MC-GPGV - Double-Blind Period

	Placebo (N=34)	TZP 5mg (N=32)	TZP 10mg (N=33)	TZP_ALL (N=65)
Category	n (%)	n (%)	n (%)	n (%)
Subjects Evaluable for TE ADA *[a]	29 [85.3]	29 [90.6]	32 [97.0]	61 [93.8]
Evaluable Subjects with ADA Present at Baseline	1 (3.4)	0 (0.0)	4 (12.5)	4 (6.6)
Subjects Postbaseline TE ADA+ *[b]	0 (0.0)	15 (51.7)	15 (46.9)	30 (49.2)
Treatment-Induced TE ADA+	0 (0.0)	15 (51.7)	14 (43.8)	29 (47.5)
Treatment-Boosted TE ADA+	0 (0.0)	0 (0.0)	1 (3.1)	1 (1.6)

Subjects Postbaseline TE ADA Inconclusive *b	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects Postbaseline TE ADA- *b	29 (100.0)	14 (48.3)	17 (53.1)	31 (50.8)

*a A subject is TE ADA Evaluable if there is at least one non-missing test result for ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of TE ADA Evaluable subjects in each treatment group.

*b A TE ADA Evaluable subject is considered to be TE ADA+ if the subject has at least one postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA NOT Present, then the subjects is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= 2x MRD (Minimum Required Dilution) (treatment-induced). A TE ADA evaluable subjects is TE ADA Inconclusive if >=20% of the subject's postbaseline samples, drawn pre-dose, are ADA Inconclusive and the subject is not otherwise TE ADA+. A TE ADA Evaluable subject is TE ADA- if not TE ADA+ and not TE ADA Inconclusive.

The ADA did not affect PK of TZP. A graphical comparison of tirzepatide concentrations did not show any overt pattern associated with participants who did or did not develop detectable ADA (figure below).

Table 35: Summary of Cross-Reactive and Neutralising Antibodies from Tirzepatide-Treated Participants with TE ADA Modified Intent-to-Treat - Immunogenicity Analysis Set 1 I8F-MC-GPGV - Double-Blind Period

	TZP 5mg (N=32)	TZP 10mg (N=33)	TZP_ALL (N=65)
Category	n (%)	n (%)	n (%)
Subjects Postbaseline TE ADA+ *b	15 (51.7)	15 (46.9)	30 (49.2)
Neutralising TZP for GIPR	0 (0.0)	0 (0.0)	0 (0.0)
Neutralising TZP for GLP-1R	0 (0.0)	0 (0.0)	0 (0.0)
GIP Cross-Reactive	8 (27.6)	8 (25.0)	16 (26.2)
In Silico Neutralising to Native GIP	0 (0.0)	0 (0.0)	0 (0.0)
GLP-1 Cross-Reactive	2 (6.9)	3 (9.4)	5 (8.2)
In Silico Neutralising to Native GLP-1	0 (0.0)	0 (0.0)	0 (0.0)

*a - A subject 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 subjects in each treatment group.
*b - A TE ADA Evaluable subject is considered to be TE ADA+ if the subject has at least one postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA NOT Present, then the subject is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= 2x MRD (treatment-induced).

Physical and sexual development

In order to assess growth and development, the applicant measured height, height SDS, and weight SDS. For a reliable analysis, the 30-week treatment period was rather short. Height increased by around 0.5 cm in this period with no relevant differences between the groups. Weight SDS dose-dependently decreased from baseline with TZP compared to plc. This is an expected effect of GLP-1RAs.

Sexual development was addressed by Tanner staging.

For females, a score was used for pubic hair (PH1 to PH5 and for breast development (B1 to B5).

For males, also a pubic hair score was used (PH1 to PH5) as well as a genital development score (G1 to G5).

The applicant presented shift tables, from baseline to last post-baseline. Most participants had the highest score already at baseline so that a shift was not possible. The remainder mainly had Stage 4 in all parameters, and a part of them shifted to Stage 5. The number of subjects in each relevant category (remined at Stage 4 vs. shifted from 4 to 5) was too low for meaningful conclusions.

Serious adverse event/deaths/other significant events

No deaths occurred.

The SAEs are summarised in the following table. One individual in each group suffered a SAE. Due to the low number of events, meaningful conclusions are not possible.

Table 36: Serious Adverse Events Preferred Term by Decreasing Frequency within System Organ Class mITT - Safety Analysis Set 1 I8F-MC-GPGV - Double-Blind Period

	Placebo (N=34	TZP 5mg (N=32)	TZP 10mg (N=33)	TZP_ALL (N=65)	Total (N=99)
System Organ Class Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with >=1 SAE	1 (2.9)	1 (3.1)	1 (3.0)	2 (3.1)	3 (3.0)
Infections and infestations	0	1 (3.1)	1 (3.0)	2 (3.1)	2 (2.0)
Appendicitis	0	1 (3.1)	0	1 (1.5)	1 (1.0)
Mastoiditis	0	0	1 (3.0)	1 (1.5)	1 (1.0)
Psychiatric disorders	1 (2.9)	0	0	0	1 (1.0)

Borderline personality	1 (2.9)	0	0	0	1 (1.0)
disorder Suicidal ideation	1 (2.9)	0	0	0	1 (1.0)
Suicide attempt	1 (2.9)	0	0	0	1 (1.0)

Laboratory findings

Serum chemistry, haematology

Clinical chemistry evaluations targeting liver, kidney, pancreas and C-cell function are discussed in the section on AEs of special interest. Otherwise, no remarkable findings on clinical chemistry or haematology were made.

Vital signs

GLP-1RAs are known to increase heart rate (HR) This can be accompanied by a decrease in blood pressure. In the present paediatric study, a dose-dependent increase from baseline in mean HR was observed, which lasted throughout the treatment period. The increase was up to around 5 bpm. Simultaneously, mean systolic and diastolic blood pressure (SBP, DBP) decreased by up to around 5 mmHg. In the plc group, no major changes from baseline were observed. All values tended towards baseline again after cessation of treatment. For details, see figure below.

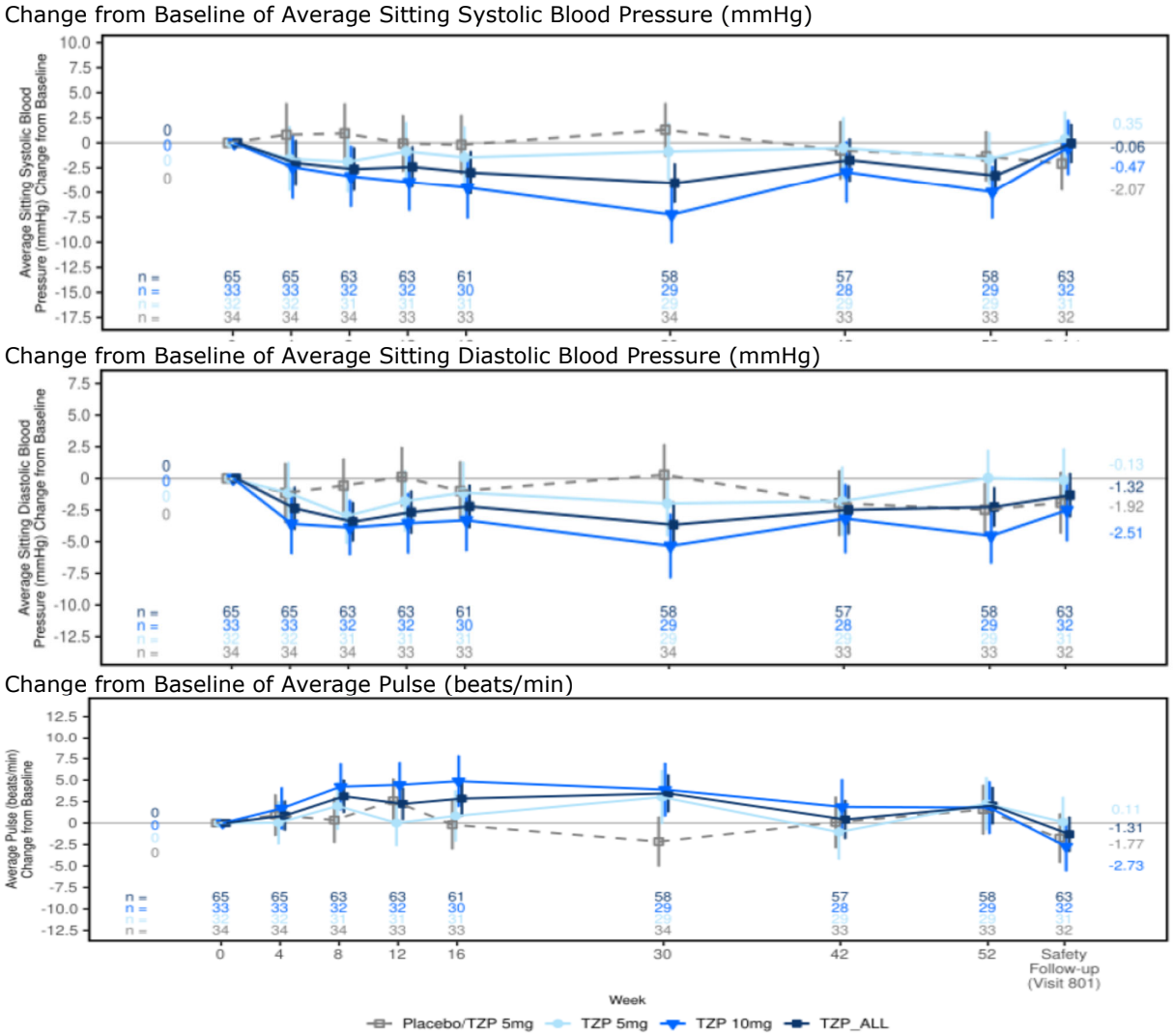


Figure 41: Change from baseline in vital signs: SBP, DBP, and pulse rate MMRM by treatment and visit from baseline to safety follow-up; mITT - Safety Analysis Set 2; I8F-MC-GPGV - double-blind, open-label, and follow-up periods. Results are presented in LS Mean +/- 1.96 SE.

Safety in special populations

This study deals with a special population, children and adolescents.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

A total of 2 (2.0%) participants discontinued the study due to an AE. These 2 participants were in the tirzepatide 5 mg group. The 2 AEs that led to study and treatment discontinuation were nausea and suicidal ideation.

2.5.1. Discussion on clinical safety

The applicant has performed an extensive safety analysis of the paediatric population in Study GPGV. All adverse effects of TZP known from adult studies were addressed as AEs of special interest. No new safety issues were detected in children and adolescents. However, rare events may have escaped attention due to the limited number of subjects studied and the rather short duration of the study.

Most AEs were mild or moderate in intensity, and serious AEs were infrequent. The most frequent kind of AE were gastrointestinal (GI) symptoms such as diarrhoea, nausea, vomiting and abdominal pain. They were mainly prevalent shortly after treatment start and became less frequent during the further course of the study. This is in line with the observation made in adult studies.

As expected from adult studies again, pancreatic enzymes in blood slightly increased with TZP treatment as well as the serum calcitonin level. It is assumed that the increase in pancreatic enzymes is functional and is not related to pancreatitis. Cases of the latter were not observed in Study GPGV.

TZP may also increase gall bladder disease. One event of cholelithiasis with cholecystitis was reported in Study GPGV. Furthermore, TZP is known to be more immunogenic than certain other GLP-1RAs, e.g. semaglutide. This usually manifests itself in a rather high proportion of patients, around 50%, who develop antibodies against TZP. However, these anti-drug antibodies (ADA) usually do not cause adverse effects, potentially besides an increased risk of injection site reactions. Comparable to adults, 49.2% of the participants of the paediatric study GPGV reported treatment-emergent (TE-)ADA. AEs related to ADA were not reported; also, PK and efficacy were not affected. Injection site reactions were numerically more frequent with TZP than with plc (4.6% TZP vs. 2.9% plc); however, the number of events was very low so that reliable conclusions on a relationship between tirzepatide and an increased risk of injection site reactions are not possible.

Another topic of special interest were hypoglycaemia events. Serious events (Level 3) did not occur in Study GPGV. Level 2 events with blood glucose <54 or BG<70 were more frequent with TZP than with placebo. At least for the events with BG<54, most of them occurred in subjects using basal insulin in addition to the study drug (TZP or plc). In the TZP group (doses combined), 29 events of BG<54 occurred. Twenty-two of them were in subjects using insulin. Thus, the tendency of TZP alone to cause more pronounced hypoglycaemias was rather low.

Regarding renal function, it became obvious in Study GPGV that the mean estimated glomerular filtration rate (eGFR) declined immediately after onset of TZP treatment but stabilised itself thereafter. The applicant assumed that this could be due to the correction of a hyperfiltration that could be present at baseline; hyperfiltration was defined as eGFR >128.6 mL/min/1.73 m^2. Therefore, the applicant conducted a respective analysis, regarding eGFR decline separately for subject with and without hyperfiltration at baseline. It turned out that eGFR decrease was markedly more pronounced in subjects with than without baseline hyperfiltration. Compared to baseline and plc, eGFR declined by 28.0 mL/min/1.73m² with vs. 7.7 mL/min/1.73m² without hyperfiltration (TZP, doses combined).

Hyperfiltration is thought to be related to hyperglycaemia, when larger amounts of glucose are filtrated by the renal glomeruli. Tubular reabsorption of these higher amounts is accompanied by reabsorption of higher amounts of sodium because the responsible carrier is a glucose-sodium co-transporter. In turn, less sodium reaches the macula densa, which leads to increased intra-glomerular pressure and hence higher GFR. Since high intra-glomerular pressure is unfavourable and is thought to contribute to diabetic kidney disease, the decrease in eGFR caused by TZP is not considered adverse. After cessation of treatment, eGFR tended towards baseline again.

The applicant also addressed potential effects of TZP on physical and sexual development. No relevant differences between the plc and TZP groups were observed, apart from body weight as expected. This is reassuring; however subtle effects cannot be excluded since the study duration was too short for firm conclusions on growth velocity. Regarding sexual development, quantified by Tanner staging, the robustness of the findings is limited by the fact that most participants already had reached the highest stage at baseline so that further changes could not be observed.

It was discussed in previous procedures whether TZP and other GLP-1RAs could increase psychiatric disorders like depression. In the present study, there was a numerical imbalance in respect to AEs of the SOC "Psychiatric disorders", driven by the term "Anxiety". However, the absolute numbers were very low so that reliable conclusions are not possible. Reassuringly, the number of subjects reporting "Suicidal ideation" was balanced across the groups, and suicide attempt (one event) was only reported in the plc group.

2.5.2. Conclusions on clinical safety

The safety profile of TZP in the paediatric population of Study GPGV was well in line with TZP's safety profile known from previous adult studies. No new safety issues appeared.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 7.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.1 is acceptable.

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medullary thyroid cancer Pancreatic malignancy Diabetic retinopathy complications
Missing information	Use in pregnancy and lactation

In this procedure, no amendment to the safety concerns is proposed. In the conclusion on the clinical safety, it is stated that the safety profile of TZP in the paediatric population of Study GPGV was well in

line with TZP's safety profile known from previous adult studies. No new safety issues appeared. Therefore, the current list of safety concerns proposed by the MAH is acceptable.

Pharmacovigilance plan

The MAH did not propose changes to the pharmacovigilance plan.

Risk minimisation measures

The MAH did not propose changes to the risk minimisation measures.

2.7. Update of the Product information

As a consequence of this extension of indication, section 4.1 is being updated to include "adolescents and children aged 10 years and above" in the Type 2 diabetes mellitus indication:

Type 2 diabetes mellitus
*Mounjaro is indicated for the treatment of adults**, adolescents and children aged 10 years and above** with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise*

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

For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.

In this context, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are also being updated. The PL is being adjusted accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

User testing was already 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 adult T2DM indication. The Mounjaro package leaflet met the pass criteria for readability testing. The extension of the T2DM indication to children and adolescents aged 10 years and above targets the same patient group and their parents or caregivers as the one that made up the representative test population, which also included 30% carers, for the performed user testing. The proposed text modifications to the package leaflet resulting from the addition of this new indication are considered minor and do not include text that is significantly different from that already user tested. The structure and design of the revised Mounjaro Package Leaflet has not changed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Current approved indication in adults (for Type 2 diabetes mellitus):

Type 2 diabetes mellitus
Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

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

For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.

Proposed amendment of the indication, inclusion of paediatric patients (**in bold**)
Type 2 diabetes mellitus
*Mounjaro is indicated for the treatment of adults**, adolescents and children aged 10 years and above** with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise*

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

For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.

Proposed dosage form, route of administration, and dosing regimen
The applicant does not propose any changes to the dosage form, route of administration, or dosing regimen via this application.

3.1.2. Available therapies and unmet medical need

The recommended treatment for paediatric type 2 diabetes is similar to that in adults, with emphasis on a step-wise approach starting with lifestyle modifications, particularly diet and exercise, followed by the use of a single medical therapy and, later, by two therapies in combination. The aim is that the patient achieves and maintains low levels of glucose in the blood in order to prevent long-term complications.

For a long time, the only two approved treatment options for paediatric patients with type 2 diabetes in most countries were metformin and insulin. Recently, additional treatment options have become available in the EU for children and adolescents aged 10 to less than 18 years with type 2 diabetes, e.g. the GLP-1 receptor agonists Liraglutide (Victoza), Exenatide extended-release once-weekly injection (Bydureon), Dulaglutide (Trulicity) and the SGLT-2 inhibitors Dapagliflozin (Forxiga), Empagliflozin (Jardiance) and Canagliflozin (Invokana).

3.1.3. Main clinical studies

The applicant is seeking to extend the indication for Mounjaro (tirzepatide), which is currently approved for glycaemic control in adults with T2DM, to include also paediatric patients ≥ 10 to <18 years of age with T2DM based on the final results from clinical trial I8F-MC-GPGV (SURPASS-PEDS).

Study I8F-MC-GPGV (SURPASS-PEDS) was a randomized, double-blind (22 weeks), placebo-controlled, phase 3 study with an open-label extension (30 weeks) assessing the efficacy, safety, and pharmacokinetics/pharmacodynamics of tirzepatide in paediatric and adolescent participants with Type 2 Diabetes Mellitus (T2DM) inadequately controlled with metformin, or basal insulin, or both.

3.2. Favourable effects

The primary endpoint results and the secondary endpoint analyses from study GPGV show that tirzepatide is effective at reducing HbA1c in paediatric T2DM patients between 10 and 18 years of age. For the treatment-regimen estimand, the least squares (LS) mean difference of the HbA1c change from baseline for pooled tirzepatide versus placebo at week 30 was -1.80 (95% CI: -2.35, -1.25; p<0.001), which indicated clinically relevant anti-hyperglycaemic efficacy and significant superiority of tirzepatide over placebo. The treatment effect showed a trend indicating some dose dependency [Difference from placebo (95% CI): tirzepatide 5 mg: 1.67 (-2.31, -1.02); tirzepatide 10 mg: -1.93 (-2.57, -1.29)]. The robustness of the results was confirmed by a 2-way tipping point analysis. The blood glucose-related key secondary endpoints (Individual Dose Mean Change in HbA1c at Week 30, Proportion of Participants with HbA1c ≤6.5% at Week 30 and mean change from baseline in FSG at week 30) all confirm the primary endpoint result and show that tirzepatide at any dose level is significantly superior in comparison to placebo. Like the primary endpoint, these key secondary endpoints also suggest dose dependency of the tirzepatide effect. This effect was associated with a pronounced reduction in body weight, which is considered a favourable effect in overweight/obese paediatric T2DM patients.

The treatment-regimen estimand was preferred in this assessment, since it reflects the actual therapeutic effect to be expected in later clinical reality. However, the Applicant proposed to use the efficacy estimand in the SmPC for consistency with the rest of section 5.1, where the tables show efficacy estimand data. This was agreed with.

3.3. Uncertainties and limitations about favourable effects

SGLT-2 inhibitors were not permitted as background therapy in study GPGV.

Only 4% of study participants were from Europe (Italy, UK). However, the results are considered transferable to a European population due to the large proportion of participants from the US (~30%).

Due to the small study size, there were some imbalances in demographic properties across the study arms. However, it is difficult to conclude, to which extent such imbalances eventually influence the efficacy results.

Only children with a BMI above the 85th percentile were included, i.e. the vast majority of study participants were overweight or obese at study initiation, which was reflected in SmPC sections 4.2 and 5.1.

Only a very limited number of participants have entered BG values into their diary correctly. Thus, no meaningful analysis of self-measured blood glucose profiles (6-SMBG) was possible and no information on the ability of tirzepatide to reduce postprandial glucose peaks in children with T2DM is available.

The patient-reported outcomes included as additional secondary and as exploratory endpoints (PedsQL (3.2) Diabetic Module, PedsQL Generic Core Scales as well as EQ-5D-Y-3L and EQ VAS Scores) do not show a statistically significant improvement in quality of life in the tirzepatide-treated participants in comparison to the placebo group.

3.4. Unfavourable effects

The most frequent AEs were related to the gastrointestinal (GI) tract and included diarrhoea, nausea, vomiting and abdominal pain. They were mainly prevalent shortly after treatment start and became less frequent during the further course of the study. This is in line with the observation made in adult studies.

As also expected from adult studies, pancreatic enzymes in blood slightly increased with TZP treatment as well as the serum calcitonin level. It is assumed that the increase in pancreatic enzymes is functional and is not related to pancreatitis. Cases of the latter were not observed in Study GPGV. TZP may also increase gall bladder disease. One event of cholelithiasis with cholecystitis was reported in Study GPGV.

Furthermore, TZP is known to be more immunogenic than certain other GLP-1RAs. This usually manifests itself in a rather high proportion of patients, around 50%, who develop antibodies against TZP. However, these anti-drug antibodies (ADA) usually do not cause adverse effects, potentially besides an increased risk of injection site reactions. Comparable to adults, 49.2% of the participants of the paediatric study GPGV reported treatment-emergent (TE-) ADA. AEs related to ADA were not reported; also, PK and efficacy were not affected. Injection site reactions were numerically more frequent with TZP than with placebo (4.6% TZP vs. 2.9% plc); however, the number of events was very low so that reliable conclusions on a relationship between tirzepatide and an increased risk of injection site reactions are not possible.

Overall, most events were mild or moderate in severity. Serious AEs were infrequent and most likely not related to the study drug.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of TZP is well established in adults. According to the data from Study GPGV, the safety profile in paediatric patients appears to be well in line with the findings in adults. However, the number of participants in Study GPGV as well as its duration were limited, therefore, the available data may be insufficient to fully identify very rare adverse events specific to children and adolescents. Furthermore, subtle differences in the AE profile, e.g. the frequency of certain AEs, between children, adolescents and adults cannot be detected or confirmed with this study size.

3.6. Effects Table

Table 37: Effects Table for Mounjaro in treatment of T2D in paediatric and adolescent patients from 10 years of age.

Effect	Short descrip-tion	Unit	TZP 5 mg N=32	TZP 10 mg N=33	Plc or Plc/TZP 5 mg* N=34	Uncertainties Strength of evidence	Refere nce
Favourable Effects							
at 30 weeks (end of double-blind period) – Treatment regimen estimand							
Δ HbA1c from baseline (**pooled**)	**Primary endpoint**	%	**TZP_ALL (pooled):** -2.03 Δ Plc (95% CI): -1.80 (-2.35, -1.25)		-0.23	versus Placebo: p <0.001	CSR Study GPGV
Δ HbA1c from baseline, (5 and 10 mg TZP)	Key sec-ondary endpoint	%	-1.90 Δ Plc (95% CI): -1.67 (-2.31, -1.02)	-2.16 Δ Plc (95% CI): -1.93 (-2.57, -1.29)	-0.23	versus Placebo: 5 mg: p<0.001 10 mg: p<0.001	
Incidence of HbA1c ≤6.5%	Key sec-ondary endpoint	%	66.4	80.6	28.5	versus Placebo: 5 mg: p<0.001 10 mg: p<0.001	
Change in BMI SDS (age- and sex-matched) from baseline	Key sec-ondary endpoint	N/A	-0.45 Δ Plc (95% CI): -0.36 (-0.55, -0.16)	-0.76 Δ Plc (95% CI): -0.66 (-0.86, -0.47)	-0.092	versus Placebo: 5 mg: p<0.001 10 mg: p<0.001	
Change in FSG from baseline	Key sec-ondary	mg/dl	-35.5	-50.6	-6.58	versus Placebo: 5 mg: p=0.007	

Effect	Short descrip-tion	Unit	TZP 5 mg N=32	TZP 10 mg N=33	Plc or Plc/TZP 5 mg* N=34	Uncertainties Strength of evidence	Refere nce
% change in BMI from baseline	endpoint	%	Δ Plc (95% CI): -28.9 (-49.7, -8.05)	Δ Plc (95% CI): -44.0 (-64.3, -23.6)	-0.55	10 mg: p<0.001	
	Key sec-ondary endpoint		-6.73	-11.07		versus Placebo: 5 mg: p<0.001 10 mg: p<0.001	
			Δ Plc (95% CI): -6.18 (-9.31, -3.05)	Δ Plc (95% CI): -10.52 (-13.67, -7.38)			
at 52 weeks (end of open-label period) – Treatment regimen estimand							
Δ HbA1c from baseline, (5 and 10 mg TZP)	Additional secondary endpoint	%	-1.84	-2.17	-1.83	Within treatment: 5 mg, 10 mg and plc/5 mg TZP: p<0.001	
Change in BMI SDS (age- and sex-matched) from baseline	Additional secondary endpoint	N/A	-0.60	-1.06	-0.38	Within treatment: 5 mg, 10 mg and plc/5 mg TZP: p<0.001	

*The placebo-treated patients from the double-blind period were switched to 5 mg of TZP in the open-label extension, which is indicated as "Plc or Plc/TZP 5 mg

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	Reference
Unfavourable Effects						
GI effects		%	46.2	11.8		CSR Study GPGV
Diarrhoea		%	24.6	5.9		
Nausea		%	20.0	8.8		
Vomiting		%	13.8	2.9		
Headache		%	7.7	2.9		
Hypoglycaemia	BG<54	events per year	0.81	0.15	Mainly in subjects with concomitant insulin use	

Abbreviations: BG, blood glucose; Δ Plc = difference from placebo; CI = confidence interval; GI, gastrointestinal

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

The key favourable effect is a clinically relevant and significant reduction in HbA_{1C} after 22 weeks of treatment with 5 mg or 10 mg of tirzepatide [difference TZP_ALL vs. placebo (95% CI): -1.80 (2.35, 1.25)]. Improvement of blood glucose control by tirzepatide is further confirmed by the corresponding key secondary and additional secondary endpoints. Additional favourable effects are the weight-reducing effect and reduction in plasma lipids, which are well known from GLP-1 receptor agonists.

Importance of unfavourable effects

TZP may increase gall bladder disease (one event of cholelithiasis with cholecystitis reported in study GPGV). Although this unfavourable effect is mostly not life threatening, it may require surgical intervention (cholecystectomy). Thus, it is considered of high importance, specifically in case of the paediatric target population.

The most frequently occurring unfavorable effects were related to the gastrointestinal tract and are considered of minor importance, as they mostly occur temporarily and can be controlled by dose adjustment. Increase in pancreatic enzymes is also deemed of limited clinical relevance, as it appears not to be related to pancreatitis and is well known from established GLP1 receptor agonists. Injection site reactions were mostly not serious or severe and self-limiting and are therefore deemed to be of low importance.

3.7.2. Balance of benefits and risks

For the key benefit of glycaemic control, tirzepatide was superior to placebo. Glucose control with all tirzepatide doses could be achieved with only minimally increased risk of hypoglycaemia. Body weight was reduced in a statistically superior way compared to placebo in the mostly overweight/obese study population.

The safety and tolerability profile of tirzepatide was characterized in a patient population aligned with the target indication population for up to 52 weeks (double-blind *plus* open-label period). As expected, similar to the GLP-1 receptor agonist class, the most common AEs were GI related. No case of pancreatitis occurred.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.7.4. Conclusions

The overall B/R of Mounjaro is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include treatment of adolescents and children aged 10 years and above with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise for MOUNJARO, based on final results from study I8F-MC-GPGV (SURPASS-PEDS); this is a study to evaluate efficacy, safety, and pharmacokinetics/pharmacodynamics of tirzepatide compared to placebo in paediatric and adolescent participants with type 2 diabetes mellitus inadequately controlled with metformin, or basal insulin, or both. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated.

The Package Leaflet is updated in accordance. Version 7.1 of the RMP has also been submitted.

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

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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA/PE/0000237950 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.