21 July 2022
EMA/791310/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mounjaro

International non-proprietary name: tirzepatide

Procedure No. EMEA/H/C/005620/0000

Note

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

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
AEs	adverse events
ANCOVA	analysis of covariance
APPADL	Ability to Perform Physical Activities of Daily Living
ASAT	abdominal subcutaneous adipose tissue
BMI	body mass index
CIPC	Critical in-process control
CKD	chronic kidney disease
CGM	continuous glucose monitoring
COVID-19	coronavirus disease 2019
CPPS	Critical Process Parameters
CQA	Critical Quality Attribute
CSR	clinical study report
CV	cardiovascular
DoE	Design of experiments
DTSQc	Diabetes Treatment Satisfaction Questionnaire (change)
DTSQs	Diabetes Treatment Satisfaction Questionnaire (status)
EC	European Commission
eGFR	estimated glomerular filtration rate
EQ VAS	EQ visual analog scale
FBG	fasting blood glucose
FSG	fasting serum glucose
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
IC	Ion chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
ISR	incurred sample reanalysis
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
IW-SP	Impact of Weight on Self-Perception
LBA	Ligand-binding assays
LC-MS	Liquid chromatography mass spectrometry
LDL-C	low-density lipoprotein cholesterol
LFC	liver fat content
LLDPE	Linear low density polyethylene

Min	minimum
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
NMR	Nuclear Magnetic Resonance
OAM	oral antihyperglycaemic medication
Ph. Eur.	European Pharmacopoeia
PPQ	Process performance qualification
PPs	Process Parameters
PRO	patient-reported outcome
PVDF	Polyvinylidene fluoride
RP	Reverse Phase
RP-HPLC	Reverse Phase-High Performance Liquid Chromatography
RP-LC-MS	Reverse Phase- Liquid Chromatography- Mass Chromatography
RP-LC-UV	Reverse Phase- Liquid Chromatography-Ultraviolet
QTPP	Quality target product profile
QW	once weekly
SEC	Size exclusion chromatography
SGLT-2i	sodium-glucose cotransporter-2 inhibitor
SFS	Semi-finished syringe
SMBG	self-monitored blood glucose
Study GPGA	I8F-MC-GPGA
Study GPGB	I8F-MC-GPGB
Study GPGF	I8F-MC-GPGF
Study GPGH	I8F-MC-GPGH
Study GPGI	I8F-MC-GPGI
Study GPGK	I8F-MC-GPGK
Study GPGL	I8F-MC-GPGL
Study GPGM	I8F-MC-GPGM
SmPC	Summary of Product Characteristics
SU	sulfonylurea
TAMC	Total Aerobic Microbial Count
TYMC	Total Combined Yeasts/Moulds Count
T2DM	type 2 diabetes mellitus
TTT	treat-to-target
TZP	tirzepatide
UV	Ultraviolet
VAT	visceral adipose tissue
VLDL-C	very-low-density lipoprotein cholesterol

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 6 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Mounjaro, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

The applicant applied for the following indication

Tirzepatide (Mounjaro) is indicated for the treatment of adults with 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, weight and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0311/2019 on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0311/2019 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance tirzepatide contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
18 October 2018	EMEA/H/SA/3939/1/2018/III	Armin Koch, Peter Mol

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Drug product process validation requirements
- General non-clinical strategy
- Clinical pharmacology plans: studies, study and model based DDI characterisation, population PK plans, evaluation of QTc prolongation potential
- Dosing regimen
- Phase 3 clinical development programme: number of studies, general strategy, primary and secondary efficacy endpoints, definition of study populations, background treatments, treatment durations, safety monitoring, rescue therapy provisions, choice and dose of comparators
- Immunogenicity strategy

1.7. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise Co-Rapporteur: Kristina Dunder

The application was received by the EMA on	6 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 January 2022
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	31 January 2022

The PRAC Rapporteur's Updated Assessment Report was circulated to all PRAC and CHMP members on	08 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 May 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	15 June 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 June 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	05 July 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Mounjaro on	21 July 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	21 July 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tirzepatide is intended to be used in the following indication (indication worded in line with the initial submission):

Tirzepatide (Mounjaro) is indicated for the treatment of adults with 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, weight and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist which is administered subcutaneously once-weekly.

2.1.2. Epidemiology and risk factors

Type 2 diabetes (T2D) is a metabolic disease which is highly prevalent in western and worldwide societies, attributed to unhealthy lifestyle.

Type 2 diabetes remains a substantial health care challenge that affects the individual patient and the society profoundly. The prevalence of the chronic and progressive metabolic disorder is expected to increase worldwide markedly; projections suggest that around 10% of the global adult population will be affected by 2045.

2.1.3. Aetiology and pathogenesis

Most subjects with T2D are overweight or obese, which is important in the aetiology as it increases insulin resistance and leads to persistent hyperglycaemia.

The pathogenesis is seemingly heterogeneous and also involves environmental, lifestyle, and genetic components. All of these factors contribute to chronic hyperglycaemia, which (if left untreated) is associated with β-cell failure and increased risk of long-term micro- and macrovascular complications.

2.1.4. Clinical presentation, diagnosis

The typical presentation of diabetes includes polyuria and polydipsia. However, many patients with T2D are asymptomatic and are diagnosed with screening or general investigations of a specific complaints like fatigue. The diagnosis is made by measurement of hyperglycaemia.

2.1.5. Management

The guidelines of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) for treatment of T2D have been developed in cooperation and are widely agreed. The major steps recommended for managing type 2 diabetes are lifestyle changes such as diet and exercise. For glycaemic control, primarily metformin, other non-insulin anti-diabetic agents and finally insulin (in various forms) are used.

To avoid the microvascular complications associated with the disease, it is a crucial aim to establish adequate glycaemic control as soon as possible after a T2D diagnosis. Besides anti-glycaemic therapy, antihypertensive, antithrombotic and lipid lowering treatments might be indicated to avoid other associated co-morbidities (e.g. hypertension, obesity, dyslipidemia) and macrovascular complications (MI, stroke).

Recently, SGLT-2 inhibitors and GLP-1 RAs in T2D patients at high CV risk have shown not only improvements in glycaemic control but also a reduction in body weight and CV events.

2.2. About the product

Tirzepatide (Mounjaro) is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist and is intended as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.

Proposed Indication: see above.

Proposed Posology

The starting dose of tirzepatide is 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose. The recommended doses are 5, 10 and 15 mg.
The maximum dose is 15 mg once weekly.

2.3. Type of application and aspects on development

Development program

Completed studies

This application for tirzepatide as a novel adjunct treatment to diet and exercise to improve glycaemic control in adults with T2DM is supported by 19 completed clinical studies in healthy participants or patients with T2DM:

- 3 biopharmaceutic studies
- 7 clinical pharmacology studies, including 1 mechanism of action study
- 2 Phase 2 studies
- 5 global (pivotal) Phase 3 studies, and
- 2 regional (Japan) Phase 3 studies

The 10 biopharmaceutic and clinical pharmacology studies were designed to assess the PK, PD, the effects of extrinsic and intrinsic factors on tirzepatide PK, the impact of tirzepatide on PK of orally administered drugs, and safety and tolerability of tirzepatide. Single doses of tirzepatide were administered over a range of 0.25 to 8 mg, and multiple once-weekly doses that ranged from 0.5 to 15 mg for up to 28 weeks. The effect of tirzepatide on insulin and glucagon secretion and insulin sensitivity was assessed in a dedicated mechanism of action study.

The two Phase 2 studies (GPGB and GPGF) were multicenter, double-blind studies conducted to provide assessments of the efficacy, safety, and tolerability of tirzepatide between 1 and 15mg to support dose selection and optimization of the dose-escalation scheme for Phase 3 studies. Patients had T2DM and inadequate glycaemic control on diet and exercise with or without a stable dose of metformin. Study GPGB was a 26-week study that compared tirzepatide with placebo and dulaglutide 1.5 mg. Study GPGF was a 12-week study that compared tirzepatide with placebo. These Phase 2 studies used different dose-escalation schemes than the scheme that was used in the Phase 3 studies; hence, the data are not included in the efficacy assessments but contribute exposures to the safety assessment.

The 5 global Phase 3 studies (GPGK, GPGL, GPGH, GPGM, and GPGI) were designed to assess the efficacy and safety of tirzepatide 5, 10, and 15 mg once-weekly (40- or 52-week treatment duration at the primary endpoint) versus placebo or active comparators in adults with T2DM. The treatment exposure in Study GPGM lasted up to 104 weeks. Within Study GPGH, 2 sub-studies were performed, and were designed to investigate the 24-hour glucose profile captured with CGM or characterize potential changes in hepatic fat content through magnetic resonance imaging. The clinical studies utilized double-blinded or open-label designs and included patients with varying disease severity, differing in duration of disease, background therapy, comorbidities, and complications. Background therapies ranged from diet and exercise alone, to 1 to 3 OAMs, and basal insulin with or without metformin.

The 2 regional Phase 3 studies (GPGO and GPGP) were 52-week, multicenter studies conducted in Japan. Study GPGO was a double-blind study designed to assess the safety and efficacy of tirzepatide compared with dulaglutide 0.75 mg in patients with T2DM who discontinued OAM monotherapy or were OAM-naïve. Dulaglutide 0.75 mg is the only dulaglutide dose currently registered in Japan and was the active comparator chosen since it is marketed in Japan as monotherapy in patients with T2DM. Study GPGP was an open-label study without comparator, designed to assess safety and efficacy of tirzepatide in combination with monotherapy of OAMs. These 2 regional studies used the tirzepatide 5, 10, and 15 mg maintenance doses and the same tirzepatide dose-escalation scheme as was used in the global Phase 3 studies. The data from these studies are not included in the efficacy assessments but contribute exposures to the safety assessment.

Compliance with CHMP Guidance

The design of the registration program was informed by available regulatory guidance documents and advice from the EMA/CHMP and FDA, among others:

- FDA 2008: Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.
- ICH 2017: ICH harmonised guideline: estimands and sensitivity analysis in clinical trials, E9(R1), Step 2 version.
- EMA 2018: Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus (draft rev.2).

Scientific Advice

SA was requested and advice was sought on quality, pre-clinical, and clinical aspects of the development.

Conclusion:

In general, regulatory feedback has been implemented in the study program. A different approach for dose-de-escalation was chosen by the Applicant (see 2.5.4.1.3). In addition, PK/PD modelling to address the use of tirzepatide in patients with hepatic impairment was not performed as patients with hepatic impairment were excluded from the phase 3 study program. Instead, a clinical pharmacology study (GPGQ) was conducted.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection in pre-filled pen containing 2.5, 5, 7.5, 10, 12.5 and 15 mg of tirzepatide as active substance.

Other ingredients are: sodium phosphate dibasic heptahydrate, sodium chloride, concentrated hydrochloric acid, and sodium hydroxide (for pH adjustment) and water for injections

The product is available in glass syringe encased in a disposable pre-filled pen as described in section 6.5 of the SmPC.

2.4.2. Active Substance

General information

The chemical name of tirzepatide is L-Serinamide, L-tyrosyl-2-methylalanyl-L-α-glutamylglycyl-L-threonyl-Lphenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-tyrosyl-L-seryl-L-isoleucyl-2-methylalanyl-L-leucyl-L-α-aspartyl-L-lysyl-L-isoleucyl-L-alanyl-L-glutaminyl-N6-[(22S)-22,42-dicarboxy-1,10,19,24-tetraoxo-3,6,12,15-tetraoxa-9,18,23-triazadotetracont-1-yl]-Llysyl-L-alanyl-L-phenylalanyl-L-valyl-L-glutaminyl-L-tryptophyl-L-leucyl-L-isoleucyl-Lalanylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolylcorresponding to the molecular formula $C_{225}H_{348}N_{48}O_{68}$. It has a relative molecular weight of 4810.52 Da (monoisotopic mass) or 4813.45 Da (average mass IUPAC 2007) g/mol and the following structure:

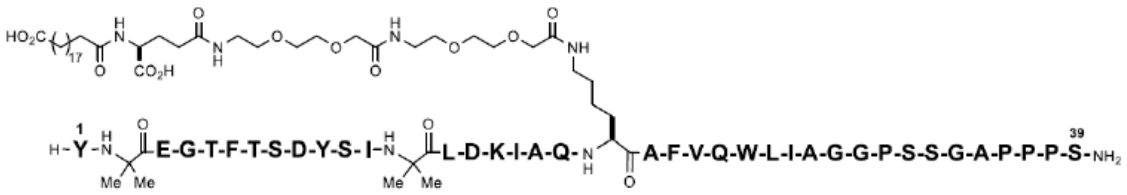


Figure 1: active substance structure

Tirzepatide is a 39-amino acid synthetic peptide. It consists of a peptide component based on the GIP sequence containing 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 is attached to 1,20-eicosanedioic acid via a linker which consists of a γ-Glu and two 8-amino-3,6-dioxaoctanoic acids. The higher order

structure of tirzepatide was characterized using orthogonal biophysical techniques. The

secondary structure of tirzepatide is predominantly α-helical under native conditions.

The chemical structure of the active substance was elucidated by a combination of LC-MS, LC-MS/MS, of Intact Molecule, LC-MS Peptide Mapping, Chiral GC-MS, RP-HPLC and IC, NMR, far-UV CD spectroscopy, FT-IR spectroscopy, near-UV CD spectroscopy, composition gradient multiangle light scattering, and cell based bioassays.

The active substance is a hygroscopic white to practically white solid, and freely soluble in 5 mM phosphate buffer pH 7.0 at 25°C

Regarding stereoisomerism, the active substance exhibits L-form for natural amino acids except no chiral center for Gly and 2-aminoisobutyric acid (Aib) in positions 2 and 13.

Polymorphism has not been observed for active substance.

Manufacture, characterisation and process controls

The active substance is manufacture by one manufacturing site.

The active substance is synthesized using solid-phase peptide synthesis, dissolution and chromatographic purification, isolation and drying concentration and solvent exchange, and using well defined starting materials with acceptable specifications.

The manufacturing process utilizes a standard solid phase peptide synthesis (SPPS) manufacturing procedure including addition of the linear sidechain at Lys20. The peptide is cleaved from the resin with simultaneous side-chain deprotection. The tirzepatide crude active substance is purified by reverse phase chromatography, concentrated, solvent exchanged, isolated, and dried to produce the final active substance.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on degradation impurities was investigated. Degradation pathways were discussed in detail, including identification of most degradation products for solid active substance and active substance solution/finished product based on stress stability results. No degradation was observed under the proposed storage conditions for the active substance and the degradation occurring over the shelf-life of the finished product solution is discussed in this section.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The development of the manufacturing process for the tirzepatide synthetic routes included the use of Quality by Design principles, however, no design space was claimed, and the linking of elements of risk management to rigorous scientific understanding. Robustness of unit operations, process parameters, and controls were evaluated against the CQAs of the final active substance, ultimately linking to the CQAs of the finished product. The commercial process development approach is described in full detail. Purge of impurities are discussed for SPPS and purification. The active substance manufacturing process was extensively characterized, and the data provided in the dossier demonstrate thorough understanding of the manufacturing process.

The active substance is packaged in a primary liner which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for identification, (RP-LC-UV, peptide map, cell-based bioassay), assay (RP-LC-UV), purity tests (RP-LC-UV, RP-LC-MS), high molecular weight (SEC), residual solvents (GC), description (visual), water content (Ph. Eur.), bacterial endotoxins (Ph. Eur.), and TAMC and TCYMC (Ph. Eur.).

All CQAs have been included in the specification. The proposed acceptance criteria have been adequately justified.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity and impurities testing has been presented.

Batch analysis data on 3 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 12 months under long term conditions (-20°C) and for up to 12 months under accelerated conditions (5°C) according to the ICH guidelines were provided.

Supportive stability data from 1 batch manufactured using the Initial Phase 3 Process and used in clinical trialsfor up to 24 months under long term conditions (-20°C) and for up to 6 months under accelerated conditions (5°C) according to the ICH guidelines was provided.

The following parameters were tested: assay, purity, related substances/impurities (total, specified, and largest unspecified), high molecular weight species, water content, and description. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long-term and accelerated conditions. While packaged in a different container than the primary stability batches, the supporting stability batch has shown similar stability profiles to the primary stability batches.

Results on stress conditions (25°C/ 60% RH) for 6 months were also provided on one batch. Increases in impurities were observed over 6 months with a corresponding decrease in purity. These changes are consistent with degradation pathways observed in stress studies and were not observed at either the -20°C long-term or 5°C accelerated conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when stored frozen (-25°C to -10°C) in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as a clear to opalescent, colourless to slightly yellow or brown, essentially free of particles, sterile and non-pyrogenic parenteral solution for subcutaneous administration.

The pharmaceutical development for the finished product was based on a Quality by Design approach, however, no design space was claimed. A comprehensive QTTP was presented. The Quality Target Product Profile (QTPP) was defined by taking into consideration the pharmaceutical product quality attributes required to meet the needs of the patient. The defined QTPP formed the basis for the finished product design. Formulation and manufacturing process development considered the necessary CQAs for a sterile solution in a semi-finished syringe assembled in an autoinjector. The Critical Quality Attributes (CQAs) were defined based on the understanding derived from the risk assessment from a safety and efficacy perspective, taking into consideration CQAs related to the active substance, excipients and those specific to the parenteral dosage form. The QTPP and CQAs were used to design pre-formulation and formulation development studies with the goal of developing a stable commercial finished product formulation.

The active substance characteristics with a possible impact on the finished product formulation were provided.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Extensive formulation development studies were conducted taking into account solubility of the active substance, tonicity, the effect of pH and agitation. The commercial formulation was already used during phase 3 clinical studies.

The finished product does not contain overages. However, an overfill is required to discharge the nominal volume from the autoinjector containing the syringe. Sufficient justification of the proposed overfill in the syringes assembled in the autoinjector has been provided.

The manufacturing process is a common process for aqueous sterile finished products, which cannot be subjected to terminal sterilisation: buffer formulation and filtration, finished product formulation and first filtration, sterile filtration, filling and plunger insertion. The semi-finished syringe is finally assembled into the autoinjector.

The choice of sterile filtration with aseptic filling has been adequately justified in accordance with the guideline on sterilisation EMA/CHMP/CVMP/QWP/850374/2015.

Following a risk-based approach, manufacturing process development studies were performed. The overall control strategy was defined based on the results from these studies. Detailed lists of critical and non-critical process parameters as well as in-process controls with limits and ranges were provided and considered satisfactory.

Product contact materials have been evaluated under worst case processing times for their impact on the finished product quality and were found to have no negative impact. Potential extractables and leachables have sufficiently been evaluated.

In conclusion, the manufacturing process development of the finished product is sufficiently described.

The commercial primary container system for the finished product consists of a 1 mL clear glass staked needle syringe barrel closed with a plunger and a rigid needle shield.

The semi-finished syringe is assembled into an autoinjector. The same autoinjector is used for all six strengths. This container closure system was also used in Phase 3 clinical trials.

For the semi-finished syringe, sufficient information with respect to protection, safety, compatibility and performance has been provided.

The finished product is a medicinal product that falls under the second sub-paragraph of Article 1(9) of Regulation (EU) 2017/745 (MDR). The medical device/device parts and the medicinal product form an integral product which is intended exclusively for use in the given combination and which is not reusable. In accordance with Article 117 of the Medical Device Regulation, all applications for an integral medicinal product should include evidence of the conformity of the device parts with the relevant GSPRs set out in Annex I of Regulation (EU) 2017/745. Therefore, for the prefilled pen part of the finished product, a Notified Body Opinion must be provided. The originally missing Notified Body Opinion constituted a major objection, to which as a response the applicant provided the requested opinion from the Notified Body. Sufficient documentation in accordance with the Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019) has also been provided.

Manufacture of the product and process controls

The finished product is manufactured by two manufacturing sites.

The manufacturing process consists of 5 main steps: buffer solution preparation, finished product formulation, bioburden reduction and in-line sterile filtration (immediately before filling), aseptic filling, plungering, and assembly of the semi-finished syringes with the autoinjector components. The process is considered to be a non-standard manufacturing process.

Critical and non-critical process parameters, in-process controls, as well as processing time limits (hold times) were given with ranges or limits in accordance with the knowledge gained during development. Process parameters and in-process controls for assembly of the semi-finished syringe into the autoinjector were also provided.

Validation data on production scale batches covering the entire manufacturing process including processing times and assembly of semi-finished syringe into the autoinjector were missing and resulted in a major objection (MO). Data for PPQ batches of the semi-finished syringe (SFS) and autoinjectors were provided. CPPs, PPs, CIPC, IPC and release data are all within specifications. Processing time limits were also successfully validated. Four batches of SFS were assembled into autoinjectors. All test parameters in accordance with the finished product specification are within specifications. Overall, the PPQ data submitted are considered sufficient to demonstrate that the manufacturing process of the finished product is under control and results in consistent quality.

Validation of the membrane filters was performed, and respective data is considered sufficient.

Results of media fill runs at both manufacturing sites sufficiently demonstrated the maximum filling time for the finished product solution into the syringes.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: identity (RP-LC-UV, peptide map), assay (RP-LC-UV), purity (RP-LC-UV), high molecular weight species (SEC), description (visual), color (Ph. Eur.), clarity (Ph. Eur.), bacterial endotoxin (Ph. Eur.), sterility (Ph. Eur.) pH (Ph. Eur.), osmolality (Ph. Eur.), particle matter (Ph. Eur.), volume of injection (Ph. Eur.), and syringe functionality break loose force and glide force (compression test).

The autoinjector specifications include appropriate tests for identity (RP-LC-UV), dose accuracy (volume by weight, visual/functional inspection (inspection), and injection time (timing).

The specifications cover the necessary tests for a sterile solution in a semi-finished syringe assembled into an autoinjector including two orthogonal identity tests, assay, purity, related substances, HMWS, safety tests (sterility, bacterial endotoxins, particulate matter) and functionality tests for syringe and device.

The finished product manufacturing process does not lead to new degradation products compared to the active substance. The specification limits for total and identified impurities are considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using an ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Reference standards are used for both active substance and finished product. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing

Stability of the product

Stability data from 6 batches (four of the batches are pilot scale and two are commercial scale for both semi-finished syringe and autoinjector batches of finished product (for 2.5 mg and 15 mg strength) manufactured by one manufacturing site stored for up to 18 months under long term conditions (2 - 8 °C) and for up to 6 months under accelerated conditions (30 C/ 65% RH) according to the ICH guidelines were provided. The

batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supporting stability studies cover long term stability for finished product from phase 3 clinical trial batches, intermediate strength batches, batches in container closure from alternate supplier and chemical and physical stability in the autoinjector.

Samples were tested for assay, purity, HMWS, description, colour, clarity, bacterial endotoxins, sterility, container closure integrity, pH, particulate matter, break loose and glide force, and autoinjector testing. The analytical procedures used are stability indicating.

A bracketing approach consistent with the guidelines in ICH Q1D was applied for the finished product. This is considered acceptable as the finished products contain the same excipients in the same concentrations, the fill volume is the same and primary container closure system and autoinjector are identical.

Long-term stability data show no obvious trends.

The finished product was exposed to stress degradation conditions with respect to thermal, pH, and oxidative stress. Based on the results, the potential degradation pathways are well understood and characterized. The analytical methods are capable of detecting degradation products from the likely and potential degradation pathways.

Batches of the finished product in semi-finished syringes were exposed to ICH Q1B confirmatory photostability conditions. These studies demonstrated that the finished product in the SFS is susceptible to degradation under the ICH photostability conditions. The analytical methods were capable of detecting photo-induced degradation products. Based on the results of the study in the SFS, follow-up photostability studies were conducted in the autoinjector, and the autoinjector packaged in the marketing pack. Degradation was reduced in the finished product incorporated into the autoinjectors and no degradation was observed under the ICH confirmatory photostability conditions for the autoinjectors packaged in the marketing pack.

As part of the stability assessment of the finished product, a patient-use study was conducted at the 11-month time point by transferring a subset of syringes that had been stored at 5 °C to 30 °C / 65% RH storage and evaluating product quality attributes for up to 30 days to encompass the period that the finished product may be stored out of refrigeration (up to 30 °C) by the patient. Additional patient-use studies are planned at the end of shelf life, and the patient-use stability is also supported by the stability data generated at the accelerated condition of 30 °C / 65% RH. The primary stability data at the long-term storage condition (5 °C) and the patient-use study data were compared to the proposed commercial specifications. At the recommended storage condition of 5 °C, all available results including the autoinjector performance requirements tests have remained within the proposed acceptance criteria. In addition, the results remained within the proposed acceptance criteria for at least 21 days at 30 °C / 65% RH for patient-use.

Based on available stability data, the proposed shelf-life of 2 years and store in a refrigerator (2 ºC - 8 ºC), do not freeze as stated in the SmPC (section 6.3 and 6.4) are acceptable. The finished product may be stored unrefrigerated for up to 21 days at a temperature not above 30 ºC.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Two issues were raised by CHMP as Major Objections (MO) related to the request of validation data on production scale batches covering the entire manufacturing process including processing times and assembly of semi-finished syringe into the autoinjector and the missing Notified Body Opinion of the prefilled pen part of the finished product. The issues were resolved satisfactorily by the applicant as discussed above.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

In-vitro and in-vivo studies were performed to characterise tirzepatide's effects in relation to its intended indication Type 2 diabetes. The focus laid – according to its mechanism of action – on binding to the GLP-1 and GIP receptor and on its effects on glucose-dependent insulin secretion. Special studies were performed to elaborate the contribution of the GIP receptor on the tirzepatide effects using GIP receptor deficient mice or cells of them. Furthermore, the effect of albumin on tirzepatide's binding to its target receptors was specifically studied in vitro since tirzepatide is intended to bind rather tightly to serum albumin to prolong its duration of action. Other special studies addressed tirzepatide's effect on gastric emptying; this effect is due to GLP-1 receptor activation and is already known from pure GLP-1 RAs.

2.5.2.1. Primary pharmacodynamic studies

The following table provides an overview of the submitted in-vitro studies and the main observations made. A more detailed description of the most relevant individual studies is provided thereafter.

In-vitro studies

Study ID	Test system	Main results
DBT201	HEK293 cells expressing GIP- or GLP1 receptors from various species	Tirzepatide has Ki values in the nanomolar range towards GIP and GLP1 receptors from human, monkey, rat and mouse. Binding strongly affected by serum albumin as expected
ENDO123	HEK293 cells expressing human GIP- or GLP1 receptors	Binding results in line with DBT201; furthermore, cAMP production was measured. EC50 of cAMP production in the nanomolar or sub-nanomolar range, depending on receptor expression level in the HEK cells
ENDO124	HEK293 cells expressing human GIP- or GLP1 receptors	GTP recruitment to Gs protein was measured after cell stimulation with tirzepatide (compared to the endogenous ligands, GIP and GLP1). EC50 of tirzepatide was in the sub-nanomolar range; Emax was only around 50% (compared to GIP) at the GIP receptor
QSB171	CHO cells expressing human GIP- or GLP1 receptors	beta-arrestin-2 recruitment was measured to address receptor internalisation and inactivation upon prolonged stimulation. EC50 and Emax were similatr on the GIP receptor for tirzepatide and GIP. In contrast tirzepatide had virtually no effect on the arrestin recruitment to the GLP1recptor
ENDO125	HEK293 cells expressing tagged human GIP- or GLP1 receptors	Receptor internalisation was measured. Effect of tirzepatide and GIP were similar on GIP receptors. In contrast, EC50 was markedly higher and Emax was markedly lower for tirzepatide than for GLP1 on the GLP1 receptor. This is in line with Study QSB171
DBT203	Pancreatic islets from rats and mice (WT, GLP1R-KO or GIPR-KO)	Tirzepatide increased insulin liberation in the presence of glucose (11.2 mM) in WT animals. The effect size was roughly comparable with GLP1. In GIPR-KO mice, the effect of various tirzepatide concentrations was highly similar to WT animals. In GLP1R-KO mice, the tirzepatide effect was stronger than in WT animals at the high tirzepatide concentration of 1000 nM.
ENDO130	Human adipocytes	cAMP production and lipolysis were measured. Effects of GIP and tirzepatide were similar; EC50 of tirzepatide was lower than EC50 of GIP

DBT201:

In Vitro Receptor Binding Affinity of LY3298176 for the Cloned Human, Monkey, Rat, and Mouse Gastric Inhibitory Peptide (GIP) and Glucagon-like Peptide 1 (GLP-1) Receptors

The purpose of this study was to assess the in vitro binding affinity of LY3298176 against various species using cell membranes prepared from HEK-293 cells over-expressing the cloned human, monkey, rat, or mouse gastric inhibitory peptide (GIP) receptor or glucagon-like peptide (GLP-1) receptor. Equilibrium dissociation constants (Ki) determined by competitor inhibited radioligand binding in membrane preparations of the HEK cells. The amount of bound radioligand was determined by a scintillation proximity assay (SPA). Since LY3298176 contains a long chain acyl moiety, binding affinity was determined both in the absence and presence of 0.1% fatty-acid free bovine serum albumin (BSA) where feasible.

The following four tables show the binding affinities of tirzepatide (LY3298176) on the GIP (upper two figures) and the GLP-1 (lower two figures) receptor of different species. The endogenous ligand served as comparator. Binding assays were performed in the absence and presence of 0.1% bovine serum albumin (BSA). The presence of BSA markedly reduced the apparent affinity of tirzepatide to the GIP and GLP-1 receptor. This was probably due to the fact that tirzepatide was designed for strong binding to albumin. The

endogenous ligands were not affected by BSA. Binding affinities towards the GLP-1 receptors from different species were in the low nanomolar range (in the absence of BSA).

Table 1 of study report: GIP Receptor Binding Affinity in the Absence of Bovine Serum Albumin
GIP Receptor Binding Affinity with Bacitracin, Ki, nM (SEM, n)

Peptide	Human GIPR	Monkey GIPR
GIP	0.85 (0.03, n = 3)	0.67 (0.21, n = 3)
LY3298176	0.37 (0.04, n = 3)	0.32 (0.05, n = 3)

Table 2: GIP Receptor Binding Affinity in the Presence of Bovine Serum Albumin
GIP Receptor Binding Affinity with BSA, Ki, nM (SEM, n)

Peptide	Human GIPR	Monkey GIPR	Rat GIPR	Mouse GIPR1
GIP	0.072 (0.008, n = 6)	0.018 (0.003, n = 6)	0.431 (0.070, n = 7)	0.296 (0.067, n = 7)
LY3298176	4.02 (0.37, n = 6)	1.48 (0.38, n = 6)	386 (69, n = 7)	646 (138, n = 7)

Table 3: GLP-1 Receptor Binding Affinity in the Absence of Bovine Serum Albumin
GLP-1 Receptor Binding Affinity with Bacitracin, Ki, nM (SEM, n)

Peptide	Human GLP-1R	Monkey GLP-1R	Rat GLP-1R	Mouse GLP-1R
GLP-1	0.92 (0.12, n = 7)	1.22 (0.14, n = 3)	1.34 (0.34, n = 3)	1.49 (0.44, n = 3)
LY3298176	2.88 (0.31, n = 5)	5.08 (0.41, n = 4)	1.40 (0.37, n = 4)	0.84 (0.06, n = 4)

Table 4: GLP-1 Receptor Binding Affinity in the Presence of Bovine Serum Albumin
GLP-1 Receptor Binding Affinity with 0.1% BSA, Ki, nM (SEM, n)

Peptide	Human GLP-1R	Monkey GLP-1R	Rat GLP-1R	Mouse GLP-1R
GLP-1	1.04 (0.23, n = 7)	0.97 (0.19, n = 7)	1.07 (0.14, n = 7)	1.65 (0.26, n = 7)
LY3298176	378 (52, n = 7)	391 (60, n = 7)	129 (13, n = 7)	88.4 (5.2, n = 7)

The affinity of tirzepatide towards the human and monkey GIP receptor was remarkable high (low Ki) in the presence of BSA (second table). In these species and at this receptor the Ki was in the low nanomolar range whereas otherwise it was in the range of one or a few hundred nanomolar.

ENDO123:

In Vitro LY3298176 GLP-1 and GIP Receptor Radioligand Binding and Induced Intracellular cAMP Accumulation on Recombinant Human GLP-1, GCG, and GIP Receptors in HEK293 Cell Lines with Varying Receptor Densities

Functional cAMP data for LY3298176 and comparator peptides was generated using clonal cell lines (from HEK-293) having a low-, medium-, and high-expression density of human glucagon-like peptide-1 receptor (hGLP-1R), low-, medium-, and high-expression density of human glucose-dependent insulinotropic peptide receptor (human gastric inhibitory polypeptide receptor, hGIP-R), or low expression density of human glucagon receptor (hGCGR). Assays were carried out in the presence of bovine casein with and without human serum albumin (HSA).

As shown in the following figure, EC50 of cAMP production following receptor stimulation strongly decreased with increasing receptor expression level. Emax virtually remained unchanged. This shown for the GLP-1 receptor in the following table. A similar effect was observed for the GIP receptor.

Tirzepatide had only a very low affinity at the glucagon receptor (EC50 2350 nM in the absence of HSA).

Note that the receptor expression should not affect EC50 because this depends on affinity, which is a property of the individual molecule. In contrast, Emax should increase with increasing receptor number (or density). But this was not the case.

Table 1: GLP-1R Functional cAMP Potency (EC50) and Efficacy (Emax) for Compounds Incubated at 37°C in the Presence of 0.1% Bovine Casein

Peptide	Human GLP-1R Low Expression		Human GLP-1R Med Expression		Human GLP-1R High Expression	
	EC50, nM, SEM (n)	Emax, % ± SEM	EC50, nM, SEM (n)	Emax, % ± SEM	EC50, nM, SEM (n)	Emax, % ± SEM
Human GLP-1(7-36)NH2	0.366 0.032 (57)	104 ± 1	0.0721 0.0061 (24)	100 ± 2	0.00624 0.00056 (14)	101 ± 2
LY3298176	6.54 0.71 (22)	102 ± 2	1.38 0.19 (11)	94 ± 2	0.132 0.006 (9)	101 ± 3

Abbreviations: GLP-1R = glucagon-like peptide-1 receptor, n = number of observations, SEM = standard error of the mean.

It was also shown in this study (and in a corresponding publication by Lilly employees) that human serum albumin markedly increases the EC50 of tirzepatide in respect to cAMP formation (as it did for receptor binding, see Study DBT201 above).

QSB171:

In Vitro LY3298176 Induced β-Arrestin-2 Recruitment to Recombinant Human GIP and GLP-1 Receptors in CHO-K1 PathHunter® Cells

In this study, the ability of tirzepatide was tested to induce β-arrestin recruitment at the human GLP-1 and GIP receptor. This was done in cell lines overexpressing the respective receptor. Recruitment of β-arrestin leads to receptor internalisation and thereby inactivation or desensitisation upon binding of a ligand.

At the human GLP-1 receptor, tirzepatide was not able to recruit β-arrestin. In contrast, β-arrestin recruitment was observed with the endogenous ligand GLP-1 in nanomolar concentrations as positive control, indicating that the test system works. For details, see table below.

Table 1: Affinity and Efficacy of LY3298176 at the Human GLP-1 Receptor

	EC50, nM	% Top
	(SEM, n)	(SD, n)
LSN306263 (GLP-1)	3.3	117
	(0.7, 14)	(8, 14)
LY3298176 (tirzepatide)	> 10,500	ND
	(ND, 5)	(ND, 5)

At the human GIP receptor, there were no relevant differences between tirzepatide and GIP. Both peptides were able to recruit β-arrestin to the human GIP receptor in a similar way.

ENDO125:

In Vitro LY3298176 Induced Receptor Internalization of Recombinant Human GIP and GLP-1 Receptors in HEK293 Cells

This study, like QSB171, also addressed receptor inactivation in response to binding of a ligand. In this study internalisation was determined directly by suitable cytological methods. Human GLP-1R and GIP-R were

tagged at the C-terminus with enhanced green fluorescent protein (EGFP). These constructs were stably expressed in HEK293 cells. Internalisation was assessed by confocal imaging. Thereby, EGF fluorescence could be located either at the cell membrane or in the cytoplasm after counter-staining of the cell nuclei.

Representative images of the transfected HEK cells after ligand treatment are shown below (GFP fluorescence). The upper row (A-C) shows GIP receptor expressing cells, the lower row (D-F) GLP-1 receptor expressing cells. Note that in the latter the endogenous ligand GLP-1 (Panel E) caused a marked internalisation of receptor fluorescence (green) but tirzepatide (Panel F) did not.

In case of the GIP receptor, GIP and tirzepatide caused a similar internalisation (Panels B and C) as compared to vehicle control (Panel A).

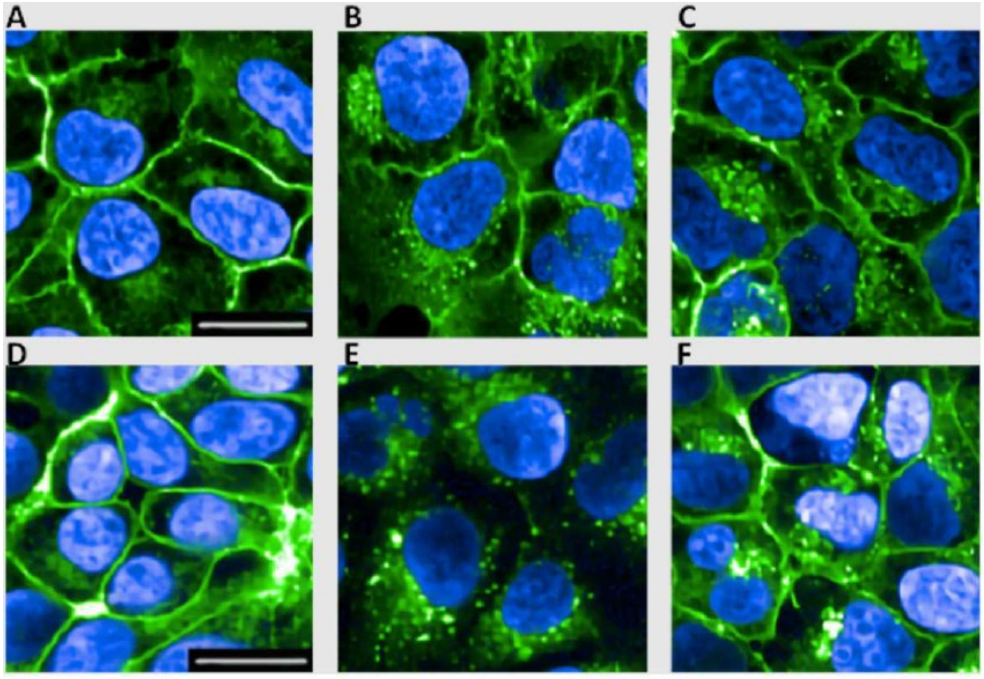


Figure 2.6.2.1. Internalization of GLP-1R and GIPR in HEK-293 cells.
Representative confocal images of HA-GIPR-EGFP cells detecting EGFP fluorescence following treatment with (A) vehicle, (B) 100 nM GIP(1-42), or (C) 100 nM tirzepatide. Representative confocal images of HA-GLP-1R-EGFP cells detecting EGFP fluorescence following treatment with (D) vehicle, (E) 100 nM GLP-1(7-36), or (F) 100 nM tirzepatide. Scale bars: 20 µm.

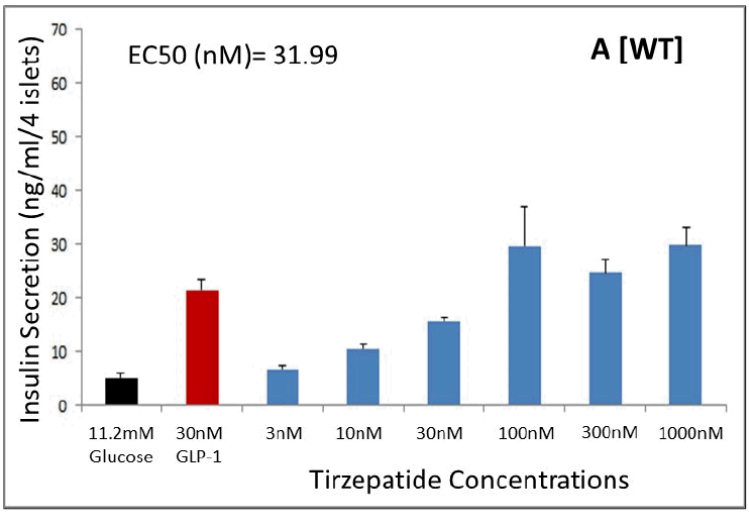
Internalisation was also assessed by measuring the decrease of the N-terminal HA tag from the cell surface in unpermeabilised cells. The results are in line with the findings from the GFP approach. Again, TZP caused poor internalisation of the GLP-1 receptor (markedly weaker than GLP-1 did) whereas internalisation of the GIP receptor was similar with GIP and tirzepatide.

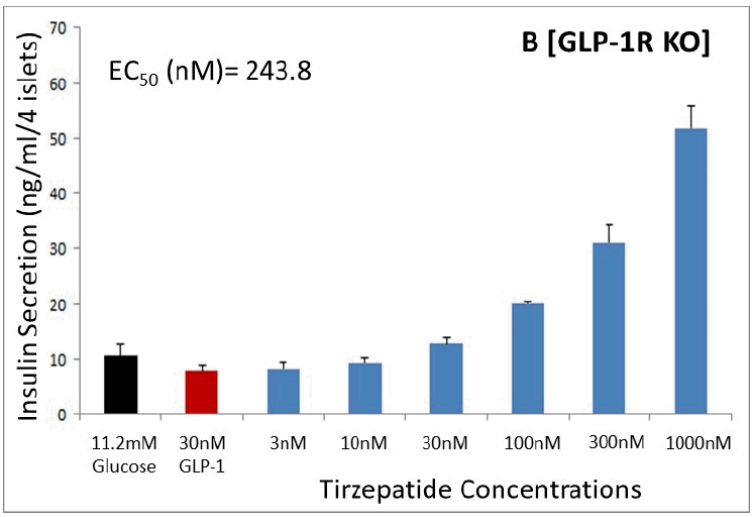
DBT203:
Effects of LY3298176 on Insulin Secretion In Vitro from Rat and Mouse Pancreatic Islets

In this study, the potency of LY3298176 in stimulating insulin secretion from rat and mouse pancreatic islets was evaluated. Islets were isolated from rats and from wild-type (WT) mice as well as from genetically modified mice lacking the GIP or the GLP-1 receptor.

In islets from rats (not genetically modified), tirzepatide dose-dependently increased insulin liberation in the presence of glucose; the effect in the absence of glucose was not tested. The maximal effect size of tirzepatide was similar to GLP-1, and the tirzepatide effect was virtually maximal with concentrations of 300 nM and above.

The following figure shows the tirzepatide effect on insulin liberation in islets prepared from mice lacking the GLP-1 receptor or the GIP receptor, compared to islets from wild-type (WT) mice. Effect size and concentration-response relationship were highly similar in WT and GLP-1 receptor KO mice, with nearly maximal responses at 100 to 300 nM onwards. The picture in GIP receptor KO mice is somewhat different with still increasing effect size at the highest doses tested. Furthermore, the maximal effect appears to be larger.





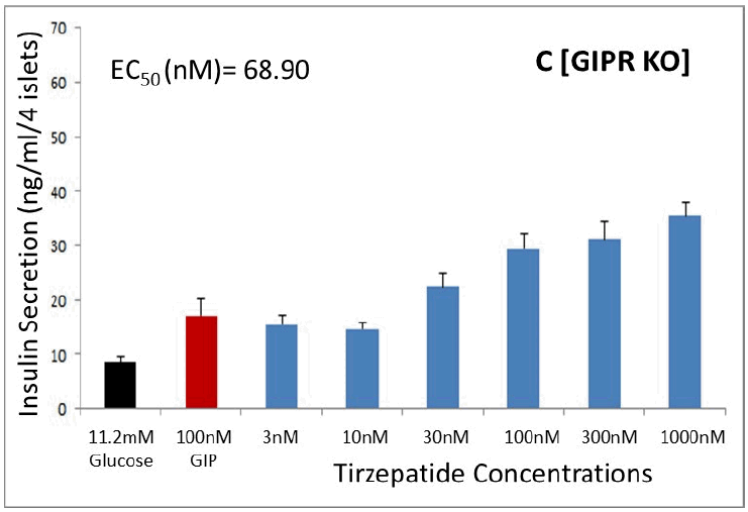


Figure 2: LY3298176 dose-dependently enhance insulin secretion from mouse islets.
(A) Insulin secretion from wildtype mouse islets stimulated by LY3298176 (B) Efficacy in islets from GLP1R knockout mice and (C) Potentiation of insulin secretion by LY3298176 in islets from GIPR knockout mice.

In-vivo studies

The following table provides an overview of the submitted in-vivo studies and the main observations made. A more detailed description of the important studies is provided thereafter.

Overview of the in-vivo studies

Study ID	Species/strain	Main results
ENDO126	Mouse, WT, GLP1R-KO and GIPR-KO	An Intraperitoneal Glucose Tolerance Test (ipGTT) was performed. Glucose AUC strongly decreased with ascending doses of tirzepatide in WT animals; EC50 was 0.2 nmol/kg. Tirzepatide was also effective in GIPR-KO and GLP1R-KO animals whereas semaglutide was not effective in GLP1R-KO mice
DBT205	Rat	An Intravenous Glucose Tolerance Test was performed. A dose-dependent decrease in glucose AUC was observed; EC50 was 0.87 nmol/kg
ENDO127	Long-Evans rats, made obese and insulin-resistant by diet	A hyperinsulinaemic, euglycaemic clamp was performed. Tirzepatide markedly rduced the glucose infusion rate. Furthermore, 2-deoxyglucose uptake into muscle and adipose tissue was measured during the clamp. Tirzepatide increased glucose uptake.
ENDO128	C576/BL6 mice, made obese and insulin-resistant by diet	A hyperinsulinaemic, euglycaemic clamp was performed. Results were in line with the rat study ENDO127. Semaglutide was tested as comparator in the mouse study. Effects of semaglutide and tirzepatide were qualitatively similar; effect size was smaller with semaglutide, but the question remains whether comparable doses were tested.
ENDO129	DIO mice	Levels of glutamic acid, branched-chain amino acids and ketoacids were measured in plasma and brown adipose tissue (BAT). There was a tirzepatide-related increase of the amino acids in BAT and a decrease in plasma. The ketoacids decreased in plasma and were not tested in BAT.
DBT207; Publication Urva et al. (authors mostly Eli Lilly employees)	mice, normal and DIO	Acute and chronic effects of tirzepatide on gastric emptying in lean and obese mice were tested. Acute tirzepatide treatment dose-dependently inhibited gastric emptying. A pure GIP receptor agonist had no effect. After two weeks' treatment with tirzepatide, delay of gastric emptying was no longer observed.
DBT206	DIO mice	Effect of tirzepatide on body weight was studied. Semaglutide served as comparator. Tirzepatide and semaglutide hat qualitatively similar effects on body weight and food intake; the effect of tirzepatide was larger with the doses used.

ENDO126:
The In Vivo Effect of LY3298176 in Intraperitoneal Glucose Tolerance Test in Mice

An intraperitoneal glucose tolerance tests (ipGTT) were performed in normal C57Bl/6 mice as well as in mice lacking the GIP receptor or the GLP-1 receptor to demonstrate that LY3298176 improved glucose tolerance by acting through both the GIP and GLP-1 receptors

In wild-type (WT) mice, tirzepatide dose-dependently lowered the blood glucose excursion after IP glucose administration. EC50 was 0.22 nmol/kg, see figure below.

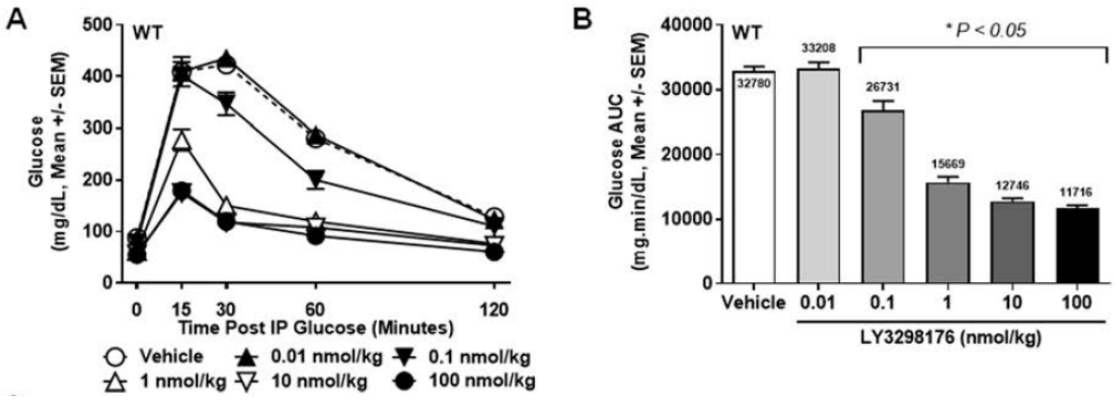


Figure 1: Effect of LY3298176 on glucose tolerance in an ipGTT in normal mice
Overnight-fasted, WT mice subcutaneously (SC) dosed with LY3298176 (17 to 18 hours prior to glucose) from 0.01 to 100 nmol/kg (0.048 to 480 µg/kg) were challenged with a 2 g/kg intraperitoneal dose of glucose. Blood glucose was recorded with glucometers from 0 to 120 minutes post glucose dose (A), followed by area under the curve analysis (AUC, B). Data are presented as mean ± SEM of 7 to 8 mice per group. p<.05 using one-way analysis of variance (ANOVA) and Dunnett's post hoc test versus vehicle (*).

In GIP receptor KO mice, tirzepatide (30 nmol/kg) also reduced glucose excursion in the IPGTT, essentially to the same extent as the same molar dose semaglutide, see figure below.

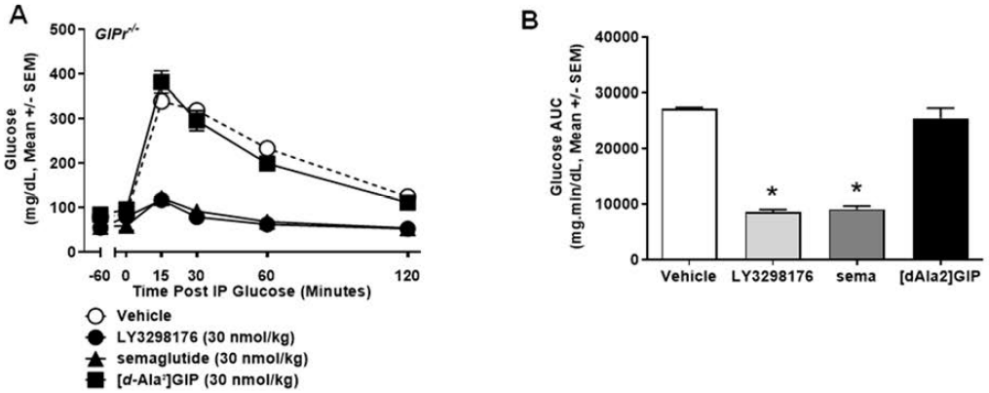


Figure 2: Effect of LY3298176 on glucose tolerance in an ipGTT in GIPR KO mice.
Overnight-fasted GIPr null mice (GIPr-/-) subcutaneously dosed with LY3298176 at 30 nmol/kg (144 µg/kg; 17 to 18 hours prior to glucose), semaglutide at 30 nmol/kg (123 µg/kg, 17 to 18 hours prior to glucose), or the DPP4-resistant GIP analogue [d-Ala2]GIP at 30 nmol/kg (1 hour prior to glucose), were challenged with a 2 g/kg intraperitoneal dose of glucose. Blood glucose was recorded with glucometers from 0 to 120 minutes post glucose dose (A), followed by area under the curve analysis (AUC, B). Data are presented as mean ± SEM of 5 mice per group. p<.05 using one-way analysis of variance (ANOVA) and Dunnett's post hoc test versus vehicle (*).

In GLP-1 receptor KO mice, tirzepatide reduced glucose excursion to nearly the same extent as a GIP receptor agonist ([dAla2]GIP). In contrast, semaglutide had no effect in these animals, see figure below.

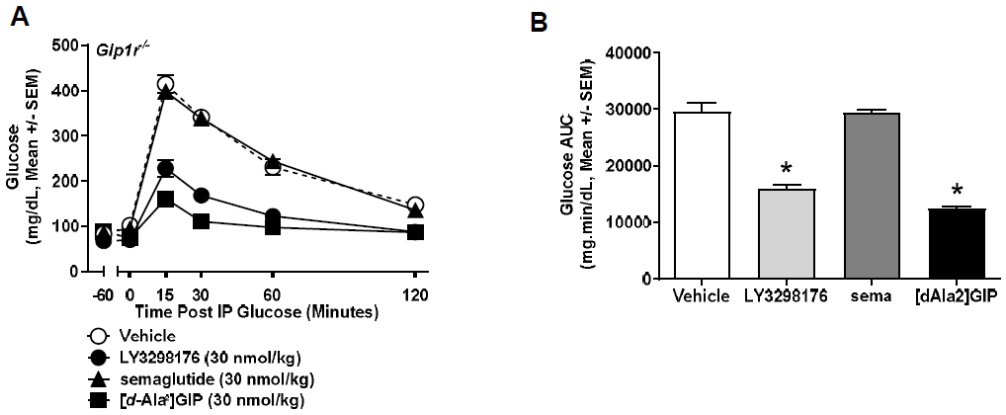


Figure 3 Effect of LY3298176 on glucose tolerance in an ipGTT in GLP-1R KO mice..
Overnight-fasted GLP-1 receptor null mice (Glp1r-/-) subcutaneously dosed with LY3298176 at 30 nmol/kg (144 µg/kg; 17 to 18 hours prior to glucose), semaglutide at 30 nmol/kg (123 µg/kg; 17 to 18 hours prior to glucose), or the DPP4-resistant GIP analogue [d-Ala2]GIP at 30 nmol/kg (1 hour prior to glucose), were challenged with a 2 g/kg intraperitoneal dose of glucose. Blood glucose was recorded with glucometers from 0 to 120 minutes post glucose dose (A), followed by area under the curve analysis (AUC, B). Data are presented as mean ± SEM of 5 mice per group. $p<.05$ using one-way analysis of variance (ANOVA) and Dunnett's post hoc test versus vehicle (*).

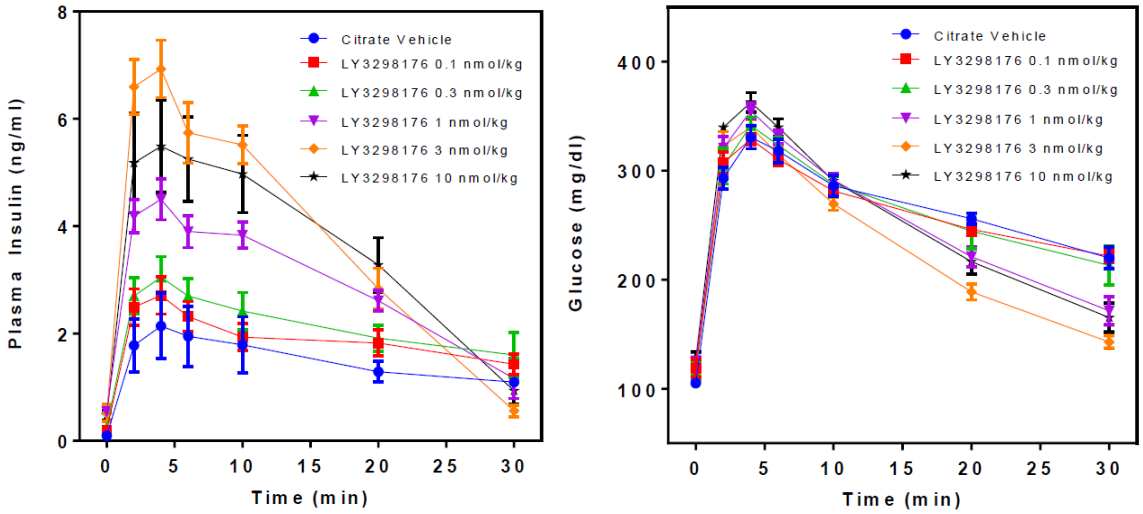
DBT205:

In Vivo Effect of LY3298176 on Insulin Secretion in Male Wistar Rats in an Intravenous Glucose Tolerance Test

In this study, LY3298176 was subcutaneously dosed to naïve male Wistar rats 16 hours prior to an intravenous glucose tolerance test (IVGTT), in order to determine its effect on insulin secretion.

Insulin secretion (upper figure) and glucose excursion (lower figure) were measured after IVGTT. Insulin liberation increased with increasing doses of tirzepatide (LY3298176). The maximal response was reached at a tirzepatide concentration of 3 nmol/kg (14.4 µg/kg).

Note that the effect of tirzepatide on glucose excursion (right panel) was markedly smaller than on insulin liberation (left panel) in this model. The applicant assumes that pentobarbital used for anaesthesia caused insulin resistance and hence prevented a major insulin effect on blood glucose level. As similar phenomenon was observed when using semaglutide instead of tirzepatide. Therefore, the reduced glucose response was not related to tirzepatide.



Figures 1and 3 from study report: Effect of LY3298176 on glucose stimulated insulin secretion (left) and blood glucose level (right) in vivo.

ENDO128:
Chronic Dosing of LY3298176 Improves Insulin Sensitization in an Insulin-Resistant Mouse Model

A similar study (ENDO127) was performed in rats. The results were in line with the results of Study ENDO128 presented below. Studies ENDO127 and ENDO128 were intended to investigate whether LY3298176 improves insulin sensitivity in an insulin resistant rat or mouse model.

In Study ENDO128, two euglycaemic clamp experiments were performed in the diet induced obese C57BL/6 mouse model to assess insulin sensitivity. First, body weight and glucose infusion rates needed to maintain glucose steady state were determined. A second experiment was executed to determine the insulin sensitization effects of LY3298176, semaglutide, or pair feeding at more closely matched body weight loss. Whole body glucose utilization, insulin-mediated effects on liver glucose production, and muscle and adipose tissue glucose uptake were measured.

The following doses were used in the two parts of the study:

Part 1
Vehicle: 40 mM Tris-HCl, pH = 8; 10 mL/kg.
Semaglutide: 10 nmol/kg (41 µg/kg)
LY3298176 (tirzepatide): 10nmol/kg (48 µg/kg)

Part 2
Vehicle: 40 mM Tris-HCl, pH 8; 5 mL/kg.
Semaglutide: 10 nmol/kg (41 µg/kg)
LY3298176 (tirzepatide): 3 nmol/kg (14.4 µg/kg)

Pair-fed group was matched to the food intake of the LY3298176 group.

The results in the two parts of the study were similar; therefore, data are only shown for the more extensive second part, which also included a semaglutide and a pair-fed group as controls.

The following figure shows food intake and development of body weight over 14 days in all groups of the second series of experiments. Reduction food intake was marked compared to control in all other groups

(reduction was forced in the pair-fed group). Accordingly, there was similar body weight reduction from baseline in all treatment groups. Only in the vehicle control group development of body weight was markedly different from the other groups (only slight reduction).

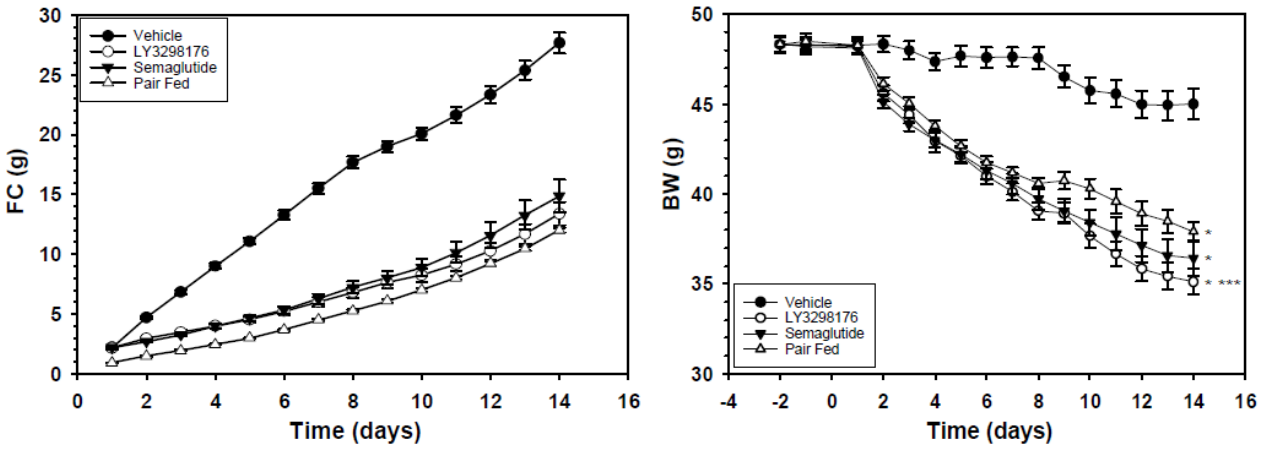


Figure 7: Cumulative food intake (left) and cumulative body weight (right) of diet-induced obese C576/BL6 mice treated with vehicle (n = 15), semaglutide (n = 14), LY3298176 (n = 15), or pair-feeding (n = 14). Abbreviations: BW = body weight, FC = food consumption. Data shown are mean ± standard error of the mean (SEM). Statistical analysis (*p<.05 versus vehicle, ***p<.05 LY3298176 versus pair-fed) was completed by Modified Krushal-Wallis test followed by Bonferroni adjustment for multiple comparisons.

Glucose uptake into muscle was increased by semaglutide and by tirzepatide compared to vehicle control. The effect of tirzepatide appeared stronger than that of semaglutide in both series of experiments; the results of the second series are shown in the figure below. Notably, in the first series of experiments (upper one of the following two figures) the effect of semaglutide and tirzepatide was nearly of the same magnitude. In contrast, in the second series (lower one of the following two figures) the semaglutide effect was rather weak compared to tirzepatide and was even numerically lower than the effect of pair-feeding (i.e. the effect of weight reduction alone).

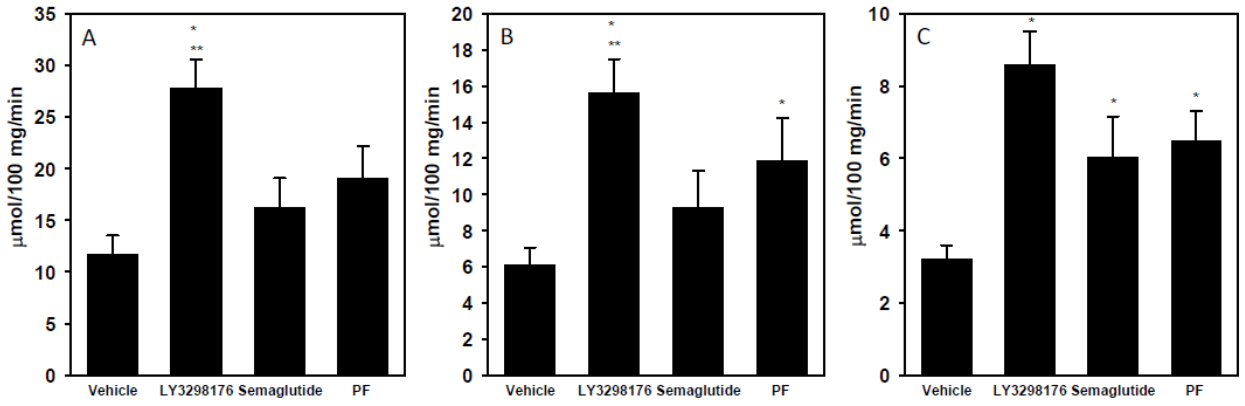


Figure 11: 2-deoxyglucose uptake in soleus muscle (A), red gastrocnemius muscle (B), and white gastrocnemius muscle (C) during an euglycaemic clamp in fasted diet-induced obese C576/BL6 mice treated with vehicle (n = 15), semaglutide (n = 14), LY3298176 (n = 15), or pair-feeding (n = 14). Abbreviation: PF = pair-fed. Data shown are mean ± standard error of the mean (SEM). Statistical analysis

(*p<.05 versus vehicle, **p<.05 LY3298176 versus semaglutide) was completed by Modified Krushal-Wallis test followed by Bonferroni adjustment for multiple comparisons.

According to the figure above, glucose uptake in response to semaglutide was similar to (or even lower than) that in pair-fed animals. This indicates that semaglutide has no direct effect on glucose uptake (only indirect, probably via improvement of insulin resistance). In contrast, tirzepatide increased glucose uptake above the level seen in pair-fed animals, arguing for a direct effect via the GIP receptor.

However, this finding was not consistent. In adipose tissue, glucose uptake tended to be higher in the semaglutide than in the pair-fed group (figure below). Furthermore, in the first set of experiments, there was no marked difference between tirzepatide and semaglutide in respect to effect size. A difference in effect size between the two compounds was only seen in the second set of experiments. Thus, the question remains whether there is indeed a fundamental, qualitative difference between the actions of tirzepatide and semaglutide (which could be due to GIP receptor activation by tirzepatide). The observed differences may also be gradual in nature (e.g. because the dose levels of semaglutide and tirzepatide were not equivalent) or due to random fluctuation.

The following figures shows the effect of the different treatments on glucose uptake into adipose tissue. The effect of semaglutide was consistently noticeably weaker than that of tirzepatide, but the semaglutide effect was numerically higher than the effect of weight loss alone (i.e. of pair-feeding).

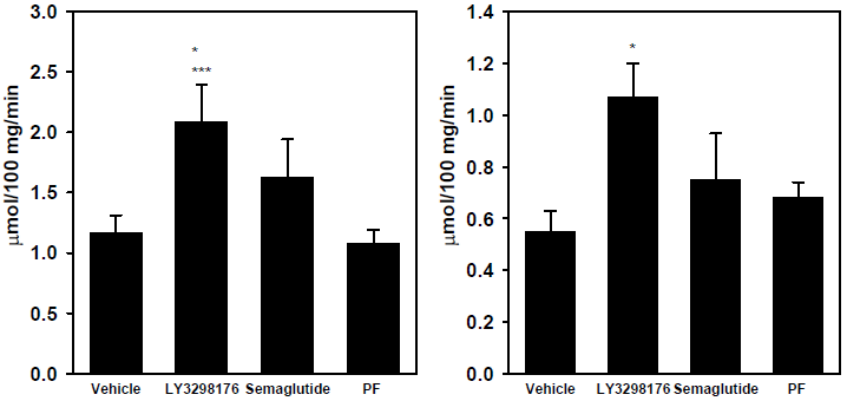


Figure 12: 2-deoxyglucose uptake in epididymal adipose tissue (left) and subcutaneous adipose tissue (right) during an euglycaemic clamp in fasted diet-induced obese C576/BL6 mice treated with vehicle (n = 15), semaglutide (n = 14), LY3298176 (n = 15), or pair-feeding (n = 14).
Abbreviation: PF = pair-fed. Data shown are mean ± standard error of the mean (SEM). Statistical analysis (*p<.05 versus vehicle, ***p<.05 LY3298176 versus pair-fed) was completed by Modified Krushal-Wallis test followed by Bonferroni adjustment for multiple comparisons.

Publication Urva et al.:
"The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists"; Diabetes Obes Metab. 2020;22:1886–1891

The GE effect of the long-acting dual GIP and GLP-1RA tirzepatide versus selective GLP-1RAs was investigated in non-clinical (and clinical) studies after repeated administration of the test compounds to Diet-

induced obese (DIO) mice. Gastric emptying was assessed by weighing residual gastric content at the given time-points after a semi-liquid diet.

Gastric emptying delay was assessed after acute single dosing as well as following chronic (ie, daily) treatment with semaglutide (1, 3 and 10 nmol/kg [4.1, 12.3 and 41 µg/kg]) or tirzepatide (1, 3 and 10 nmol/kg [4.8, 14.4 and 48 µg/kg]) for 14 days.

Tirzepatide and semaglutide, given as single dose, retarded gastric emptying in a clearly dose-dependent manner; the effect of semaglutide appeared somewhat stronger (panels A and B of the figure below). A GIP receptor agonist did not affect gastric emptying (panel C). The results of repeated administration of three doses of semaglutide and tirzepatide, respectively, is shown in panel E. After daily administration for 14 days, an effect of the two compounds on gastric emptying no longer was detectable.

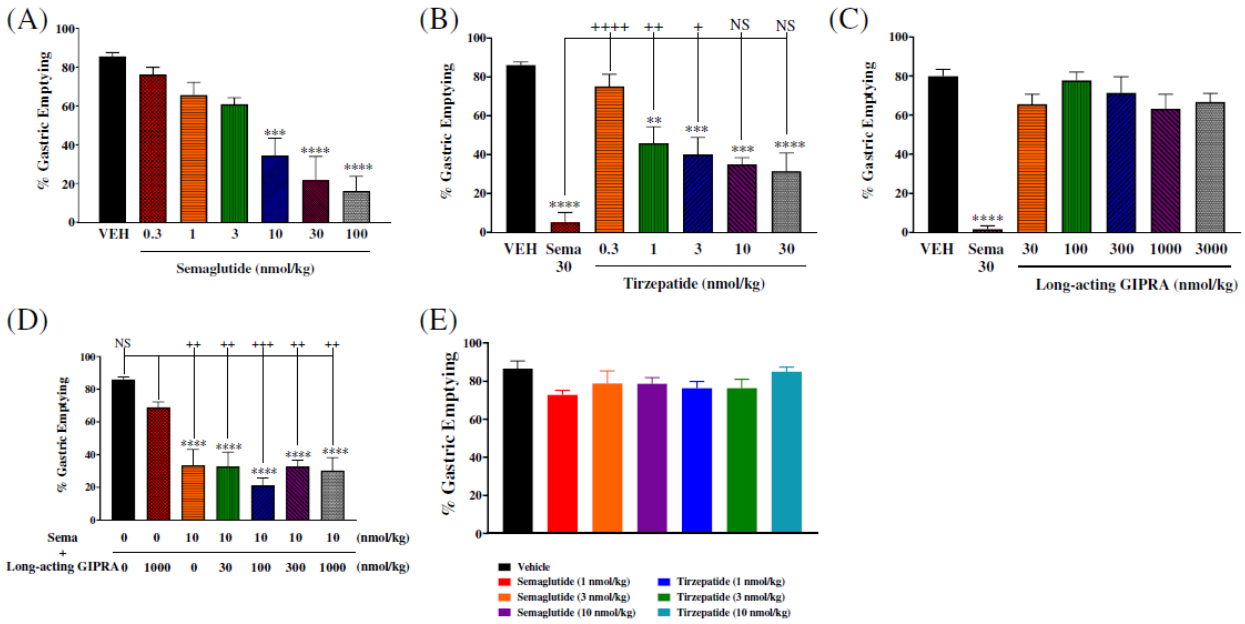


FIGURE 1 Effect of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) on gastric emptying (GE) in mice.
Data presented as mean ± SE of five mice per group. A, Effect of semaglutide on GE. B, Effect of tirzepatide on GE. C, Effect of long-acting GIPRA on GE. D, Impact of ascending doses of long-acting GIPRA, combined with a fixed dose of semaglutide, on GLP-1-induced GE. E, Effect of chronic treatment with semaglutide or tirzepatide on GE. +P <0.05, ++P ≤0.01, +++P ≤0.001 and ++++P ≤0.0001 versus semaglutide; *P<0.05, **P ≤0.01, ***P ≤0.001 and ****P ≤0.0001 versus vehicle (VEH). Sema, semaglutide

Obviously there is no information of tirzepatide's effect on gastrointestinal transit time although altered intestinal transit time also could affect absorption of concomitantly taken drugs.

2.5.2.2. Secondary pharmacodynamic studies

The following study was performed on secondary PD aspects

Study ID	Test system	Main results

QSB24	HEK293 cells expressing human GLP2 receptors	EC50 for cAMP production of tirzepatide was 249 nM on the human GLP2 receptor

QSB24:

In-Vitro Functional Activity of LY3298176 on Human and Mouse GIP, Human GLP-1, Human GLP-2, and Human Glucagon Receptors

The glucose-dependent insulinotropic peptide receptor (GIP-R), glucagon-like peptide-1 receptor (GLP-1R), glucagon-like peptide-2 receptor (GLP-2R), and glucagon receptor (GlucR or GCGR) activate adenylyl cyclase resulting in elevated intracellular cAMP. These studies were conducted to determine the potency of LY3298176 for activation of human GIP-R, human GLP-1R, human GLP-2R, and human GCGR by measuring elevation of intracellular cAMP in cell lines expressing these cloned receptors.

The following two tables provide the EC50 and Emax values of tirzepatide compared to the respective endogenous ligands on the human glucagon and GLP-2 receptor; GIP receptor and GLP-1 receptor are also included for comparison. Tirzepatide had no detectable affinity at the glucagon receptor and only low affinity at the GLP-2 receptor.

Table 1: Functional Potency (EC50) for LY3298176 and Comparator Compounds

Serial No.	Human GIP-R		Human GLP-1R		Human GCGR	
	EC50, nM ± SEM (n)	Emax,%	EC50, nM ± SEM (n)	Emax, %	EC50, nM ± SEM, (n)	Emax, %
LY3298176	11.0 ± 0.9 (17)	97.9 ± 3.0	71.2 ± 7.2 (17)	85.2 ± 4.4	>1000 (13)	ND
Human GLP-1(7-36)NH2	-		0.176 ± 0.015 (17)	102 ± 2		
Human GIP(1-42)NH2	0.135 ± 0.010 (17)	100 ± 1				
Human Glucagon					0.0208 ± 0.0024 (13)	115 ± 2

Means for EC50 are expressed as Geometric means ± standard error of the mean (SEM) with the number of replicates (n) indicated in parenthesis.
Means for Emax are expressed as the arithmetic mean ± standard error.

Table 2: Functional Potency (EC50) for LY3298176 and Comparator Compound at Human GLP-2R

	EC50, nM ± SEM (n)	Emax,%
LY3298176	249 ±6 (4)	96.5 ± 1.9
Human GLP-2(1-33)OH	0.0114 ± 0.0009 (4)	100 ± 0

Experiments measuring cAMP formation instead of binding yielded similar results.

2.5.2.3. Safety pharmacology programme

The following safety pharmacology studies were performed:

Study ID	Test system	Main results

8323700	instrumented male cynomolgus monkeys	No changes in QTc; increased HR (up to 23%); increase in diastolic BP (up to 11%); systolic BP unchanged
180917.FMD	HEK cells expressing hERG	hERG inhibition at 30 µM and 300 µM tirzepatide close to control level

ECG measurements were also obtained within the frame of the monkey repeated-dose toxicology studies 8325823 and 8336517.

Neurological and respiratory examinations as well as body temperature measurement were done within the frame of the one-month repeated-dose toxicology study in monkeys (8325823). No relevant findings were made. A tirzepatide increase in heart rate was observed, in line with the findings of Study 8323700.

Study 8323700:
Cardiovascular Safety Pharmacology Evaluation of LY3298176 Administered by Subcutaneous Injection to Male Telemetry-Instrumented Conscious Nonhuman Primates

Heart rate (HR)

LY3298176-related increases in heart rate and decreases in dP/dtmax occurred in animals given ≥0.05 mg/kg.

In animals given 0.15 mg/kg, overall LSMeans of HR for 1 to 6, 21 to 31, and 45 to 55 hours post-dose were higher by 14, 19, and 11 bpm (12, 16, and 10%), respectively, compared with control.

In animals given 0.05 mg/kg, HR was also increased 1 hour post-dose and for the overall mean 45 to 55 hours post-dose.

Blood pressure (BP)

Administration of LY3298176 was associated with increased diastolic and mean arterial pressure and decreased pulse pressure in animals given 0.15 mg/kg. No compound-related effect on systolic pressure occurred.

For diastolic pressure, the overall LSMeans for 9 to 19 hours post-dose (first dark phase) and 57 to 67 hours post-dose (third dark phase) in animals given 0.15 mg/kg were 6 and 4 mmHg higher (8 and 6%) than control, respectively.

For mean arterial pressure, the overall LSMean for 9 to 19 hours post-dose in animals given 0.15 mg/kg was 5 mmHg higher (6%) than control.

ECG

No abnormal ECG waveforms or arrhythmias were attributed to administration of LY3298176 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

No studies on PD DDI were performed.

2.5.3. Pharmacokinetics

The following table provides an overview of the submitted PK studies and the main observations made.

Study ID	Test system / Species	Main results
Absorption		
8404127	Rat	Single-dose PK with radiolabelled tirzepatide SC. Intact tirzepatide had a plasma half-live of 9 h; Radioactivity in plasma had a half-life of 25.6 h and in blood of 57.2 h
8332485	Rabbit (female)	Single-dose PK, SC. PÜlasma half-life of tirzepatide was 44.9 h so that onne-weekly dosing was selected for rabbit DART studies
8301451 LO PK	Cynomolgus monkey	Single-dose PK, IV vs. SC. Bioavailability after SC administration was 83%
Distribution		
8404127	Rat; Sprague Dawley (not pigmented) and Long Evans (pigmented)	Quantitative whole-body autoradiography using C14-labelled tirzepatide; highest radioactivity levels were found at the injection site and in the kidneys
LY3298176-fu	In vitro protein binding	Fluorescent N- or C-labelled tirzepatide was used in a florescence polarization method. In monkeys, 99.15% were bound to plasma proteins; in rats 97.70% and in humans 99.06%
Metabolism		
8404-127ME	Bile duct-cannulated rats	C14-labelled tirzepatide was used. A total of 13 metabolites were identified in plasma, urine, bile or faeces from rats
8404128ME	Monkeys	C14-labelled tirzepatide was used. A total of 11 metabolites were identified in plasma, urine, or faeces from monkey. Eight of them were also found in rats. Native tirzepatide was the predominant form in the plasma of rats and monkeys
Excretion		
8404127	Bile duct-cannulated rats	C14-labelled tirzepatide was used. Excreted radioactivity was mainly found in bile and urine.
8404128	Monkeys	C14-labelled tirzepatide was used. Excreted radioactivity was mainly found in faeces and urine.
DDI		
XT195111	Human hepatic microsomes	Inhibition of CYP enzymes by tirzepatide was studied. No relevant CYP inhibition was detected
XT193106	Cultured human hepatocytes	CYP induction by tirzepatide was investigated at the level of mRNA expression and enzyme activity. Positive controls were included. Tirzepatide did not induce CYP enzymes
LY3298176 MATE1 and 2K Inh	HEK cells transfected with human transporter proteins	Inhibition of MATE1 and MATE2-K by tirzepatide was measured. No inhibition was observed in the presence of 0.1% human serum albumin (HSA)
LY3298176-2020TP-SLC-Inh	HEK cells transfected with human transporter proteins	Transporter of the OATP, OAT and OCT families were tested for inhibition by tirzepatide. In the presence of 0.1% HSA, a slight inhibition of OATP1B1 and OATP1B3 was observed. This was markedly reduced in the presence of 4% HSA (the physiologic concentration)
LY3298176-2020TP-BCRP-Pgp-In	HEK cells transfected with human transporter proteins	BCRP and MDR1 (=P-gp) were tested for inhibition by tirzepatide. In the presence of 0.1% HSA, no inhibition was detected.

TK was done in the repeated –dose toxicity studies and will be presented in the toxicology section

Methods: Determination of tirzepatide in plasma

Plasma samples were analyzed to determine tirzepatide concentrations using a liquid chromatography with tandem mass spectrometry (LC/MS) method. The LC/MS methods quantitated tirzepatide intact mass, which comprised the full-length peptide plus the acyl side chain. The methods used a protein precipitation extraction procedure with a high-performance liquid chromatography (HPLC)/exact mass spectrometry assay. Qualified LC/MS methods were used to support the single dose PK studies. The LC/MS methods were validated in mouse, rat, rabbit, and monkey plasma to support the GLP toxicology studies. The validated methods for all species were conducted by Q2 Solutions (Ithaca, New York). The table below provides the quantifiable range, precision, accuracy, and stability of the assays utilized in the determination of tirzepatide in plasma. Samples above the limit of quantitation were diluted and reanalyzed to yield results within the calibrated range. Incurred sample reanalysis (ISR) was conducted for mouse, rat, rabbit, and monkey studies and results indicated that the assay methods performed according to established ISR acceptance criteria. Samples were handled and analyzed within demonstrated stability parameters.

Results

Tirzepatide is injected subcutaneously. Therefore, the applicant has not conducted studies on the mechanisms of absorption. In the following descriptive PK/TK parameters after single-dose administration and after repeated administration (from tox studies) in different species are shown, after the first and the last tirzepatide administration to address changes in PK over time.

In mice (following table), no consistent differences in PK parameters between males and females were observed, At Day 176, compared to Day 1, AUC and Cmax were increased.

Table 2.6.4.8. Toxicokinetics of Tirzepatide in 001178-W (Wild Type) **Mice** Following Twice-Weekly Subcutaneous Administration of Tirzepatide at Doses of 1, 3, or 10 mg/kg in a Carcinogenicity Study for 26 Weeks

	1 mg/kg		3 mg/kg		10 mg/kg	
	Male	Female	Male	Female	Male	Female
Parameter	(N = 3)	(N = 3)	(N = 3)	(N = 3)	(N = 3)	(N = 3)
Day 1 Cmax (ng/mL)	3500	3880	13500	11400	41100	39900
SD Cmax (ng/mL)	612	206	624	321	5870	7740
AUC0-96hr (ng•hr/mL)	109000	102000	359000	332000	1220000	1140000
SEM AUC0-96 (ng•hr/mL)	11600	4530	12600	7700	39900	41600
Day 176 Cmax (ng/mL)	5270	5660	15500	18500	45700	53100
SD Cmax (ng/mL)	598	417	819	700	6990	2290
AUC0-96hr (ng•hr/mL)	166000	171000	484000	498000	1520000	1530000
SEM AUC0-96 (ng•hr/mL)	6280	4310	14600	6350	61200	51500

Note: Values represent three animals/sex/group/time point; PK parameters were generated from a composite analysis from sparse sampling to enable a complete plasma profile in the mice

PK parameters in rats, measures after administration of a single (radiolabelled) dose of 3 mg/kg tirzepatide are tabulated below.

Table 2.6.4.4. Pharmacokinetic Parameters of Tirzepatide in Male **Rats** Following a Single Subcutaneous Administration of [14C]Tirzepatide

Dose	3 mg/kg (133 µCi/kg)		
Parameter	Radioactivity in Blood	Radioactivity in Plasma	**Tirzepatide in Plasma**

Cmax (ng eq/g or ng/mL)	8340	16300	**19600**
Tmax (hr)	6.00	6.00	**6.00**
t1/2 (hr)	57.2	25.6	**9.03**
AUC0-t (ng-eq•hr/g or ng•hr/mL)	284000	551000	**477000**
AUC0-∞ (ng-eq•hr/g or ng•hr/mL)	285000	551000	**478000**

n=3 animals/time point

No consistent differences in Cmax and AUC at Day 1 and Day 176 are obvious. Accordingly, no consistent differences between males and females can be observed, see following table.

Table 2.6.4.9. Toxicokinetic Parameters of Tirzepatide in Sprague Dawley **Rats** Following Twice-Weekly Subcutaneous Administration of 0.5, 1.5, or 3 mg/kg Tirzepatide for 6 Months

	0.5 mg/kg		1.5 mg/kg		3 mg/kg	
	Male	Female	Male	Female	Male	Female
Parameter	(N = 3)	(N = 3a)	(N = 3)	(N = 3)	(N = 3)	(N = 3a)
Day 1 Cmax (ng/mL)	1130	1020	3610	3040	13800	5470
SD Cmax (ng/mL)	65.1	59.7	625	721	4000	839
AUC0-96hr (ng•hr/mL)	44400	33800	113000	92600	279000	173000
SEM AUC0-96hr (ng•hr/mL)	1790	1140	8680	4450	17000	10000
Day 176 Cmax (ng/mL)	1040	1310	3320	3950	5580	6980
SD Cmax (ng/mL)	89.5	45.1	605	749	1290	352
AUC0-96hr (ng•hr/mL)	45600	62300	128000	156000	257000	302000
SEM AUC0-96hr (ng•hr/mL)	2670	2870	7030	7270	11000	12500

a Values represent 3 animals/sex/group, except for 0.5 and 3 mg/kg females on Day 176 at the 4-hour postdose and predose collections, respectively, where N=2, due to outlier exclusions (excluded data were outside ±3 SD of other data in males and females collected at the same time point).

PK parameters were generated from a composite analysis from sparse sampling to enable a complete plasma profile in the rat.

PK parameters in monkeys (beyond Cmax and AUC) after a single-dose administration are tabulated below.

Table 2.6.4.6. Mean Pharmacokinetic Parameters of Tirzepatide in **Monkeys** Following a Single Intravenous or Subcutaneous Administration of Tirzepatide at 0.2 mg/kg

	Tmax (hr)	Cmax (ng/mL)	AUC0-∞ (ng•hr/mL)	t1/2 (hr)	CL or CL/F (mL/hr/kg)
Intravenous (N = 2)	NA	6410	333000	56	0.61
Subcutaneous (N = 2)	8	3090	276000	55	0.73

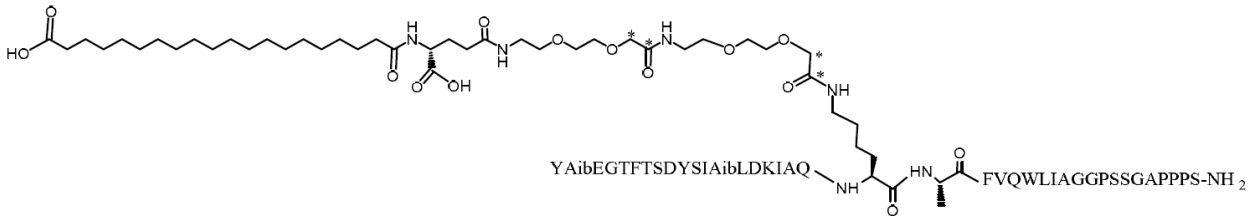
The following table shows AUC and Cmax after repeated administration. At Day 176, AUC and Cmax in general slightly higher (except for the high dose) than at Day 1. No consistent differences between males and female became obvious.

Table 2.6.4.13. Toxicokinetic Parameters of Tirzepatide in **Monkeys** Following Weekly Subcutaneous Administration of 0.05, 0.15, or 0.5 mg/kg Tirzepatide for 6 months

	0.05 mg/kg		0.15 mg/kg		0.5 mg/kg	
	Male	Female	Male	Female	Male	Female
Parameter	(N = 4)	(N = 4)	(N = 4)	(N = 4)	(N = 7)	(N = 7)
Day 1 Mean Cmax (ng/mL)	306	336	1140	1070	4590	4800
SD Cmax (ng/mL)	21.1	84.6	214	85.8	995	615
Mean AUC0-168hr (ng•hr/mL)	26200	28300	91100	86500	333000	340000

SD AUC0-168hr (ng•hr/mL)	2370	4420	11100	10200	45200	27700
Day 176 Mean Cmax (ng/mL)	389	438	1340	1210	4190	4580
SD Cmax (ng/mL)	15.0	128	250	42.4	605	1030
Mean AUC0-168hr (ng•hr/mL)	34000	34100	121000	102000	342000	331000
SD AUC0-168hr (ng•hr/mL)	3540	19300	18300	11200	19000	62000

For **distribution** studies, radiolabelled tirzepatide was used. The c14-labels were contained in the linker to the fatty acid side chain, see figure below.



* signifies the position of the [14C] radiolabel

Tissue distribution

Quantitative whole-body autoradiography (QWBA) was conducted to determine the tissue distribution of [14C]tirzepatide in male nonpigmented (Sprague Dawley) rats and male pigmented (Long Evans) rats following a single SC administration of 3 mg/kg of [14C]tirzepatide (report 8404127). Highest tissue exposure (AUC, Cmax) was observed in the kidneys (beside injection site). Accordingly, half life was rather long in the kidneys (46.6 h); a longer half-life was observed in brown fat (53.1 h). A remarkably long half–life was found in the uveal tract of the eye (147 h).

Plasma protein binding

The in vitro plasma protein binding of tirzepatide was determined in rat and monkey plasma by a florescence polarization (FP) method (Report LY3298176-fu). In the presence of a fixed 0.05 µM concentration of the fluorescent ligand, binding was measured over a range of protein concentrations (0.120 to 240 µM) for the following matrices: rat serum albumin, rat plasma, monkey serum albumin, and monkey plasma (table below). The protein binding of fluorescent-labeled tirzepatide in plasma was attributed to albumin.

Table 2.6.5.6. Plasma Protein Binding

	Rat plasma	Rat serum albumin	Monkey plasma	Monkey serum albumin	Human plasma	Human serum albumin	Human α1-acid glycoprotein
Protein concentration (µM)	0.1 to 200	0.02 to 50	0.07 to 150	0.02 to 40	0.12 to 250	0.01 to 20	NA
% binding	97.70 ± 0.22	99.68 ± 0.00	99.15 ± 0.34	99.76 ± 0.02	99.06 ± 0.28	99.77 ± 0.02	No binding

Tirzepatide concentration: 50 nM
Number of samples: 3/matrix human plasma: 6 samples)

In vivo metabolism of tirzepatide was evaluated following a single subcutaneous administration of 3 mg/kg [14C]tirzepatide to intact rats, bile duct-cannulated (BDC) rats (Report 8404-127ME), and a single subcutaneous administration of 0.5 mg/kg [14C]tirzepatide to intact monkeys (Report 8404128ME). The

table below summarizes the parent drug and metabolites detected in various matrices from rats and monkeys.

Table 2.6.4.15. Tirzepatide Metabolites Detected in Plasma, Urine, Bile, and Feces of Rats and Monkeys

Metabolite ID	Rat				Monkey		
	Plasma	Urine	Bile	Feces	Plasma	Urine	Feces
Tirzepatide	**X**	-	-	-	**X**	-	-
M1	**X**	-	**X**	-	**X**	-	-
M2	**X**	-	-	-	**X**	-	-
M3	**X**	-	-	-	**X**	-	-
M4	**X**	-	-	-	**X**	-	-
M5	-	-	**X**	-	-	**X**	**X**
M6	-	-	**X**	-	-	-	-
M7	-	-	**X**	-	-	-	-
M8	-	-	**X**	-	-	-	-
M9	-	-	**X**	-	-	-	-
M10	-	-	**X**	-	-	-	-
M11	-	**X**	-	-	-	**X**	**X**
M12	-	**X**	-	**X**	-	**X**	**X**
M13	**X**	-	-	-	**X**	-	-
M14	-	-	-	-	**X**	-	-
M15	-	-	-	-	-	**X**	-
M16	-	-	-	-	-	**X**	-

The structures of the metabolites found in rat and/or monkey plasma are depicted below. Metabolisation steps of tirzepatide include proteolytic cleavage, beta-oxidation, taurine conjugation, oxidation, amide hydrolysis, N-formylation, dehydrogenation and decarboxylation.

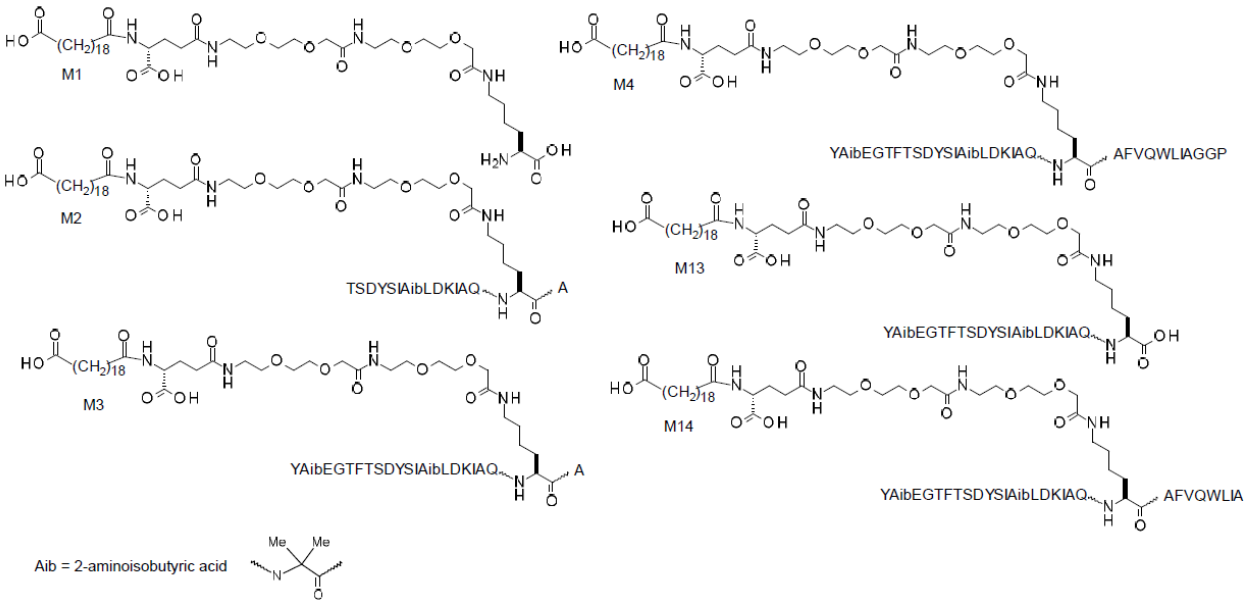


Figure 2.6.4.2. Plasma metabolites of tirzepatide in rats and monkeys.

Excretion profiles were determined in male intact and bile-duct cannulated (BDC) Sprague Dawley rats following a single subcutaneous dose of 3 mg/kg [14C]tirzepatide (Report 8404127). Total recovery of

radioactivity in both intact and BDC rats was complete by 336 hours. In intact and BDC rats, [14C]tirzepatide-related radioactivity was slowly excreted with measurable radioactivity out to 336 hours, however approximately 92% of the radioactive dose was recovered from 0-120 hours. In intact rats, the recovery of the administered radioactive dose was comparable between urine and feces, likewise in BDC rats, the amounts eliminated were comparable between urine and bile.

In male cynomolgus monkeys, the excretion profiles were determined following a single subcutaneous dose of 0.5 mg/kg [14C]tirzepatide (Report 8404128). [14C]Tirzepatide-related radioactivity was slowly excreted with measurable radioactivity out to 672 hours post-dose, however approximately 80% of the total radioactivity was recovered from 0-240 hours post-dose. The primary route of elimination for [14C]tirzepatide-related radioactivity was via urine, followed by faeces.

Potential **drug-drug interactions** (DDIs) via CYP enzymes and via drug transporters were addressed by the applicant in in-vitro studies using standard procedures. Inhibition and induction of CYP enzymes by tirzepatide was studied as well as inhibition of drug transporters. No relevant effects were found.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single-dose studies were performed.

2.5.4.2. Repeat dose toxicity

The repeated-dose studies performed are tabulated below). The pivotal 6-month studies are described in more detail after the table. The findings of the shorter studies were generally in line with the observations made in the 6-month studies.

Study ID	Species Animals per main group	Duration of study	Doses [mg/kg]	Main results
8376621	Mouse RasH2 10M, 10F	4 wk	0, 1 3, 30 twice weekly	Pilot study for the carcinogenicity study Body weight loss at all doses (despite supplementation of DietGel) Decreased corpora lutea; epithelial atrophy in the vagina Vacuolar degeneration of the X-zone of the adrenal cortex Decreased glycogen in the hepatocytes of males
8325822	Rat (Sprague Dawley) 10M, 10F	1 mo	0, 0.15, 0.5, 1.5 twice weekly	decreases in body weight decreased food consumption mildly lower serum calcium
8337876	Rat	6 mo; 4 wk recovery	0, 0.5, 1.5, 3 twice weekly	hunched posture decreases in mean body weight decreased food consumption mildly lower amylase activity in males Diffuse atrophy of the pancreas; zymogen depletion in acinar cells; decreased incidence of islet fibrosis Adipocyte atrophy in skin/subcutis

8325823	Monkey (cynomolgus) 3M, 3F	1 mo	0, 0.05, 0.15, 0.5 once weekly	Reduced food consumption, body weight loss; dehydration requiring intervention with SC fluid; increased HR in the dark phase (F); decreased volume of zymogen granules in the pancreas; adipose tissue atrophy
8336517	Monkey (cynomolgus) 4M, 4F	6 mo; 4 wk recovery	0, 0.05, 0.15, 0.5 mg/kg once weekly	Reduced food consumption and body weight gain; dehydration (intervention needed only in 1 high-dose animal); increased HR; decreased pancreatic zymogen granules in 2 high-dose females

The maximally tolerated dose in the repeated-dose (and other) toxicology studies was rather low in all species. Dose-limiting was dehydration and weight loss due to strongly decreased food and water intake of the animals. In mice and monkeys, tasty food and fluid supplementation was offered to increase fluid and caloric intake. In contrast to toxicology studies with other GLP1RAs, no dose up-titration was performed. The animals started with the nominal dose. This may have contributed to the poor condition of the animals (following reduced food and water intake) and to the need of food and fluid supplementation. This also has limited the maximally tolerated dose and hence the safety margin to human therapeutic exposure.

Study 8337876 (rat 6 mo, 4 wk recovery)

Male and female rats were assigned to four groups, and doses were administered as indicated in the following table. Animals were dosed via subcutaneous injection in the dorsal region twice weekly at a volume of 1 mL/kg. The vehicle control article was 10 mM tris, 150 mM sodium chloride (NaCl), and 0.02% Polysorbate 80, pH 7.0 ± 0.2.

		No. of Animals		Dose Level	Dose Concentration
Group	Subgroup	Male	Female	(mg LY3298176/ kg)	(mg LY3298176/mL)
1 (Control)	1 (Toxicity)	20	20	0	0
	2 (Toxicokinetic)	6	6	0	0
2 (Low)	1 (Toxicity)	15	15	0.5	0.5
	2 (Toxicokinetic)	18	18	0.5	0.5
3 (Mid)	1 (Toxicity)	15	15	1.5	1.5
	2 (Toxicokinetic)	18	18	1.5	1.5
4 (High)	1 (Toxicity)	20	20	3	3
	2 (Toxicokinetic)	18	18	3	3

Assessment of toxicity was based on mortality, clinical observations, body weights, body weight change, food consumption, ophthalmic observations, laboratory parameters (haematology, serum chemistry, coagulation, urine chemistry; calcitonin plasma levels were not determined) and macroscopic and microscopic pathology. Blood samples were collected for toxicokinetic evaluations and active drug assessment.

Mortality

Two males were sacrificed at an unscheduled interval. The moribund condition of these animals was considered not test article related. One male (Animal B56642) administered 1.5 mg/kg, was sacrificed on Day 71 because of limited use of the right front limb which was related to a bone fracture. One male (Animal

B56674) administered 3 mg/kg, was sacrificed in a moribund condition on Day 127 because of clinical observations attributed to spontaneous perforation of the aortic root.

Clinical signs

Appearance of hunched posture occurred in two males and seven females administered 3 mg/kg on Day 180. No other test article-related clinical observations occurred.

Body weight

Dose-dependent decreases in mean body weight, compared with control, were observed in animals administered ≥0.5 mg/kg. At the conclusion of the dosing phase, mean body weights were decreased by 21.6, 23.7, and 29.5%, for males, and 21.4, 23.8, and 23.8%, for females administered 0.5, 1.5, or 3 mg/kg, respectively, compared with final mean control body weights. During recovery, control males and females gained 82 and 66 grams, respectively during the course of the recovery phase while males and females previously administered 3 mg/kg LY3298176 gained 194 and 104 grams, respectively. At the conclusion of the recovery phase, mean body weights were decreased 4% for males and 16% for females administered 3 mg/kg compared with final mean control body weights.

Food consumption was decreased accordingly.

Laboratory findings

There were some minor effects of LY3298176 on laboratory parameters. They were no longer present at the end of the recovery phase. Effects included mildly lower amylase activity in males administered ≥1.5 mg/kg and females administered ≥0.5 mg/kg. Additional minor findings in rats administered ≥0.5 mg/kg included mildly lower absolute reticulocyte count, mildly lower total protein concentration (due to minimally to mildly lower albumin and/or globulin concentrations), and minimally to mildly lower total cholesterol and triglycerides concentrations

Organ weights

Test article-related changes in organ weight parameters were generally considered secondary to significant decreases in terminal body weights in animals administered LY3298176. No macroscopic findings were reported.

Microscopic findings

Test article-related microscopic findings at the terminal sacrifice were present in the **pancreas** (increased incidence of lobular atrophy in females administered ≥1.5 mg/kg; zymogen depletion in rats administered ≥0.5 mg/kg; diffuse atrophy in males administered ≥1.5 mg/kg and females administered ≥0.5 mg/kg; and decreased incidence of islet fibrosis and/or pigment in males administered ≥0.5 mg/kg); **spleen** (decreased incidence of extramedullary hematopoiesis (EMH) in rats administered ≥1.5 mg/kg, which correlated with decreased splenic weight parameters and lower absolute reticulocyte count in rats administered ≥0.5 mg/kg); **skin/subcutis** (increased incidence and/or severity of **adipocyte** atrophy in rats administered ≥0.5 mg/kg); **marrow** of the femur (decreased adipocytes in females administered ≥0.5 mg/kg and one male administered 3 mg/kg); **adrenal cortex** (decreased incidence and/or severity of vacuolation in males administered ≥1.5 mg/kg); and **heart** (decreased incidence of cardiomyopathy in males administered ≥1.5 mg/kg and females administered 3 mg/kg).

At the terminal sacrifice, increased incidence of lobular atrophy in the pancreas of females was a test article-related exacerbation of a background finding, with uncertain relationship to decreased terminal body weights

and/or decreased food consumption. All other microscopic findings were considered by the applicant secondary to decreased terminal body weights and/or decreased food consumption.

At the recovery sacrifice, no test article-related differences were noted in microscopic findings, except for persistence of lobular atrophy in the pancreas (females).

Study 8336517 (monkey 6 mo, 4 wk recovery)

Male and female cynomolgus monkeys were assigned to four groups, and doses were administered as indicated in the following table. Animals were dosed via subcutaneous injection once weekly for 26 weeks at a volume of 0.1 mL/kg. The vehicle control article was 10 mM tris, 150 mM sodium chloride (NaCl), and 0.02% Polysorbate 80, pH 7.0 ± 0.2.

	No. of Animals		Dose Level	Dose Concentration
	Male	Female	(mg LY3298176/kg)	(mg LY3298176/mL)
1 (Control)	7	7	0	0
2 (Low)	4	4	0.05	0.5
3 (Mid)	4	4	0.15	1.5
4 (High)	7	7	0.5	5

Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmic observations, electrocardiographic (ECG) measurements, laboratory parameters (haematology, serum chemistry, coagulation, urine chemistry; calcitonin plasma levels were not determined) and macroscopic and microscopic pathology. Blood samples were collected for toxicokinetic and active drug assessment evaluations.

Results

Mortality

All animals survived to their scheduled sacrifice.

Clinical signs

Dehydration was noted by technical staff on Day 12 in five males and one female administered 0.5 mg/kg, on Day 33 in two females administered 0.5 mg/kg, and on Day 33 and 34 in one male administered 0.15 mg/kg. A request for veterinary services was made for some of these occurrences. All groups were supplemented with fruit and other dietary options for the duration of the study to avoid dehydration and body weight loss as far as possible.

Body weight

Test article-related decreased body weights were observed for individual animals administered 0.5 mg/kg through the first 12 days of the dosing phase. Overall body weight gains were significantly lower for males administered ≥0.05 mg/kg and for females administered 0.5 mg/kg (non-significant). These decreases correlated with a higher incidence of low food consumption,

ECG

Administration of 0.15 or 0.5 mg/kg was associated with higher heart rates, primarily during the dark cycle (8 through 19 hours postdose), on all three occasions (Day 8, 78, or 169 of the dosing phase) where an ECG was obtained. Increase was 19 (18%) and 31 bpm (30%) in animals administered 0.15 or 0.5 mg/kg.

Laboratory findings

The only finding was mildly and transiently increased serum lipase activity on Day 15 of the dosing phase in two males administered 0.5 mg/kg. Otherwise no changes in haematology, coagulation or clinical chemistry were noted.

Organ weights

There was non-statistically significant trend toward decreased spleen weight parameters in males administered 0.15 or 0.5 mg/kg

No test-article-related macroscopic findings were made

Microscopic findings

At the terminal sacrifice, LY3298176-related microscopic findings were limited to the pancreas and consisted of minimally decreased zymogen granules in two females administered 0.5 mg/kg. This finding correlated with the increased frequency of low food consumption in females administered 0.5 mg/kg (compared with controls).

All other microscopic findings were considered by the applicant spontaneous and/or incidental because they occurred at a low incidence, were randomly distributed across groups (including concurrent controls), and/or their severity was as expected for cynomolgus monkeys of this age.

2.5.4.3. Genotoxicity

Tirzepatide a chemically synthesized peptide is not expected to interact directly with DNA. Therefore, according to ICH S6 [R1] a mutagenicity assessments (e.g. AMES) was not conducted.

In vivo tirzepatide was negative for clastogenic effects in a chromosome aberration test (micronuclei in bone marrow cells) in rats. The exposure (AUC) at the highest dose tested (3 mg/kg → MTD) corresponded approximately to the clinical exposure and no safety margin was established (SM ~ 1). Dose limiting effects on body weight and food consumption were consistent with, or secondary to, incretin pharmacology and effects reported with long acting GLP-1 receptor agonists.

In conclusion, tirzepatide did not exert any genotoxic potential based on the studies performed.

2.5.4.4. Carcinogenicity

Carcinogenicity testing of tirzepatide was carried out in a 2-year study in Crl:CD(SD) rats and a 6 month study in hemizygous Tg.rasH2 mice [CByB6F1-Tg(HRAS)2Jic (+/-hemizygous c-Ha-ras)] in compliance with GLP.

As observed in the toxicology studies in rodents, in both carcinogenicity studies dose-limiting effects on body weight and food consumption were consistent with, or secondary to, exaggerated incretin pharmacology and effects reported with long acting GLP-1 receptor agonists. No other signs of direct target organ toxicity or off-

target effects were observed in mice. In rats dose dependent mild to severe unilaterally and bilaterally focal C-cell hyperplasia in the thyroid was considered as a pre-neoplastic lesion and is consistent with findings reported for GLP-1 receptor agonists.

Tirzepatide was not carcinogenic in a short-term carcinogenicity study in mice at exposures 12 x above expected clinical exposures. Neoplasms that occurred in control and tirzepatide treated groups represented the types commonly reported and representative of the spontaneous, background findings observed for the RasH2 mouse model in 6-months studies.

In the long-term carcinogenicity study in rats, tirzepatide showed an increase in C-cell adenomas in all dose groups and C-cell carcinomas in the high dose groups in rodents at exposures comparable to clinical exposure (MoE ~ 1 x) without mortality up to the end of the study. The increase in C-cell hyperplasia/neoplasia is known for other long-acting GLP-1 receptor agonists (liraglutide, dulaglutide, semaglutide) and presumably rodent specific. Particularly for tirzepatide a relevance for humans cannot be ruled out since in contrast to "pure" GLP-1 receptor agonists tirzepatide caused an increase in serum calcitonin in humans (see clinical section). All other neoplasms that occurred in control and tirzepatide treated groups represented the types commonly reported and representative of the spontaneous, background findings observed for rats in a lifespan two year study.

2.5.4.5. Reproductive and developmental toxicity

In the rat, male fertility and early embryonic development study there were no effects on sperm parameters, reproductive performance, male reproductive organs, or early embryonic survival. In the rat female fertility and early embryonic development study, numbers of corpora lutea were decreased, resulting in decreased numbers of implantation sites and viable embryos. Estrous cycles were also disrupted. These effects were considered secondary to the decreased body weight and food consumption, noted at all dose levels. Similar effects were reported with long acting GLP-1 receptor agonists. There were no effects on mating, conception and fertility indices, pre-coital intervals, or implantation loss.

In embryo-fetal development (EFD) studies with both rats and rabbits, tirzepatide caused pharmacology related effects on body weight, body weight gain, and/or food consumption in both rats and rabbits.

At the high dose of 0.5 mg/kg (rat) and 0.1 mg/kg (rabbit), the maternal toxicity was significant and included clinical signs and sustained maternal body weight decreases, decreased body weight gain and food consumption. Increased incidences of malformations and developmental variations at 0.5 mg/kg in the rat were considered secondary to the lower mean fetal body weights at this dose level, which is seen in a consense to the maternal bodyweight decreases. Effects on fetal morphology, including increased numbers of malformations, have already been reported for other long-acting GLP-1 receptor agonist class. Overall, it can be concluded that the developmental and reproductive effects occurred only at doses associated with maternal toxicity. In the rat pre-/postnatal study maternal systemic toxicity based on effects on body weight, body weight gain, and food consumption was seen at 0.25 mg/kg. In the offspring body weight and body weight gain for F1 males at 0.25 mg/kg was also negatively affected. Exposure and distribution in the milk of lactating rats was not investigated. A safety margin to the human exposure at therapeutic dose levels was not calculated.

The effects in the rat juvenile toxicity study were the same/similar (pharmacology related effects on body weight, body weight gain, and/or food consumption) as in the toxicity studies with adult animals. Delays in the attainment of balanopreputial separation and vaginal patency at 0.5 and 1.5 mg/kg were considered secondary to the decreased body weight, which is an effect of tirzepatide.

Exposures at the NOAEL of all studies performed for reproductive and juvenile toxicity were in general below exposures at the MRHD. Accordingly, there are no safety margins to the human exposure at therapeutic dose levels in all studies.

The findings in the fertility and embryo-fetal development studies as well as in the rat pre-/postnatal study are described in the SmPC.

2.5.4.6. Toxicokinetic data

TK data were obtained in all larger toxicology studies. The results, sorted by species and dose, are tabulated below. The low doses (<1 mg/kg) given to rats are of little toxicological relevance and were omitted for clarity.

	Mice				**Rats**			
Dose (mg/kg)	**Cmax**		**AUC**		**Cmax**		**AUC**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
1	5400	6290	164000	179000				
1	5270	5660	166000	171000				
1.5					3320	3950	128000	156000
1.5					4730		145000	
1.5						4560		129000
1.5					5130	5330	145000	133000
1.5					4290	5220	124000	143000
1.5					3060	3370	130000	159000
3	16100	23500	476000	510000				
3	15500	18500	484000	498000				
3					5580	6980	257000	302000
3					9110		241000	
3						9340		269000
10	45700	53100	1520000	1530000				
30	217000	252000	4860000	5470000				

	Monkeys				**Rabbits**	
Dose (mg/kg)	**Cmax**		**AUC**		**Cmax**	**AUC**
	M	**F**	**M**	**F**	**F**	**F**
0.01					46.6	3560
0.02						
0.03					159	14700
0.05	389	438	34000	34100		
0.05	459	468	27600	39000		
0.1						
0.1					567	56400
0.15	1340	1210	121000	102000		
0.15						
0.15						
0.15						
0.15	1210	1510	105000	124000		
0.5						
0.5	4190	4580	342000	331000		
0.5						
0.5						
0.5	5230	4600	427000	421000		

The exposure multiples (based on AUC) to human therapeutic exposure are tabulated below for the highest dose used in each toxicology study. Since the dosing interval was different between animals and humans, the applicant calculated an average plasma level (C_{ave}) to allow comparison. C_{ave} was obtained by dividing the AUC in the dosing interval (AUC(0-τ)) by the interval τ.

The table below shows only the highest doses of each toxicology study for brevity. The main toxic effects were due to exaggerated pharmacodynamics, i.e. reduced water/food consumption and body weight loss so that a clear NOAEL cannot be derived. Even at the highest doses given, the exposure multiples were low in most cases. In the embryo-foetal studies they were markedly below one.

Table 2.4.2 of NCO (shortened) Exposure Multiples for Subcutaneous Administration of Tirzepatide in Pivotal Toxicology Studies

Species, Dose	**AUC0-τ, steady-state (ng•hr/mL)**	**Multiple**
Human 15 mg/week	250000[a]	–
Repeat-Dose Toxicology		
4-Week 001178-WT Mouse (Study 8376621)[b,c]		
30 mg/kg/twice weekly	5165000	36.16
1-Month Rat (Study 8325822)		
1.5 mg/kg/twice weekly[d]	133500	0.93
6-Month Rat (Study 8337876)		
3 mg/kg/twice weekly[d]	279500	1.96
1-Month Monkey (Study 8325823)		
0.5 mg/kg/weekly[d]	424000	1.70
6-Month Monkey (Study 8336517)		
0.5 mg/kg/weekly[d]	336500	1.35
Carcinogenicity		
26-Week Transgenic Mouse (Study 8392063)		
10 mg/kg/twice weekly	1520000	10.64
104-Week Rat (Study 8392734)		
1.5 mg/kg/twice weekly	145000	1.02
Reproductive and Developmental Toxicology		
Rat Male Fertility (Study 00353430)		
3 mg/kg/twice weekly	241000	2.25
Rat Female Fertility (Study WIL-353356)		
3 mg/kg/twice weekly	269000	1.88
Rat Embryo/Fetal Development (Study WIL-353354)		
0.5 mg/kg/every 3 days	35800	0.45
Rabbit Embryo/Fetal Development (Study WIL-353355)		
0.1 mg/kg/weekly	56400	0.23

a The human dose shown is the highest clinical dose. Plasma PK parameters shown were computed based on the PK modelpredicted tirzepatide concentration-time profile (simulations using distribution of baseline body weight, baseline BMI, and sex from patients with T2DM in the population PK analysis dataset. Simulation mean body weight = 89.6 kg) (Pop PK Report).

2.5.4.7. Local Tolerance

N/A

2.5.4.8. Other toxicity studies

Phototoxicity

For tirzepatide, a protein, the ICH S10 does not generally apply. Tirzepatide absorbed light at approximately 280 nm that exhibits a spectral pattern that is typical for proteins and peptides and consistent with the known absorbance spectrum of proteins. Therefore, phototoxicity studies with tirzepatide were not conducted.

2.5.5. Ecotoxicity/environmental risk assessment

The ERA provided is considered complete and acceptable. No ERA studies are required with respect to the chemical nature of the molecule. Tirzepatide is administered in parenteral form and has been described to be not excreted in unchanged form (m1.6, m2.5, m5.3). It consists of 39 amino acids, two of them non-coded (aminoisobutyric acid, Aib in positions 2 and 13). The backbone of the peptide contains 2 methylated amid bonds, which are protected from cleavage by standard metabolic peptidases. However, the remaining amid-bonds are susceptible to peptidase activity. Therefore, the peptide part is not expected to pose a risk to the environment. Also, the 1,20-eicosanedioic acid moiety are identical to naturally occurring substances. The fate of the linker (γ-Glu and two 8-amino-3,6-dioxaoctanoic acid moieties) is not known.

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

2.5.6. Discussion on non-clinical aspects

PD

Tirzepatide was developed as a long-acting agonist at the human GLP-1 and GIP receptor PD studies were performed in vitro and in vivo to substantiate the claimed actions. Furthermore, it was demonstrated that tirzepatide also binds to the GLP-1 and GIP receptor of the animal species used in PD and toxicology studies (mouse, rat, monkey, rabbit).

In line with the mechanism that prolongs the duration of action, i.e. binding to albumin, tirzepatide's affinity towards its receptors in vitro was strongly affected by the presence of albumin. Presence of bovine serum albumin (BSA) reduced receptor affinity by around two orders of magnitude (range, 95- to 172-fold) across species and receptor type (GIPR and GLP-1R); for rodent GIPR no data are available.

The in vitro activity at the GIP receptor was clearly lower in rodents than in humans and monkey. In presence of bovine serum albumin (considered to be most relevant for the in vivo situation) the binding affinity for rat GIPR, K_i, was 96-fold higher (386 nM vs 4.02 nM) than for human GIPR. For the mouse, the difference was even higher. If this finding is true (see above), this would mean in consequence that the contribution of GIPR in in vivo studies in the rat and mouse safety studies is uncertain, in particular since the pharmacological effect on food consumption and body weight limited the exposure in these studies. The applicant argued that the measurement of affinity in presence of albumin is uncertain, and that evidence from in vivo studies is more relevant. In particular, it was referred to the studies in knock-out mice with deletion of the GLP-1 receptor. The respective findings are discussed further below.

Receptor activation was studied in vitro by measuring cAMP formation in HEK293 cells artificially overexpressing GIPR or GLP-1R. In this model, the amount of expressed receptor strongly affected EC50 (decreasing EC50 with increasing receptor density). The applicant explained this phenomenon with the presence of spare receptors. In this case, activation of a small fraction of receptors is sufficient to elicit the

maximal response, and EC50 no longer corresponds to receptor affinity. It is not known whether the presence of a large fraction of spare receptors reflects the situation in vivo or whether it is only due to the artificial overexpression.

Activation of the GLP-1 receptor is expected to enhance glucose-induced insulin secretion like established pure GLP-1 receptor agonists such as exenatide, liraglutide and semaglutide do. Therefore, in many in vivo PD studies the tirzepatide effect was compared to the effect of semaglutide. Furthermore, GLP-1 receptor agonists (RAs) reduce food intake and body weight, probably mainly by direct action on certain brain areas.

Due to this mechanism of action, the applicant studied insulin secretion and related parameters in vitro (primary cultured islets) and in vivo (glucose clamp studies, glucose uptake in vivo, food consumption etc.). Most studies were performed in animal models of diabetes and obesity, predominantly in diet-induced-obesity (DIO) mice or rats. Tirzepatide and the comparator semaglutide (if present) showed the expected effects on glucose-induced insulin secretion, food intake and body weight. In one study, the applicant also employed pair-feeding (i.e. in an untreated group food was restricted to the amount which was consumed by the tirzepatide-treated group). By this means, it was possible to distinguish direct effects of tirzepatide and semaglutide on glucose control from indirect effects of weight loss. In most cases the effect size of semaglutide was smaller than that of tirzepatide, but it is unclear whether the semaglutide dose was appropriate. In some experiments, the applicant has studied the effect of ascending semaglutide doses, but a maximally effective dose could not consistently be established. Thus, it remains unclear whether the maximal size of the semaglutide effect was reached in all studies.

As tirzepatide acts as an agonist not only on the GLP-1 but also on the GIP receptors, actions beyond the known GLP-1 receptor mediated effects would be expected. Beside insulin secretion, GIP is known to affect glucagon liberation and adipose tissue metabolism. In order to demonstrate GIP receptor activation by tirzepatide in vivo, the applicant conducted studies with animals lacking the GIP receptor (GIP receptor knock-out [KO] mice). For comparison, GLP-1 receptor KO mice were also studied in parallel. It turned out that tirzepatide had similar effects in GIP receptor KO and wild-type animals. This indicates that in the presence of the GLP-1 receptor the GIP receptor has only minor metabolic effects. GIP receptor effects became obvious in GLP-1 receptor KO mice. The GIP receptor effects in GLP-1 receptor KO mice effects were qualitatively similar to the known GLP-1 receptor effects but required somewhat higher tirzepatide doses. This indicates that GIP receptors can substitute for GLP-1 receptors if the latter are absent.

However, the applicant could not clearly demonstrate a metabolic effect of GIP receptor activation in wild-type animals. As mentioned above, the effects of semaglutide were quantitatively smaller than the effects of tirzepatide in the metabolism studies (which may depend on the doses used), but a clear qualitative difference between tirzepatide and semaglutide could not be demonstrated in vivo. In vitro, Tirzepatide, like GIP, caused cAMP production and lipolysis in cultured adipocytes after single administration. A pure GLP-1 RA was not tested in this setting.

In respect to the lack of a clear GIP-receptor-dependent component of the tirzepatide effect in vivo, it is important that the applicant also has conducted extensive studies on β-arrestin binding and internalisation of the GLP-1 and GIP receptors in vitro. By this internalisation process, triggered by binding of the receptor to β-arrestin, the receptor disappears from the cell surface and therefore becomes inactive, as it no longer can react to extracellular GLP-1 or GIP. It turned out that tirzepatide, in contrast to the endogenous ligand, did not inactivate the GLP-1 receptor after prolonged stimulation. A similar effect was reported for other therapeutic GLP-1 RAs; this probably is the mechanistic basis for the fact that GLP-1 RAs remain effective despite their permanent presence in the body during therapy. However, the GIP receptor rapidly became internalised after tirzepatide binding as it became after binding of the endogenous ligand GIP. This is a strong

hint that in case of chronic tirzepatide administration the GIP receptor becomes down-regulated so that GIP-receptor-mediated effects may not play a role in the intended long-term therapy with tirzepatide.

Taken together, there was no clear evidence for GIP-mediated effects in most rodent studies. This could be related to GIP receptor down-regulation. Alternatively, tirzepatide could have a low affinity to rodent GIP receptors.

As further discussed in other sections, the tirzepatide effects (desired and undesired) observed in clinical trials also were highly similar to the known effects of pure GLP-1 RAs. The only salient difference in respect to safety was that tirzepatide, unlike pure GLP-1 RAs, increased serum calcitonin levels in humans. This to date was only known from rodents (see toxicology section below).

Another known effect of GLP-1 RAs is the delay of gastric emptying. This may cause drug-drug interactions (DDIs) by delaying the absorption of concomitantly administered substances. However, the applicant demonstrated in animals that gastric emptying is affected by tirzepatide only for a short period of time immediately after start of treatment. Thus, the potential for DDIs would be transient. Furthermore, effects of gastric emptying on drug absorption can be modelled fairly well. On the other hand, tirzepatide may not only gastric emptying but also motility of the small intestine. This may lead to more complex DDIs which most likely are not easy to model because the factors affecting intestinal absorption of a drug are difficult to measure so that the model cannot be informed. The applicant pointed out that tirzepatide's effects on GI motility (gastric emptying and intestinal transit) most likely are related to its GLP1R agonistic effects and hence are similar to the effects of pure GLP-1RAs. No studies on the effect of tirzepatide on intestinal transit time were performed. Such data – as they are difficult to obtain – were only reported for liraglutide in the published literature. Thus, in respect to GI-related DDIs, data from pure GLP-1RAs probably can be transferred to tirzepatide.

PK

The applicant has performed a somewhat reduced PK programme since tirzepatide is a (modified) peptide. Tirzepatide consists of a peptide chain of 39 amino acids, including two non-natural amino acids (aminoisobutyric acid Aib) and a fatty acid side chain, attached to the peptide chain via a linker which in part resembles polyethylene glycol.

Due to the SC way of administration, studies on the mechanism of absorption were not needed. And since tirzepatide is not a substrate for CYP enzymes or drug transporters, the effect of CYP inhibitors/inducers and transporter inhibitors on tirzepatide metabolism were not studied.

Distribution was studies with radiolabelled tirzepatide whereby the label was attached to the linker. The highest levels of radioactivity were found at the Injection sites and in kidneys.

Despite being a peptide, extensive metabolism studies were performed with tirzepatide, primarily to follow the fate of the linker region of the molecule, which is a non-natural compound. The peptide chain and the fatty acid of tirzepatide were degraded like endogenous peptides and fatty acids, respectively, by proteolytic cleavage and beta-oxidation.

No circulating metabolites representing >10% of the total radioactive drug-related exposure were observed in rats, monkeys, or humans. All human plasma metabolites were identified in rat and monkey plasma.

Tirzepatide did not inhibit or induce CYP enzymes and did not inhibit drug transporters.

Taken together, PK of tirzepatide does not give rise to concerns.

Since tirzepatide is intended to be used chronically in humans, a rather constant plasma level is intended. Hence the applicant reported steady-state concentrations (Css) from human repeated-dose studies whereas in animal studies usually AUC(0-t) was reported. Thus, comparison of human and animal exposure is difficult, also because of the different dosing intervals (τ). To circumvent this problem, the applicant calculated average plasma levels in animals in humans by dividing AUC(0-τ) by τ. This approach is considered suitable.

Toxicology

The most prominent finding in the repeated-dose studies was a pronounced reduction in weight gain or even weight loss in the tirzepatide-treated groups of all species tested. This was obviously due to reduced food intake. There were accompanying macroscopic and microscopic findings e.g. atrophy of adipose tissue and thymus as well as changes in organ weights. The applicant assumes that all these changes are secondary to the weight loss. This is most likely true for the adipose tissue atrophy, but in other organs, it cannot fully be excluded that the massive weight loss and its sequels have masked some direct toxic effects.

A problem of this exaggerated pharmacodynamic effect was that the maximally tolerated dose was low. Not only reduced food intake but also reduced water intake reduced survival and thereby was dose-limiting. The applicant took efforts to increase food and water intake of the animals by offering tasty food and beverage (fruit juice) or a special commercial DietGel intended for use in animals of poor condition to increase water and caloric intake.

Nevertheless, the exposure resulting from highest tolerated doses in the repeated-dose, reproductive and carcinogenicity studies were not far above the human therapeutic exposure. This limits the value of the toxicology studies for predicting human safety. Higher exposures were reached with authorised pure GLP-1 RAs. This could be because slow dose up-titration at the start of treatment was performed in the repeated-dose studies, as it is done in human therapy. It is known from human studies that immediate administration of therapeutic GLP-1 RA doses leads to strong nausea and other gastrointestinal (GI) symptoms. Less severe symptoms occur upon slow dose up-titration. At least in this case the undesired GI symptoms largely disappear after a few weeks. It can be expected that similar GI symptoms are responsible for the strongly reduced food intake in the toxicology studies. One can assume that also the strong GI effects following full dosing in drug-naïve animals will disappear after a certain time, but this is not necessarily the case. It cannot be excluded that the strong GI effects limited food and water intake over the complete study period in the animals. The applicant explained that dose up-titration was not performed because no beneficial effect was expected. According to the applicant, pure GLP-1RAs reduce food intake for a certain peroid of time only whereas tirzepatide reduced food intake persisted. Hence, the applicant assumed that no accomodation takes place so that up-titration would be meaningless. However, this notion may not be fully correct since in patients dose up-titration is successfully employed

In the previous CHMP Scientific Advice (EMA/CHMP/SAWP/689326/2018) the possible anabolic effects of GIP on bone were discussed. The company was advised to study the effect of tirzepatide on bone parameters. The applicant has discussed available data, showing no anabolic activity on bone of tirzepatide in rats or monkeys. They presented evidence that such anabolic activity would readily be detected by microscopy in the context of standard toxicity studies.

Tirzepatide did not exert any genotoxic potential based on the studies performed.

Carcinogenicity testing of tirzepatide was carried out in a 2-year study in Crl:CD(SD) rats and a 6 month study in hemizygous Tg.rasH2 mice [CByB6F1-Tg(HRAS)2Jic (+/-hemizygous c-Ha-ras)] in compliance with GLP. In the 6-month study, N-methyl-N-nitrosourea (MNU) was used as positive control at a dose of 75 mg/kg, which is often used in this animal model.

As observed in the toxicology studies in rodents, in both carcinogenicity studies dose-limiting effects on body weight and food consumption were consistent with, or secondary to, exaggerated incretin pharmacology and effects reported with long acting GLP-1 receptor agonists. No other signs of direct target organ toxicity or off-target effects were observed in mice. In rats dose dependent mild to severe unilaterally and bilaterally focal C-cell hyperplasia in the thyroid was considered as a pre-neoplastic lesion and is consistent with findings reported for GLP-1 receptor agonists). The relevance for humans is considered low for established GLP-1 receptor agonists. However, since tirzepatide is not a pure GLP-1 receptor agonist, the relevance for humans is unclear in this case.

In case of pure GLP-1 RAs, it is established that C-cell proliferation is rodent-specific because non-rodents including humans do not express GLP-1 receptors on the C-cells. In rodents, C-cell proliferation is accompanied by increased plasma calcitonin levels (not measured in case of tirzepatide), indicating that C-cell hyperplasia in rodents is an adaptive response of the C-cells to increased calcitonin production and secretion. Accordingly, elevation of plasma calcitonin is not found in humans with pure GLP-1 RAs. However, a small but clear and consistent increase in plasma calcitonin was found in humans treated with tirzepatide in the phase 3 trials. Thus, in this respect the action of tirzepatide differs from the action of pure GLP-1 RAs.

Tirzepatide was not carcinogenic in a short-term carcinogenicity study in mice at exposures 12 x above expected clinical exposures. Neoplasms that occurred in control and tirzepatide treated groups represented the types commonly reported and representative of the spontaneous, background findings observed for the RasH2 mouse model in 6 months studies.

In the rat, male fertility and early embryonic development study there were no effects on sperm parameters, reproductive performance, male reproductive organs, or early embryonic survival. In the rat female fertility and early embryonic development study, numbers of corpora lutea were decreased, resulting in decreased numbers of implantation sites and viable embryos. Estrous cycles were also disrupted. These effects were considered secondary to the decreased body weight and food consumption, noted at all dose levels. Similar effects were reported with long acting GLP-1 receptor agonists. There were no effects on mating, conception and fertility indices, pre-coital intervals, or implantation loss.

In embryo-fetal development (EFD) studies with both rats and rabbits, tirzepatide caused pharmacology related effects on body weight, body weight gain, and/or food consumption in both rats and rabbits.

At the high dose of 0.5 mg/kg (rat) and 0.1 mg/kg (rabbit), the maternal toxicity was significant and included clinical signs and sustained maternal body weight decreases, decreased body weight gain and food consumption. Increased incidences of malformations and developmental variations at 0.5 mg/kg in the rat were considered secondary to the lower mean foetal body weights at this dose level, which is seen in a consense to the maternal bodyweight decreases. Effects on foetal morphology, including increased numbers of malformations, have already been reported for other long-acting GLP-1 receptor agonist class. Overall, it can be concluded that the developmental and reproductive effects occurred only at doses associated with maternal toxicity. In the rat pre-/postnatal study maternal systemic toxicity based on effects on body weight, body weight gain, and food consumption was seen at 0.25 mg/kg. In the offspring body weight and body weight gain for F1 males at 0.25 mg/kg was also negatively affected. Exposure and distribution in the milk of lactating rats was not investigated. A safety margin to the human exposure at therapeutic dose levels was not calculated.

While it is agreed that maternal toxicity have contributed to the foetal findings in the embryo-foetal toxicity studies, a direct effect on the foetus cannot fully be excluded. This is adequately reflected in the SmPC.

The effects in the rat juvenile toxicity study were the same/similar (pharmacology related effects on body weight, body weight gain, and/or food consumption) as in the toxicity studies with adult animals. Delays in the attainment of balanopreputial separation and vaginal patency at 0.5 and 1.5 mg/kg were considered secondary to the decreased body weight, which is an effect of tirzipatide.

Exposures at the NOAEL of all studies performed for reproductive and juvenile toxicity were in general below exposures at the MRHD. Accordingly, there are no safety margins to the human exposure at therapeutic dose levels in all studies.

Environmental Risk Assessment

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.

2.5.7. Conclusion on the non-clinical aspects

Non-clinical PD studies demonstrated that the effects of tirzepatide are in line with known effects of GLP-1 receptor agonists on receptor binding/activation, insulin liberation, blood glucose excursion after glucose challenge, and body weight. Effects related to the GIP receptor became clearly obvious only in animals lacking the GLP-1 receptor (GLP-1 receptor knock-out mice). Furthermore, it turned out that the GIP receptor, in contrast to the GLP-1 receptor rapidly became inactivated upon binding of tirzepatide. Thus, the relevance of GIP receptor binding for the pharmacodynamic profile of tirzepatide could not be clearly established. Virtually all PD effects of tirzepatide were qualitatively highly similar to the effects of pure GLP-1 receptor agonists.

In the toxicology studies, the predominant finding was dose-limiting strong weight loss that can be regarded as exaggerated PD effect. Therefore, the margins to human therapeutic exposure were low, but this is not regarded as a major concern since the safety profile of GLP-1 receptor agonists is well known (and the action of tirzepatide on the GIP receptor appears to play a minor role, see above).

In the 2-year rat carcinogenicity study, hyperplasia and neoplasia of the thyroid C-cells were observed, again in line with the known effects of pure GLP-1 receptor agonists. This effect usually is accompanied by increase in serum calcitonin (not measured in this study). Serum calcitonin increase followed by C-cell hyperplasia and neoplasia is considered rodent-specific in case of pure GLP-1 receptor agonists, and with the latter, no serum calcitonin increaser in humans is observed. However, in case of tirzepatide, calcitonin increase consistently was found in humans. This is further discussed in the clinical section.

The active substance is a protein covalently linked with 20 fatty acids, excretion of the intact molecule from humans does not occur. Therefore, tirzepatide is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant 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.

The main clinical studies contributing to efficacy of tirzepatide on glycaemic control in adult patients with T2DM are summarized below:

• Two Phase 2 studies: GPGB and GPGF, and

• Five global Phase 3 studies GPGK, GPGL, GPGH; GPGM, GPGI.

All Phase 3 trials were randomized, parallel group, multinational trials. These trials were designed to establish:

• superiority of tirzepatide to placebo (GPGK and GPGI), and

• non-inferiority and superiority of tirzepatide to active comparator (GPGL, GPGH and GPGM).

The active comparators in the Phase 3 studies were subcutaneous semaglutide 1 mg (GPGL), insulin degludec (U100) [GPGH], or insulin glargine (U100) [GPGM].

Efficacy in Phase 3 studies

The primary efficacy measure in all five global Phase 3 studies was mean change in HbA1c from baseline to the primary endpoint at 40 or 52 weeks. Secondary efficacy measures, including mean change in body weight, FSG, 7-point SMBG, and proportions of patients achieving HbA1c and weight loss targets, were also evaluated. Study GPGM collected long-term, comparator-controlled safety and efficacy data up to 104 weeks.

The Phase 3 studies were designed to assess safety and efficacy in a broad T2DM patient population across different stages of the T2DM treatment continuum. The study population included patients who were:

- relatively newly diagnosed and on diet and exercise only
- inadequately controlled on up to 3 OAM(s) (including patients with increased CV risk), or
- inadequately controlled on basal insulin, with or without metformin.

Study GPGM included patients with increased risk of CV events and/or impaired renal function.

Because of differences among the trials in, for example, background therapies, treatment durations, patient characteristics, and comparators, pooling of the efficacy data across these studies was not performed.

The tables below present the primary endpoint and key design features of the two Phase 2 studies and the five global Phase 3 studies.

Overview of Phase 2 Studies

	I8F-MC-GPGB	I8F-MC-GPGF
Number of Randomized Patients	318	111
Treatment (mITT population)	TZP 1 mg (n=52) TZP 5 mg (n=55) TZP 10 mg[a] (n=51) TZP 15 mg[b] (n=53) Placebo (n=51) Dulaglutide 1.5 mg (n=54)	TZP 12 mg[c] (n=29) TZP 15 mg-1[d] (n=28) TZP 15 mg-2[e] (n=28) Placebo (n=26)
Primary Objective	Demonstrate a dose-response relationship of QW SC injections of tirzepatide on HbA1c change from baseline relative to placebo	Demonstrate that at least 1 tirzepatide dose-escalation scheme was superior to placebo in HbA1c reduction at 3 months
Patient Population	Patients with T2DM, with inadequate glycemic control with diet and exercise alone or on a stable dose of metformin	
Study Design	Multicenter, double-blind, parallel-group, randomized study	
Control	Placebo and active comparator	Placebo
Total Treatment Duration	26 weeks	12 weeks
Section	2.7.3.2.1.1	2.7.3.2.1.2

Abbreviations: HbA1c = glycosylated hemoglobin A1c; mITT = modified intent-to-treat; n = number of patients in each treatment group; QW = once-weekly; SC = subcutaneous; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

[a] Patients started with tirzepatide 5 mg QW for 2 weeks, followed by 10 mg QW for the remaining duration of the study.

[b] Patients started with tirzepatide 5 mg QW for 2 weeks, followed by 10 mg for 4 weeks, and then 15 mg QW for the duration of the study.

[c] Patients started with tirzepatide 4 mg QW for 4 weeks, followed by 8 mg for 4 weeks, then 12 mg QW for the duration of the study.

[d] Patients started with tirzepatide 2.5 mg QW for 2 weeks, followed by 5 mg for 2 weeks, 10 mg for 4 weeks, and then 15 mg QW for the duration of the study.

[e] Patients started with tirzepatide 2.5 mg QW for 4 weeks, followed by 7.5 mg for 4 weeks, then 15 mg QW for the duration of the study.

Overview of Phase 3 Studies

	I8F-MC-GPGK	I8F-MC-GPGL	I8F-MC-GPGH	I8F-MC-GPGM	I8F-MC-GPGI
Number of Randomized Patients	478	1879	1444	2002	475
Treatment[a] (mITT population)	TZP 5 mg (n=121) TZP 10 mg (n=121) TZP 15 mg (n=121) Placebo (n=115)	TZP 5 mg (n=470) TZP 10 mg (n=469) TZP 15 mg (n=470) SEMA 1 mg[b] (n=469)	TZP 5 mg (n=358) TZP 10 mg[c] (n=360) TZP 15 mg[c] (n=359) Insulin Degludec[d] (n=360)	TZP 5 mg (n=329) TZP 10 mg[c] (n=328) TZP 15 mg[c] (n=338) Insulin Glargine[e] (n=1000)	TZP 5 mg (n=116) TZP 10 mg (n=119) TZP 15 mg (n=120) Placebo (n=120)
Randomization Ratio	1:1:1:1	1:1:1:1	1:1:1:1	1:1:1:3	1:1:1:1
Primary Objective	Demonstrate that tirzepatide 5, 10, and/or 15 mg QW are superior to placebo for change from baseline in HbA1c	Demonstrate that tirzepatide 10 and/or 15 mg QW are noninferior to semaglutide 1 mg QW for change from baseline in HbA1c	Demonstrate that tirzepatide 10 and/or 15 mg QW are noninferior to insulin degludec for change from baseline in HbA1c	Demonstrate that tirzepatide 10 and/or 15 mg QW are noninferior to insulin glargine for change from baseline in HbA1c	Demonstrate that tirzepatide 10 and/or 15 mg QW are superior to placebo, when added to titrated basal insulin glargine, for change from baseline in HbA1c
Key Secondary Objectives (Controlled for Type 1 Error)	Demonstrate that tirzepatide 5, 10, and/or 15 mg QW are superior to placebo for mean change in body weight, proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol), mean change in FSG, and proportion of patients with HbA1c target values of <5.7% (<39 mmol/mol)	Demonstrate that tirzepatide 5 mg QW is noninferior to semaglutide 1 mg QW for change from baseline in HbA1c	Demonstrate that tirzepatide 5 mg QW is noninferior to insulin degludec for change from baseline in HbA1c	Demonstrate that tirzepatide 5 mg QW is noninferior to insulin glargine for change from baseline in HbA1c	Demonstrate that tirzepatide 5 mg QW is superior to placebo, when added to titrated basal insulin glargine, for change from baseline in HbA1c

	I8F-MC-GPGK	I8F-MC-GPGL	I8F-MC-GPGH	I8F-MC-GPGM	I8F-MC-GPGI
		Demonstrate that tirzepatide 5, 10, and/or 15 mg QW are superior to semaglutide 1 mg QW for mean change in body weight, mean change in HbA1c, and proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol) Demonstrate that tirzepatide 10 and/or 15 mg QW are superior to semaglutide in proportion of patients with HbA1c target values of <5.7% (<39 mmol/mol)	Demonstrate that tirzepatide 5, 10, and/or 15 mg QW are superior to insulin degludec for mean change in body weight, mean change in HbA1c, and proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol)	Demonstrate that tirzepatide 5, 10, and/or 15 mg QW are superior to insulin glargine for mean change in body weight, mean change in HbA1c, and proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol)	Demonstrate that tirzepatide 5, 10, and/or 15 mg QW are superior to placebo, when added to titrated basal insulin glargine, for mean change in body weight, proportion of patients with HbA1c target values of <7.0% (<53 mmol/mol), and mean change in FSG Demonstrate that tirzepatide 10 and/or 15 mg QW are superior to placebo in proportion of patients with HbA1c target values of <5.7% (<39 mmol/mol)
Total Treatment Duration[f]	40 weeks	40 weeks	52 weeks	Up to 104 weeks[g]	40 weeks
Study Design	Multicenter, double-blind, parallel group, placebo-controlled, randomized study	Multicenter, open-label[h], parallel group, active-comparator-controlled, randomized study	Multicenter, open-label[i], parallel group, active-comparator-controlled, randomized study	Multicenter, open-label[i], parallel group, active-comparator-controlled, randomized study	Multicenter, double-blind, parallel group, placebo-controlled, randomized study
Background Antihyperglycemic Medication	None	Metformin	Metformin ± SGLT-2i	1 to 3 OAMs[j]	Insulin Glargine (100 U/mL) ± Metformin

Abbreviations: COVID-19 = coronavirus disease 2019; FBG = fasting blood glucose; FSG = fasting serum glucose; HbA1c = glycosylated hemoglobin A1c; mITT = modified intent-to-treat; n = number of patients in each treatment group; OAM = oral antihyperglycaemic medication; QW = once-weekly; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; TTT = treat-to-target; TZP = tirzepatide.

a Patients started with tirzepatide 2.5 mg QW for 4 weeks, then the dose was increased by 2.5 mg every 4 weeks until the treatment dose was reached and maintained for the duration of the study.

b Patients started with semaglutide 0.25 mg QW for 4 weeks, then the dose was increased to 0.5 mg for 4 weeks, then increased to and maintained at 1 mg QW for the duration of the study.

c In Studies GPGH and GPGM, patients in the tirzepatide 10- and 15-mg dose groups were permitted to de-escalate dose of study drug one time during the dose-escalation period if persistent intolerable GI symptoms occurred.

d The starting dose of insulin degludec was 10 IU/day ideally at bedtime, titrated to a FBG <90 mg/dL (<5.0 mmol/L), following a TTT algorithm.

e The starting dose of insulin glargine was 10 IU/day at bedtime, titrated to a FBG <100 mg/dL (<5.6 mmol/L), following a TTT algorithm.

f Impact on study procedures due to the COVID-19 pandemic are described in Sections below.

g For Study GPGM, the primary endpoint is 52 weeks with a variable treatment duration of up to 104 weeks.

h Tirzepatide doses were double-blinded; sponsor study team was blinded to treatment group.

i Sponsor study team was blinded to tirzepatide dose.

j Allowed OAMs include metformin, SGLT-2i, or sulfonylureas.

2.6.2. Clinical pharmacology

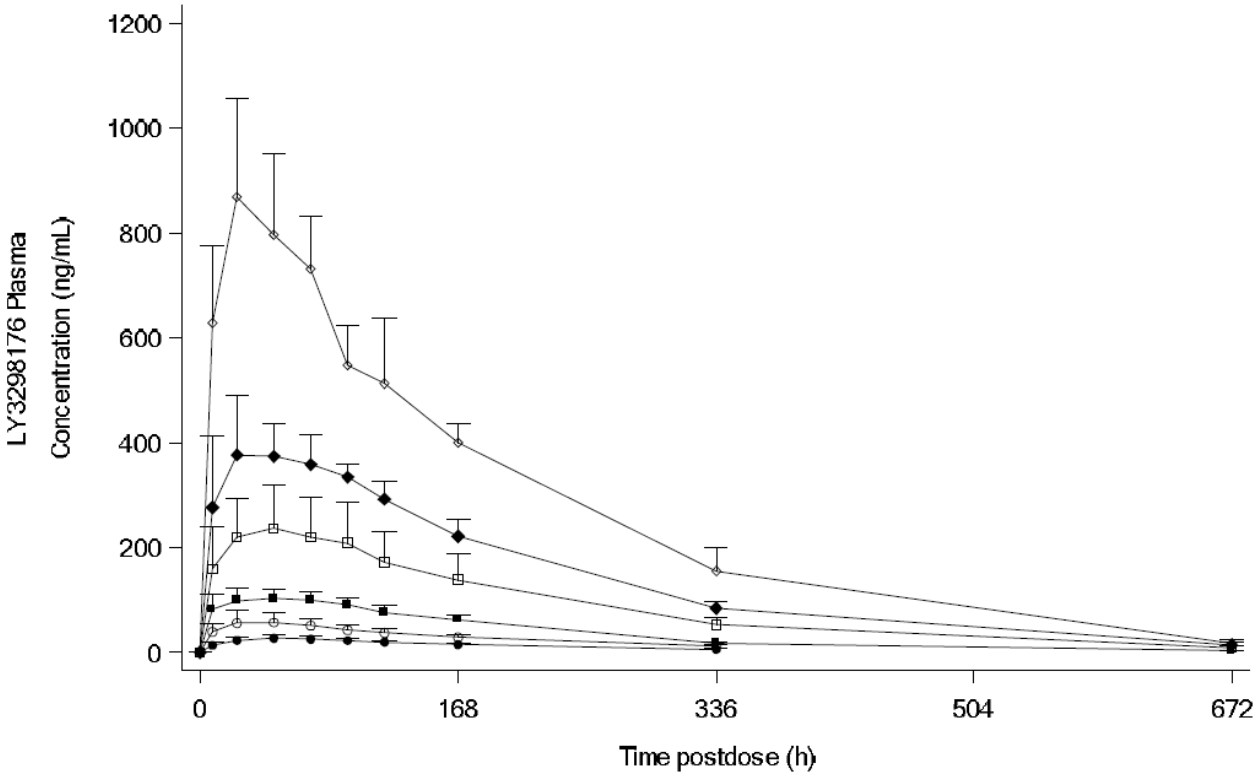
The 10 biopharmaceutic and clinical pharmacology phase 1 studies were designed to assess the PK, PD, the effects of extrinsic and intrinsic factors on tirzepatide PK, the impact of tirzepatide on PK of orally administered drugs, and safety and tolerability of tirzepatide. Single doses of tirzepatide were administered over a range of 0.25 to 8 mg, and multiple once-weekly doses that ranged from 0.5 to 15 mg for up to 28 weeks. The effect of tirzepatide on insulin and glucagon secretion and insulin sensitivity was assessed in a dedicated mechanism of action study.

2.6.2.1. Pharmacokinetics

Absorption

Following subcutaneous administration of tirzepatide, median time to peak concentration (t_{max}) was achieved approximately 24 hours (range 8 to 72 hours) postdose.

Pharmacokinetic characteristic of tirzepatide on Day 1 for Study I8F-MC-GPGA (Part A)



Dose-proportionality analysis over the single dose range of 0.25 to 8 mg resulted in a ratio of dose-normalized geometric means in exposure (AUC and Cmax) of about 0.8 to 0.85.

The absolute bioavailability of a 5-mg subcutaneous dose of tirzepatide in healthy participants was 80%.

Tirzepatide can be injected subcutaneously in the abdomen, upper arm, or thigh, without need for any dose adjustment.

Distribution

For single dose in healthy subjects, the apparent volume of distribution during the terminal phase after extra-vascular administration (Vz/F) was 7.83 L (study GPGA). Mean apparent volume of distribution (Vd/F) in patients with T2DM after multiple dosing was 10.3 L. After 0.5-mg IV bolus administration, the mean volume of distribution (Vz) was 5.52 L (study GPGE part D) indicating that tirzepatide distributes primarily in the blood volume. Tirzepatide was highly bound to albumin in human plasma with a mean percent bound of 99 %.

Elimination

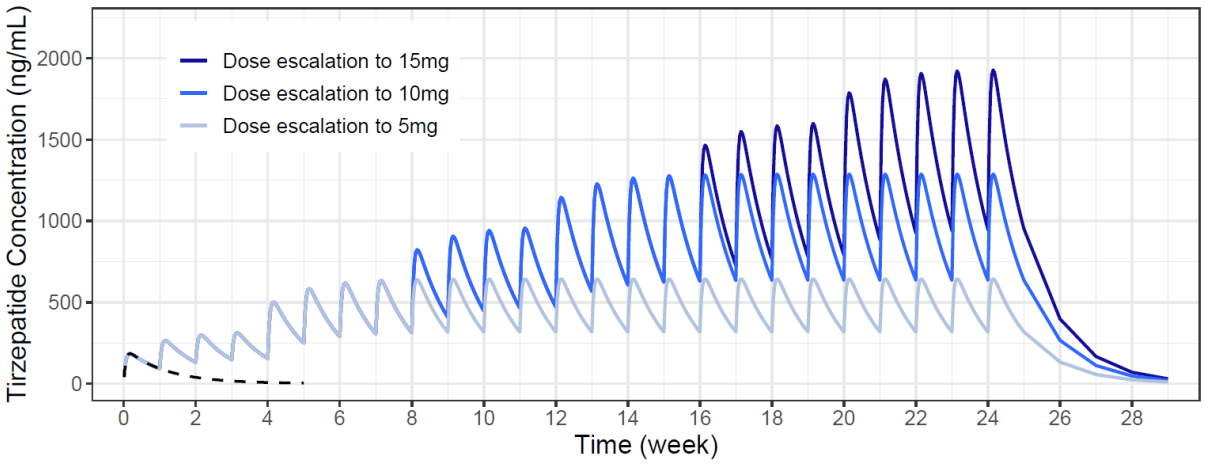
Tirzepatide is a dual-action incretin mimetic that was designed as a 39 amino acid synthetic peptide that exerts its function by binding either the GIP or GLP-1 receptor with high affinity. The structure was engineered from the GIP sequence and includes a C20 fatty diacid moiety. The molecular weight is 4.8 kDa.

Tirzepatide has a mean half-life of approximately 5 days.

Tirzepatide is eliminated through metabolism. The primary metabolic pathways that contributed to the clearance of tirzepatide were proteolytic cleavages of the peptide backbone, β-oxidation of the C20 fatty diacid moiety and amide hydrolysis.

Dose proportionality and time dependencies

The following graph show the tirzepatide concentrations in a 90-kg individual using the tirzepatide population pharmacokinetic model. The solid lines denote concentrations following dose escalation up to 5, 10, or 15 mg. Dose escalation started with 2.5 mg and dose amount was increased by a 2.5-mg increment every 4 weeks. The dashed line denotes concentrations following a single 2.5-mg dose. Tirzepatide doses were administered once weekly.



Tirzepatide PK was generally similar between healthy participants and patients with T2DM.

Special populations

No clinically relevant effects on the PK of a single SC dose of 5 mg tirzepatide were observed for participants with mild, moderate, or severe renal impairment or ESRD when compared to participants with normal renal function.

The overall exposure to tirzepatide, based on $AUC_{(0-\infty)}$ and C_{max} and t_{max}, was similar across the control and hepatic impairment groups.

Sex and race (Asian, black, or white) were not found to be of significance after accounting for influence of body weight.

Body weight was identified to have a significant influence on tirzepatide PK. As tirzepatide treatment is associated with significant weight loss over time, body weight was evaluated as a time-varying as well as a baseline covariate. Approximately, every kilogram increase in weight was associated with a 1.1% decrease in tirzepatide exposure ($AUC_{0-\tau}$).

Age was tested as a continuous covariate on tirzepatide PK and was not found to be of significance. Approximately 1427 (25%) participants were aged between 65 and 75 years and 214 (4%) participants were at least75 years.

	Number of Participants		
	Age 65-74 years	**Age 75-84 years**	**Age ≥85 years**
Overall from 19 Studies (N = 5802)	1427	207	7
Phase 1 / Clinical Pharmacology / Biopharmaceutic Studies			
Study I8F-MC-GPGA (N = 108)	5	0	0
Study I8F-JE-GPGC (N = 39)	12	0	0
Study I8F-MC-GPGG (N = 44)	8	5	0
Study I8F-MC-GPGQ (N = 32)	8	0	0
Study I8F-MC-GPGR (N = 28)	0	0	0
Study I8F-MC-GPGT (N = 45)	14	0	0
Study I8F-MC-GPHX (N = 6)	0	0	0
Study I8F-MC-GPGE (N = 40)	1	0	0
Study I8F-MC-GPGS (N = 45)	1	0	0
Study I8F-MC-GPHI (N = 54)	5	0	0
Phase 2 Studies			
Study I8F-MC-GPGB (N = 210)	41	1	0
Study I8F-MC-GPGF (N = 83)	18	0	0
Phase 3 Studies			
Study I8F-MC-GPGK (SURPASS-1) (N = 359)	73	6	0
Study I8F-MC-GPGL (SURPASS-2) (N = 1392)	302	27	2
Study I8F-MC-GPGH (SURPASS-3) (N = 1067)	249	29	0
Study I8F-MC-GPGM (SURPASS-4) (N = 982)	367	88	4
Study I8F-MC-GPGI (SURPASS-5) (N = 349)	131	19	0
Study I8F-JE-GPGO (SURPASS-J-mono) (N = 476)	98	11	1
Study I8F-JE-GPGP (SURPASS-J combo) (N = 443)	94	21	0

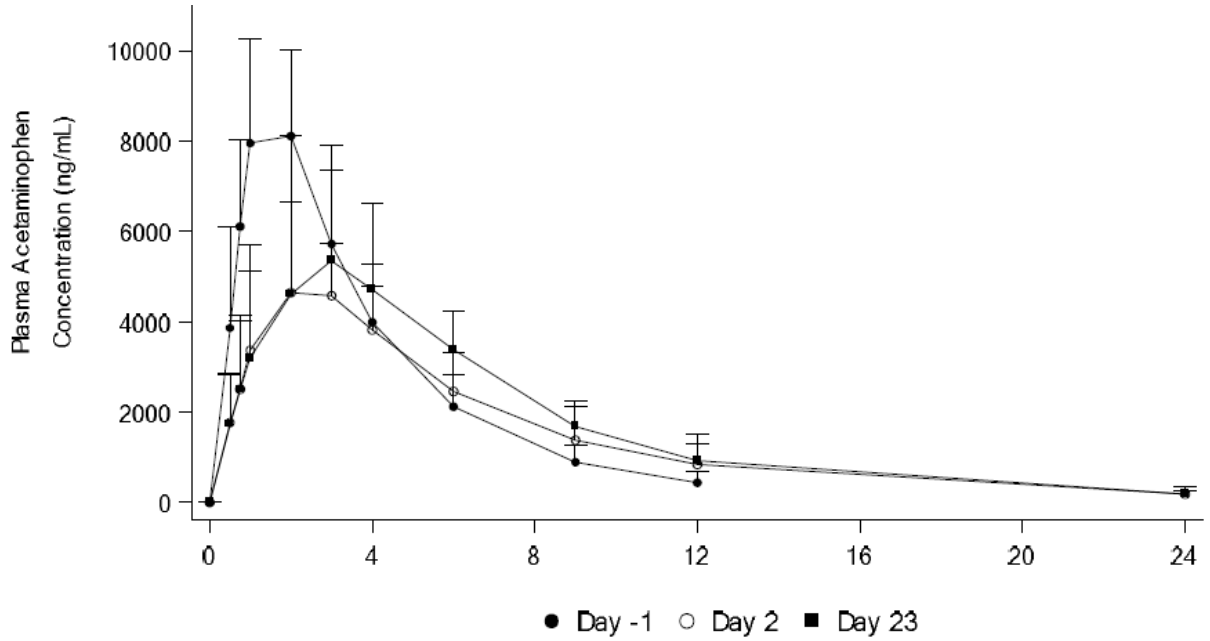
It is considered probable, that age is of limited relevance for tirzepatide PK.

Tirzepatide has not been studied in paediatric patients.

Pharmacokinetic interaction studies

The drug-drug interactions mediated by tirzepatide, are expected primarily because incretins are known to cause gastric emptying delay which can influence the rate of absorption (Cmax, tmax) without greatly influencing overall extent of absorption (AUC) of orally administered concomitant drugs. This was confirmed by studies with acetaminophen and oral contraceptive.

Within study GPGA the impact of tirzepatide on gastric emptying delay was studied using acetaminophen as a gastric emptying marker. Subjects received 1 g acetaminophen on Day −1 (prior to study drug dosing) at a time corresponding to the approximate LY3298176 C_{max} (about 24 hours after the first and fourth dose of study drug).



Data in patients with T2DM (part C) with 5 mg LY3298176 on Day 1 and Day 8, 10 mg LY3298176 on Day 15 and 15 mg LY3298176 on Day 22

Results:

- ☐ In healthy subjects and in patients with T2DM, acetaminophen C_{max} decreased approximately 50% after the first 5-mg dose of tirzepatide and Tmax was delayed by about an hour, thereby suggesting delay in gastric emptying.
- ☐ Impact on acetaminophen PK was greatest after the first dose of tirzepatide and showed diminishing effect with time (tachyphylaxis) with repeated QW dosing.

Study GPGR participants was conducted to evaluate the effects of tirzepatide on oral contraceptive.

Each OC cycle consisted of 21 days of active combination tablet (ethinyl estradiol 0.035 mg + norgestimate 0.25 mg) followed by 7 days of placebo. OC alone in period 1 was compared with OC + tirzepatide 5 mg in period 2. Additionally, each participant received 1 dose of tirzepatide on Day 20 of Period 2, administered via pre-filled syringe (i.e., one SC injection of 5 mg tirzepatide into the abdomen).

Ethinyl Estradiol (EE)

The C_{max} of EE was reduced by 59% (ratio of geometric means [90% CI]: 0.410 [0.355, 0.473]) when OC was administered in the presence of single dose of 5-mg tirzepatide compared to OC alone. This was

accompanied by a delay in t_{max} of OC of approximately 4 hours (median of differences [90% CI]: 4.23 [1.50, 6.50]).

Overall exposure, as measured by $AUC_{(0-\tau)}$, and $AUC_{(0-tlast)}$ was reduced by about 20% (ratio of geometric means [90% CI]: 0.788 [0.730, 0.850], and 0.800 [0.722, 0.888]), respectively.

Norgestimate is rapidly metabolized by first-pass (intestinal and/or hepatic) mechanisms to Norelgestromin and Norgestrel, which are the major active metabolites of Norgestimate. Hence the results for Norelgestromin are considered more robust.

Norelgestromin (NGMN)

The C_{max} of NGMN decreased by approximately 55% (ratio of geometric means [90% CI]: 0.451 [0.402, 0.505]), when OC was administered in the presence of single dose of 5-mg tirzepatide compared to OC alone. There was also a delay in tmax of OC of 4.5 hours (median of differences [90% CI]: 4.50 [1.50, 5.00]).

Overall exposure, as measured by $AUC_{(0-tlast)}$ and $AUC_{(0-\tau)}$ was reduced by 16 and 23% (ratio of geometric means [90% CI]: 0.838 [0.771, 0.912], and 0.775 [0.712, 0.843]), respectively, when OC was administered in the presence of tirzepatide compared to OC alone.

2.6.2.2. Pharmacodynamics

4 studies were submitted to adress PD endpoints in phase 1 and 2. PD assessment was included in Study GPHX (Disposition of radioactivity and PK, few PD data on glucose parameters and vital signs), study GPGA included a Single- and multiple-dose PD evaluation in healthy participants, and a multiple-dose PD evaluation in patients with T2DM. Study GPGC included a multiple-dose PD evaluation in Japanese patients with T2DM and Study GPGT investigated the effect of tirzepatide on pancreatic α and β cell function and insulin sensitivity in patients with T2DM. A concentration effect analysis for QTcF and PR interval was provided based on phase 1 and 2 clinical data and a PopPK PD analysis integrating data from the phase 3 trial.

Mechanism of action

Tirzepatide is a dual-action incretin mimetic that was designed as a 39 amino acid synthetic peptide that exerts its function by binding either the GIP or GLP-1 receptor with high affinity.

Key effects of GLP-1 and GIP as described in the literature are summarized in Table 2.5.1.1

Table 2.5.1.1. Summary of Known Physiological Functions of GIP and GLP-1 in Glucose and Energy Metabolism

Location of Action	GLP-1	GIP
Pancreas (glucose-dependent actions)		
Beta-Cells	Increased insulin synthesis, increased insulin secretion, increased beta-cell proliferation, increased glucose sensing under hyperglycemic states	
Alpha-Cells	Decreased glucagon secretion under hyperglycemic states	Increased glucagon secretion under euglycemic or hypoglycemic states
Gastrointestinal System	Decreased GI motility, delayed gastric emptying	N/A
Adipose Tissues	N/A	Increased intravascular lipolysis and increased fatty acid uptake
Brain	Decreased appetite, increased satiety	N/A

Abbreviations: GI = gastrointestinal; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; N/A = not applicable.

The concept of designing a drug with agonistic effects on both GLP-1 and GIP receptors in patients with T2DM may be to combine positive effects of both pathways: Increase the sensitivity of beta cells to glucose and insulin release via both pathways under hyperglycaemic conditions and counterregulate a decrease in GLP-1 mediated glucagon secretion by an activation of glucagon secretion via GIP receptor activation under hypoglycaemic conditions, thereby further reducing the likelihood of hypoglycaemia. In addition, GLP-1 mediated effects on GI mobility, a decrease in appetite and an increase in satiety may be complemented by GIP mediated effects on adipose tissue in order to contribute to weight reduction in overweight patients with T2DM.

Primary and Secondary pharmacology

Primary Pharmacodynamic effects

Fasting and Postprandial Plasma Glucose:

Tirzepatide decreased FPG and PPG concentrations as well as glucose AUC after an OGTT. Significant effects were seen at doses of 5 mg QW or higher after the first dose up to a maximally investigated target dose of 10 or 15 mg QW. The effect was sustained up to day 64 in phase 2 studies and up to week 52 in phase three studies. PK/PD modelling including phase 3 data showed a dose response with relevant effect on FPG between 5 mg QW and up to 15 mg QW.

In patients with T2DM who received once weekly 15 mg doses for 28 weeks (Study GPHT, Standardized Mixed-Meal Tolerance Test), fasting glucose concentrations, and post-prandial serum gAUC0-240 min were significantly reduced compared to placebo (-2.61 mMol/L, -373.7 (mMol/L)*min mg/dL, respectively). The effects were significantly larger than those observed with 1 mg Semaglutide, a GLP-1R agonist.

HbA1c

In multiple dose trials in patients with T2DM, tirzepatide consistently decreased HbA1c in a dose dependent manner. In study GBHT, a significant mean reduction in HbA1c of -2.33 % (mean baseline HbA1c 7.83%) was observed after once weekly tirzepatide 15 mg dosing for 28 weeks compared to placebo. The effect was significantly larger than the effect observed with semaglutide 1 mg QW (- 1.57%). In study GPGA the LS mean difference vs. placebo was -0.58 % on day 29 after multiple ascending doses of 5/5/10/15 mg (study GPGA). In Japanese patients with T2DM the mean decrease in HbA1c was -2.05% at day 57 at a maintenance dose of 15 mg QW after weekly uptitration from 5 to 10 to 15 mg QW (predose value 8.19%) (Study GPGC).

First and second phase insulin secretion and glucose-dependent insulin secretion and beta cell function

Tirzepatide improved first-phase insulin secretion (0 – 8 min) and increased second phase insulin (20 – 120 min) in response to i.v. glucose (hyperglycaemic clamp) in patients with T2DM (study GBCT). In addition, maximal insulin secretion, as provoked by a 5-g bolus of arginin, was increased by tirzepatide.

Beta cell function improved as assessed by an increase of the Clamp disposition index (cDI). At Week 28, change from baseline in cDI was + 4.2% for placebo, + 338.3% for semaglutide (1 mg QW), and + 596.9% for tirzepatide (15 mg QW, study GPHT). Consistently, HOMA-B improved in patients with T2DM (baseline mean value: 41.1, day 23: 95.4, for 5/5/10/15 mg QW, study GPGA).

β cell sensitivity to glucose (GS) significantly increased with tirzepatide 15 mg QW from baseline to week 28 from 17.2 to 92.3 (mean values, pmol insulin secreted/min/m2/pmol/l glucose) in patients with T2DM. The effect was significantly larger than the effect of semaglutide (from 16.8 to 77.3, clamp study GPHT). Consistently, β cell sensitivity to glucose numerically increased as assessed based on Insulin secretion rate

(ISR) from the Standardized Mixed-Meal Tolerance Test (sMMTT) by 13.5 pmol/min/m2/[mmol/L], (95% CI [-1.3, 28.4] p-value=0.074, T2DM, study GPHT).

In the sMMTT (study GPHT, T2DM) mean fasting insulin, total insulin AUC0-240 and incremental AUC0-240 decreased with tirzepatide 15 mg (week 28) by - 10.3 pMol/L (mean baseline 57.2 pMol/L), approximately 36% and 41%, respectively. The reduction in C-peptide was similar. However, at a fixed glucose concentration of 7.2 mmol/L tirzepatide increased insulin release from baseline in these patients.

Whole body insulin sensitivity

HOMA-IR increased slightly from a mean of 2.0 to 2.5 in this group (placebo from 1.8 to 2.2). However, Tirzepatide increased the M-value by approximately 63% in the Hyperinsulinemic Euglycaemic Clamp study in patients with T2DM indicating an increased whole body insulin sensitivity (GPHT, day 28 15 mg QW). The effect was significantly larger than the effect of semaglutide 1 mg QW (+ 35%)).

Glucagon secretion

Glucagon concentration parameters during sMMTT decreased significantly with tirzepatide from baseline to week 28 (15 mg QW) in patients with T2DM. Mean fasting values prior to sMMTT were 11.8 pmol/L at baseline and 8.4 at week 28 (Placebo 15.2 and 15.3, respectively). Total glucagon AUC0-240 min during sMMTT decreased by a mean of -1625.4 pmol/min (mean baseline values 4016.6 (placebo: - 207.7 study GPHT). Incremental AUC-240 was reduced by -552.0 pMol/L*min. The changes were numerically similar but overall less pronounced with semaglutide.

Secondary Pharmacodynamic effects

Gastric Emptying: Tirzepatide delayed gastric emptying at first doses of 4.5 and 5 mg in healthy subjects and patients with T2DM (study GPGA). The effect was time dependent. It disappeared after repeated administration of 4.5 mg QW and decreased upon ascending doses (5/8/15/10) mg by day 23 in healthy volunteers. In patients with T2DM the effect decreased by day 23 at a constant dose of 5 mg PW. Following the tirzepatide 5/5/10/10 mg QW and 5/5/10/15-mg QW titration regimen, the delay in gastric emptying was reduced after the fourth dose at day 23. (For details see above, PK)

Body Weight

There was a consistent and dose related effect of tirzepatide on total body weight in healthy subjects and in patients with T2DM. In healthy subjects weight decreased after 4 weeks by a mean of -1.32, -1.75, -5.09, and -4.61 kg, respectively (with 0.5 mg QW, 1.5 mg QW, 4.5 mg QW, and 5/5/8/10 mg QW titration, GPGA, part B). In patients with T2DM weight decreased by -0.38, -1.21, -2.62, and -2.07 kg for 0.5 mg QW, 5 mg QW, 5/5/10/10-mg, and 5/5/10/15-mg QW titration after 4 weeks (GPGA, part C). In Japanese patients with T2DM the placebo corrected decrease was -5.04, -6.59, and -3.39 kg (2.5/5/10 mg QW, 5/10/15 mg QW, 5-mg QW) after 8 weeks (GPGC). At Week 28, there was a statistically significant mean body weight loss from baseline in patients with T2DM treated with tirzepatide 15 mg QW when compared with placebo (-11.2 kg). The effect was larger compared to semaglutide 1 mg QW (-4.3 kg).

Body composition

Fat mass decreased by a mean of -9.6 kg (95% CI [-12.4, -6.9], p-value<0.001) in patients treated with tirzepatide 15 mg QW over 28 weeks. Fat-free mass decreased to a lesser degree by a mean of -1.5 kg. The percentage of fat mass in total body mass decreased by about 7%.

Food consumption

In Japanese patients with T2DM (GPGC) tirzepatide reduced meal intake in a dose dependent fashion by day 51. Compared to baseline (100% complete meal consumption at lunch and dinner) only 26.7 and 13.3 percent of the patients at a maximal target dose of 15 mg tirzepatide (5/10/15 mg QW increments) consumed 100%, compared with placebo values of 77.8 and 66.7%.

In patients with T2DM (GPHT) placebo corrected intake of kcals of a mixed meal decreased by week 28 by -309.8 kcal with tirzepatide (15 mg QW, baseline mean consumption Placebo: 1253 kcal, tirzepatide: 1105 kcal). In the Japanese study VAS trends towards a decrease in hunger and fullness scores and no effect on satiety and prospective food consumption scores and over all appetite scores were noted. In study GPHT at fasting and 240 min post-prandial, a significant reduction in appetite VAS score was observed with tirzepatide, at other time points there was a numerical reduction. Results for calorie intake and VAS scores were similar with semaglutide with the exception that VAS scores were significantly reduced at all pre- and post-prandial time points.

Lipids

There were no marked effects of tirzepatide on HDL- or LDL cholesterol in healthy subjects (GPGA part A and b) and patients with T2DM (GPGA part C) at day 29 and in Japanese patients with T2DM at day 51(GPGC). A downward trend in triglyceride concentrations at Day 29 was noted following a 4-week titration of both 5/5/10/10- and 5/5/10/15 mg cohorts (GPGA part C). Numerically, triglyceride levels decreased in Japanese patients from mean predose values (5/10/15 mg QW): 1.958 to 1.376 mmol/L at day 51.

Bone markers

In patients with T2DM (GPGY Part C) trends to a decrease in N-terminal propeptide of type 1 procollagen (P1NP, a marker of bone formation) concentration from Day 29 compared to Day 1 – pre-dose across all doses of study drug and a trend to small increases of arithmetic mean CTX levels (a marker of bone turnover) at Day 29 as compared to Day 1 – pre-dose for study drug at dose 5 mg and 5/5/10/10 and 5/5/10/15 mg QW titrated doses was observed.

PD interactions:

A discussion on PD interactions with other drugs has not been provided by the Applicant. PD interactions are conceivable with drugs targeting the same PD endpoints relevant for effects on glucose homeostasis, systolic blood pressure or heart rate. PD interactions with insulin or insulin secretagogues may increase the risk of hypoglycaemia in case of coadministration. There was a small and insignificant increase in PR interval which per se will not be clinically relevant in most patients but may have an impact when tirzepatide is coadministered with other PR prolonging drugs. Coadministration with drugs affecting gastric emptying may mutually potentiate the effect.

Heart rate

A PopPK-PD analysis based on phase 3 studies indicated exposure related mean increases in heart rate by 5.6 to 7.4 bpm at Css for 15 mg and a 7.0 to 9.2 bpm increase at the model-predicted tirzepatide Cmax for 15 mg.

Blood pressure

A decrease of -8.3 and -8.4 mmHg change from baseline systolic blood pressure at Weeks 40 and 52, respectively was estimated for the model-predicted tirzepatide Css for 15 mg, trends for diastolic blood pressure were not statistically significant.

ECG parameter

QTc: PopPK based analyses on phase 1 and phase 2 studies combined indicated a ddQTcF (placebo corrected) of -0.570 (-1.52; 0.352 ms) based on studies GPGA, GPGB, and GPGF. In the phase 1 and 2 studies the highest dose investigated was 15 mg, which matches the maximally proposed dose of tirzepatide of 15 mg once-weekly.

PR-Intervall: Minor numerical but overall not significant increases in PR interval by a mean of 1.55 ms (0.594; 2.36) were estimated based on the PopPK-PD analyses.

Immunogenicity

ADA antibodies: ADA titers peaked at Week 40 and showed a plateau up to Week 52. No effect of ADAs on PK of tirzepatide or PD as assessed by HbA1c was observed. The detection of ADAs did not appear to be related to tirzepatide concentrations.

Safety parameter of interest

Nausea, vomiting, diarrhoea (N/V/D): In the PopPK-PD analysis Covariate effects related to patient's race, ethnicity, and gender were identified. In the model none of these significant covariates resulted in clinically meaningful differences in N/V/D incidence to warrant an alternate dosing scheme.

Amylase, lipase, calcitonin: Analyses of amylase (absolute and change from baseline) versus observed tirzepatide concentrations showed a statistically significant positive slope. Similarly, a statistically significant positive slope was also observed for the regression analysis of lipase (absolute and change from baseline) versus observed tirzepatide concentrations (Weeks 40 and 52). Results for calcitonin (absolute) versus observed tirzepatide concentrations showed negative slopes that did not reach statistical significance, while calcitonin (change from baseline) versus concentration analyses resulted in positive slopes that attained significance only at Week 40

Post hoc PK parameters for individuals with ≥3x upper limit of normal amylase, lipase, or calcitonin did not indicate relevant differences in model predicted Css when comparing patients with values > 3x ULN vs. those < 3xULN at the respective dose level.

Hypoglycaemia: PK parameters in patients with Level 2 or 3 hypoglycaemia were comparable to those without hypoglycaemia.

2.6.3. Discussion on clinical pharmacology

Tirzepatide (also known as LY3298176) is a dual-action incretin mimetic that was designed as a 39 amino acid synthetic peptide that exerts its function by binding either the GIP or GLP-1 receptor with high affinity. The structure was engineered from the GIP sequence and includes a C20 fatty diacid moiety. The molecular weight is 4.8 kDa.

The clinical pharmacology of tirzepatide was evaluated in 7 clinical pharmacology studies, 3 biopharmaceutic studies, two Phase 2 studies, five Phase 3 studies, and two regional (Japan) Phase 3 studies.

Pharmacokinetics

Tirzepatide doses of 0.25 to 15 mg were administered over the course of these studies. Single doses of tirzepatide over a range of 0.25 to 8 mg were evaluated. A dose of tirzepatide 5 mg was identified as the maximum tolerated dose when given as a single dose in healthy participants, and hence doses greater than 5

mg were attained by stepwise dose-escalation schemes in subsequent multiple dose evaluations. Once-weekly multiple doses over a range of 0.5 to 15 mg were studied.

Tirzepatide should be injected subcutaneously in the abdomen, thigh or upper arm.

Tirzepatide has a mean half-life of approximately 5 days, which enables once-weekly dosing. Tirzepatide distributes primarily in the blood volume and is highly bound to albumin in human plasma with a mean percent bound of 99 %.

Tirzepatide was eliminated through general physiologic metabolic pathways. The primary pathways that contributed to the clearance of tirzepatide were proteolytic cleavages of the peptide backbone, β-oxidation of the C20 fatty diacid moiety and amide hydrolysis.

According to these mechanisms tirzepatide PK did not depend on specific pathways and, except weight, no major differences of pharmacokinetics in special populations should be expected. This was confirmed by dedicated studies (e.g. GPGG - Impaired renal function or GPGQ - Impaired hepatic function) or by subpopulation analyses, partly pooled or extended by POP-PK analyses. A weakness in the dedicated renal impairment and hepatic impairment studies was that unbound concentrations were not measured, although this is recommended for drugs that are highly protein-bound according to the respective guidelines. However, as no effects were seen on total concentrations and as no relevant effects on PK are expected, no concern is raised. Similarly, except consequences of delayed gastric emptying, potential drug-drug interactions mediated by tirzepatide are considered limited.

Apart from two clinical studies on drug-drug interactions, one assessing tirzepatide's effect on the PK of paracetamol (acetaminophen; study GPGA) and one assessing tirzepatide's effect on the PK of a combination oral contraceptive (study GPGR), the claims regarding no clinically meaningful impact on, and no dose adjustments (or monitoring) of, concomitantly administered oral medicinal products, rely solely on simulations from physiologically-based pharmacokinetic (PBPK) models. Although the models are the same as previously developed and/or applied to assess drug-drug interactions caused by the GLP-1 receptor agonist dulaglutide, the current application of the models to assess tirzepatide's effect (through delayed gastric emptying) on the PK of concomitantly administered oral medicinal products is not supported. The models are not able to adequately capture the data following co-administration of tirzepatide in studies GPGA and GPGR, indicating that tirzepatide's effect on gastric emptying is not estimated correctly in the semi-mechanistic model analysis of delayed gastric emptying, or there are more aspects to drug-drug interactions with tirzepatide than the models do account for.

Thus, in Section 4.5 PBPK simulation is not included. Instead, available in vivo data regarding the effects on paracetamol and oral contraceptives, and the conclusions possible to be drawn from these studies are given, along with a general wording regarding possible effects on t_{max}, which may be relevant for substances where early onset of effect is critical, the dose-dependence of the effect on gastric emptying and that the largest effects on gastric emptying are observed at initiation of treatment.

In study GPGR, investigating the effect of tirzepatide on oral contraceptives, AUC_{0-t} of ethinylestradiol and norgestimate was reduced by 20 and 16% respectively, AUC_{0-T} by 21 and 23% respectively and C_{max} by 59 and 55% respectively. For dulaglutide and other pure GLP-1 receptor agonists, effects on C_{max} but not on AUC of oral contraceptives have been observed. The the exact mechanism of this difference cannot be explained, but the effect on AUC is considered of not being of clinical relevance, especially since the starting dose in T2DM patients of 2.5 mg is expected to lead to a smaller GE delay than the 5 mg single dose used in the DDI study with oral contraceptives and since the GED effect has been shown to decrease on repeated dosing.

Pharmacodynamic effects

Characterization of primary and secondary pharmacodynamics effects was appropriately conducted. Tirzepatide decreased fasting and postprandial glucose concentrations and HBA1C dose dependently in patients with T2DM. Clinically relevant effects were observed in a dose range between 5 mg QW and 15 mg QW. First and second phase insulin secretion increased, beta cell function and sensitivity of beta cells to glucose improved. The results were inconsistent with regards to whole body insulin resistance. Mean HOMA-IR increased slightly from 2.0 to 2.5 in patients with T2DM, indicating lack of a beneficial effect or even an increase in insulin resistance. However, data were inconclusive since also in the placebo group HOMA-IR values increased from 1.8 – 2.2. On the other hand, in the Hyperinsulinemic Euglycaemic Clamp study in patients with T2DM tirzepatide increased the M-value indicating an increased whole body insulin sensitivity. The effect was significantly larger than the effect of semaglutide 1 mg QW. Taken together, the data are more in line with the assumption that tirzepatide increases whole body insulin sensitivity.

Overall, the effects as observed at a tirzepatide dose level of 15 mg QW were qualitatively similar but statistically significantly or numerically larger than those observed with the GLP-1 agonist semaglutide 1 mg QW. This raises the question, whether the additional efficacy is related to an additional effect at GIP receptors or whether tirzepatide is mainly a GLP-1 agonist with a higher potency or higher efficacy at the dose level of 15 mg QW as compared to semaglutide 1 mg QW. Higher doses of semaglutide (2.4 mg QW) were administered for weight reduction in patients with overweight (Wilding et al., N Engl J Med 2021; 384:989-100) and it is conceivable that 1 mg is not the maximally effective dose. Opposite effects on glucagon release are expected for GIP and GLP-1 agonists. GLP1-1 receptor agonists are expected to decrease glucagon levels at high blood glucose concentrations, whereas GIP agonists increase glucagon levels at low glucose concentrations counterbalancing the risk for hypoglycaemias. With a dual agonist, glucagon excretion should be higher at low blood glucose concentrations than with a pure GLP-1 agonist. However, this was not the case in the clinical program. In the sMMTT, fasting glucagon secretion and post prandial incremental glucagon 0 – 240 min secretion were lower with tirzepatide than with semaglutide. Mathiesen DS et al., Int J Mol Sci. 2019; 20: 4092 described differences in the GIP mediated regulation of the insulinotropic and glucagonotropic effect in healthy subjects and patients with T2DM and indicated that the effect on fasting glucagon levels remain to be characterized. The relevance of the GIP-R agonism of tirzepatide in patients with T2DM is therefore unclear. The applicant explained that patients in the sMMTT study were not hypoglycaemic and no increase in glucagon levels with tirzepatide were expected. There is an ongoing phase 1 study that more specifically investigates tirzepatide action on α-cell function under the conditions of induced hypoglycaemia. The results may provide a better insight into the mechanism of action.

The weight reduction observed with tirzepatide 15 mg QW was to a large degree due to a reduction in body fat mass and to a lesser degree to non-fat mass, indicating that the reduction is associated with a beneficial effect on whole body composition. The effect was larger than effects obtained with semaglutide 1 mg QW but in a cross study comparison similar effects on body weight and body composition were observed with a higher dose of semaglutide (2.4 mg QW, Wilding et al., N Engl J Med 2021; 384:989-100) indicating that GLP-1 agonistic effects alone may explain the results.

The Applicant provided extensive exposure-response modelling for several efficacy parameters (fasting plasma glucose, HbA1c, and body weight). It is believed that the models have provided valuable insights throughout the clinical development, but their role is insignificant at this stage, when there are clinical data available on both efficacy and safety from 5 global and 2 Japanese Phase 3 studies. It should be pointed out though, that the model for tirzepatide's effect on body weight is flawed since it is modelling a confounded relationship. The exposure is highly dependent on body weight, and body weight is included as a time-varying covariate in the

popPK model. Hence, individual exposures derived through the popPK model are not independent in relation to changes in body weight. The model should therefore be disregarded, and no predictions should be made based on this model.
The observed cardiovascular actions are expected class effects of GLP-1 agonists. The decrease in systolic blood pressure may be beneficial in patients at an increased CV risk. In general, an increase in heart rate is associated with an increase in CV risk (prognostic marker). However, the therapeutic administration of GLP-1 agonists has not been associated with a negative impact on CV outcome (not a predictive marker). The increase in heart rate has been adequately reflected in the SmPC.

The exposure response analyses provided for PR and QTc intervals do not raise concerns per se. PR prolongation is not mentioned in the SmPC. Since it cannot be excluded a priori that in patients with AV-block tirzepatide may exaggerate the condition, PR prolongation should be added to the PD actions (5.1 "cardiovascular evaluation"). The exposure response analyses based on phase 1 and 2 trials cover doses up to 15 mg QW but not on supratherapeutic doses. Analyses including also phase 3 data sufficiently represent high exposures in clinical practice. Model predicted values with Cmax, ss in 70 and in 90 kg individuals were provided. The data do not indicate an increase in QTc in patients at lower weight. The results are in line with the requirements as laid down in ICH E14 Question and answer documents to serve as a substitute for a TQT study. The symmetrical higher rate of patients with increased and decreased QTc values are reasonably explained by statistical effects. Since also the assessment of CV safety in the phase 3 studies did not raise concerns there is no concern of a torsadogenic potential of tirzepatide.

PD interactions are conceivable with drugs targeting the same PD endpoints relevant for effects on glucose homeostasis, systolic blood pressure or heart rate. PD interactions with insulin or insulin secretagogues may increase the risk of hypoglycaemia in case of coadministration. The concern of an increased risk of hypoglycaemia when used with insulin/SU is reflected in section 4.2, 4.4, and 4.8, but not in 4.5. This is consistent with other approved medicinal products and is acceptable. Coadministration with drugs affecting gastric emptying may mutually potentiate the effect. In the absence of data on the coadministration it can be accepted that the description of the effect on gastric emptying in section 5.1. is sufficient to bring the issue to the attention of prescribing physicians even in case of co-administration with other drugs with similar secondary PD effects.

2.6.4. Conclusions on clinical pharmacology

In general, the pharmacokinetic and PD characterisation is considered appropriate, taking the biochemical and physiological properties of tirzepatide into account. This holds true, considering the known properties of related drugs as e.g. dulaglutide or semaglutide.

The pharmacokinetic and pharmacodynamics information is reflected properly in the SmPC.

2.6.5. Clinical efficacy

A tabulated overview of clinical studies contributing to the current application is provided in section 3.3.

2.6.5.1. Dose response study(ies)

The doses and the dose-escalation scheme used in the Phase 3 studies were selected based on assessment of safety, efficacy (glycaemic and weight loss benefit), and GI tolerability data from the Phase 2 studies GPGB

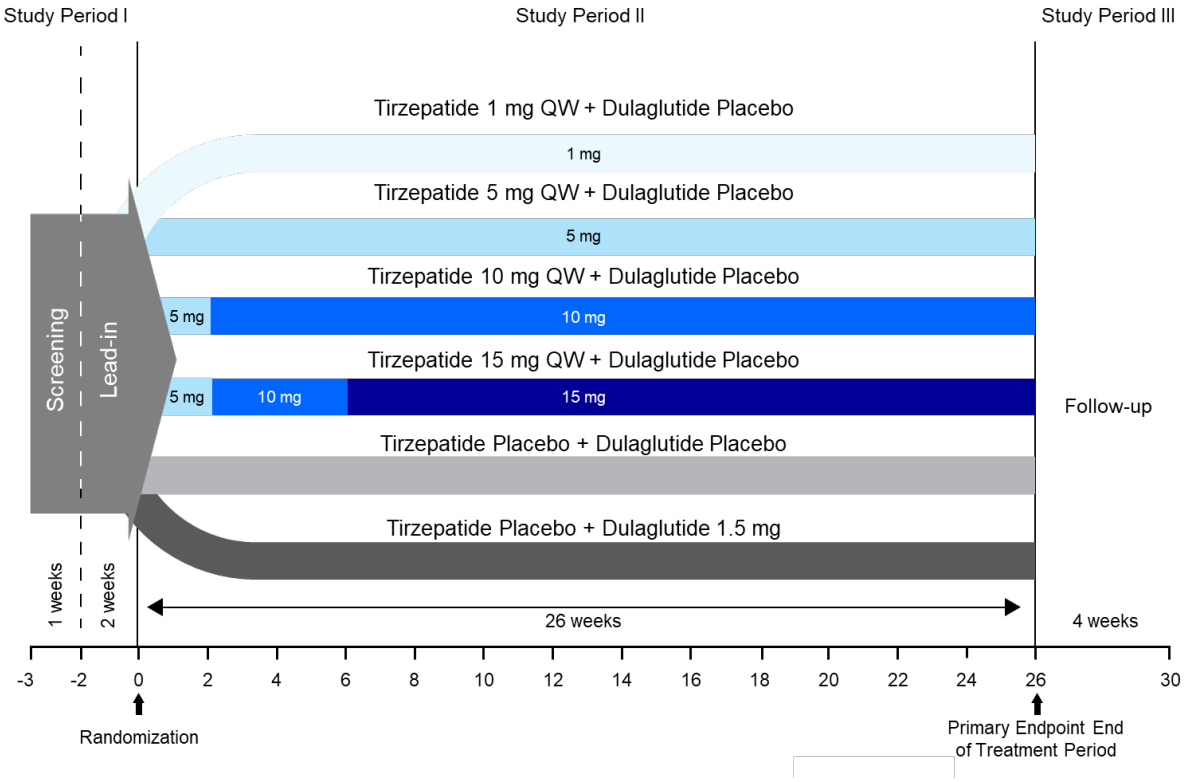
and GPGF and exposure-response modelling of data from patients with T2DM in the Phase 1 and 2 studies (for details on exposure-response modelling please refer to section pharmacodynamics of this report).

Phase 2 Study GPGB

Study GPGB was a 26-week study with the aim to explore the dose response relationship of tirzepatide (1, 5, 10, and 15 mg) and collect efficacy and safety data in comparison with placebo and dulaglutide 1.5 mg.

The escalation scheme for the investigational doses of tirzepatide was based on tolerability data from the Phase 1 Study GPGA. The figure below illustrates the study design including the dose-escalation scheme:

Study design GPGB



Study GPGB enrolled patients with T2DM with inadequate glycaemic control based on HbA1c values ranging from 7.0% to 10.5%. The table below presents key patient demographic characteristics at baseline. Approximately 90% of randomized patients were receiving a stable dose of metformin at baseline.

Summary of results

For brevity, baseline characteristics for study GBGB, which were balanced across treatment groups, are not given in this overview.

The primary efficacy measure was HbA1c change from baseline to 26 weeks. The primary analyses were performed on the mITT population using a Bayesian dose-response model. All doses of tirzepatide reduced HbA1c from baseline to 26 weeks relative to placebo in a dose-dependent manner. Superiority to placebo was met for tirzepatide doses of 5, 10, and 15 mg with a superiority margin of -0.8%. These tirzepatide doses also demonstrated non-inferiority to dulaglutide 1.5 mg. Supportive analyses using the MMRM model demonstrated similar results. MMRM model results for Study GPGB are presented here to provide a

presentation format that is consistent with the Phase 3 studies. Key efficacy results are presented in the table below.

Additionally, at 26 weeks for the mITT population on treatment without rescue dataset, compared to placebo, the tirzepatide 5, 10, and 15 mg doses had significantly greater

- proportion of patients achieving HbA1c targets (<7.0% and ≤6.5%)
- mean change in FBG, and
- mean change in body weight.

Tirzepatide 10- and 15 mg doses also had significantly greater proportions of patients achieving the HbA1c target of <5.7%. The tirzepatide 10- and 15 mg doses also demonstrated significantly greater improvements in the above efficacy measures compared with dulaglutide 1.5 mg. Reductions in HbA1c and FBG for tirzepatide 5 mg were significantly greater than with dulaglutide 1.5 mg.

Summary of Analyses for HbA1c, Proportion of Patients Achieving HbA1c Targets, Body Weight, and FBG at Week 26, Study GPGB mITT population on treatment without rescue dataset

Outcome Measure	TZP 1 mg (N=52)	TZP 5 mg (N=55)	TZP 10 mg (N=51)	TZP 15 mg (N=53)	Placebo (N=51)	Dula 1.5 mg (N=54)
HbA1c (%)						
LS Mean Change from Baseline	-0.7	-1.6	-2.0	-2.4	0.1	-1.1
Difference from placebo (p-value)	-0.8 (p<0.001)	-1.7 (p<0.001)	-2.1 (p<0.001)	-2.5 (p<0.001)	NA	-1.2 (p<0.001)
Difference from dula 1.5 mg (p-value)	0.4 (p=0.058)	-0.5 (p=0.015)	-0.9 (p<0.001)	-1.3 (p<0.001)	NA	NA
Proportion of Patients Achieving HbA1c Targets						
<7.0%, n (%)	16 (36.4)	33 (70.2)	40 (93.0)	31 (88.6)	6 (14.6)	27 (57.4)
p-Value vs placebo	p=0.007	p<0.001	p<0.001	p<0.001	NA	p<0.001
p-Value vs dula 1.5 mg	p=0.043	p=0.023	p<0.001	p<0.001	NA	NA
≤6.5%, n (%)	7 (15.9)	30 (63.8)	37 (86.0)	28 (80.0)	1 (2.4)	20 (42.6)
p-Value vs placebo	p=0.037	p<0.001	p<0.001	p<0.001	NA	p<0.001
p-Value vs dula 1.5 mg	p=0.008	p=0.003	p<0.001	p<0.001	NA	NA
<5.7%, n (%)	0	2 (4.3)	9 (20.9)	15 (42.9)	1 (2.4)	1 (2.1)
p-Value vs placebo	p=0.500	p=0.635	p=0.025	p<0.001	NA	p=0.922
p-Value vs dula 1.5 mg	p=0.545	p=0.558	p=0.017	p<0.001	NA	NA
FBG (mg/dL)						
LS Mean Change from Baseline	-6.8	-40.7	-60.7	-57.5	15.5	-21.2
Difference from placebo (p-value)	-22.4 (p=0.010)	-56.2 (p<0.001)	-76.3 (p<0.001)	-73.0 (p<0.001)	NA	-36.8 (p<0.001)
Difference from dula 1.5 mg (p-value)	14.4 (p=0.089)	-19.4 (p=0.020)	-39.5 (p<0.001)	-36.3 (p<0.001)	NA	NA
Body Weight (kg)						

LS Mean Change from Baseline	-0.9	-4.8	-8.7	-11.3	-0.4	-2.7
Difference from placebo (p-value)	-0.5 (p=0.655)	-4.4 (p<0.001)	-8.3 (p<0.001)	-10.9 (p<0.001)	NA	-2.3 (p=0.039)
Difference from dula 1.5 mg (p-value)	1.8 (p=0.105)	-2.1 (p=0.052)	-6.0 (p<0.001)	-8.6 (p<0.001)	NA	NA

Abbreviations: Dula = dulaglutide; HbA1c = glycosylated hemoglobin A1c; FBG = fasting blood glucose; LS = least-squares; mITT = modified intent-to-treat; n = number of patients in the specified category; N = number of patients in the mITT population; NA = not applicable; TZP = tirzepatide; vs = placebo.

Note: p-Values versus placebo or dulaglutide for superiority are presented.

Phase 2 Study GPGF

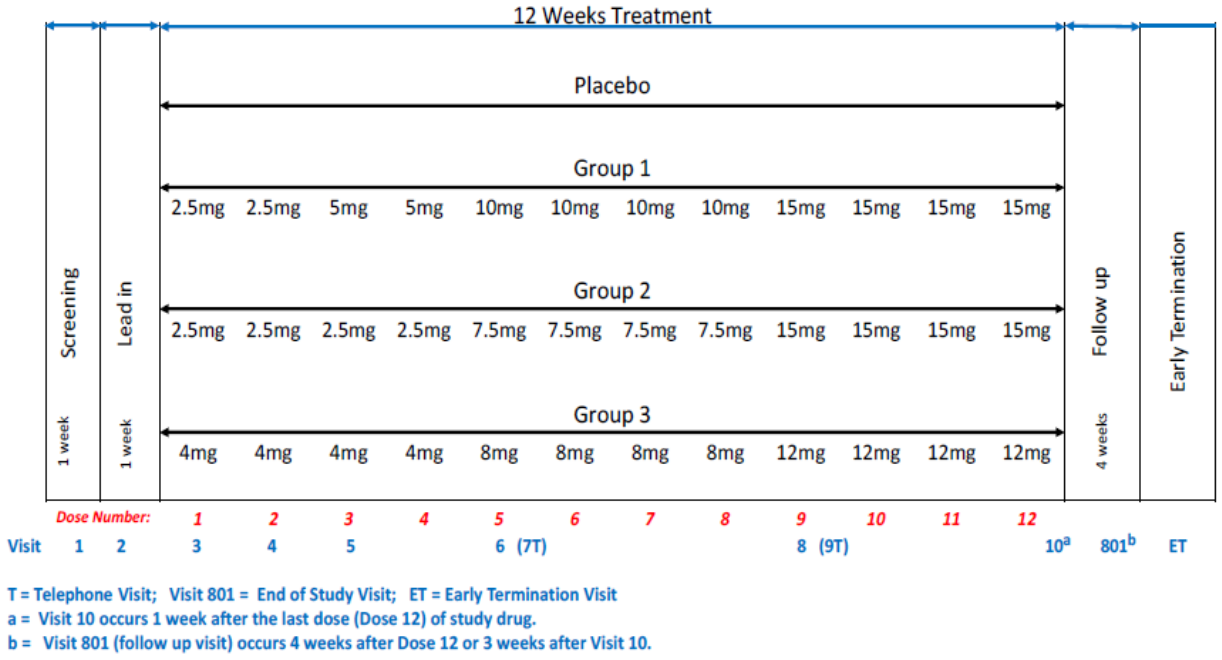
For brevity, baseline characteristics for study GBGF, which were balanced across treatment groups, are not given in this overview.

Study GPGF was a 3-month study with the aim to evaluate the efficacy, safety, and tolerability of subcutaneous once-weekly tirzepatide administered in three different dose-escalation schemes compared with placebo. Study GPGF aimed at determining which dose-escalation scheme would allow patients to reach the highest tirzepatide dose with the lowest incidence of GI AEs. The primary objective of the study was to demonstrate that at least one tirzepatide dose-escalation scheme was superior to placebo in HbA1c reduction at 12 weeks. The escalation schemes explored

- lower starting dose in 2 groups in comparison to Study GPGB (2.5 mg instead of 5 mg)
- the effect of varying duration of the initial dose-escalation steps (2 weeks versus 4 weeks), and
- the magnitude of dose increase during the dose-escalation period (2.5, 4, 5, and 7.5 mg steps).

The figure below illustrates the study design, including dose-escalation schemes. The dose escalation schemes in Study GPGF were chosen based on tolerability data from the Phase 1 Study GPGA and the highest dose and dose-escalation schemes evaluated study GPGB.

Study design GPGF



Abbreviation: QW = once-weekly.

Study GPGF enrolled patients with T2DM with inadequate glycaemic control based on HbA1c values ranging from 7.0% to 10.5%. Approximately 87% of randomized patients were taking a stable dose of metformin at baseline. Key patient demographics and baseline characteristics are given in the following table:

Summary of results

At Week 12, compared to placebo, patients in all three tirzepatide groups had statistically significant reductions in HbA1c, body weight, and FBG compared to placebo.

Summary of Analyses for HbA1c, Proportion of Patients Achieving HbA1c Targets, Body Weight, and Fasting Glucose at Week 12, Study GPGF mITT on Treatment without Rescue data

Outcome Measure	TZP 15 mg-1 (N=28)	TZP 15 mg-2 (N=28)	TZP 12 mg (N=29)	Placebo (N=26)
HbA1c (%)				
LS Mean Change from Baseline	-2.0	-1.8	-1.7	0.2
Difference from placebo (p-value)	-2.2 (p<0.001)	-2.0 (p<0.001)	-1.9 (p<0.001)	NA
Proportion of Patients Achieving HbA1c Targets				
<7%, n (%)	20 (87.0)	22 (84.6)	20 (74.1)	2 (10.0)
p-Value vs placebo	p<0.001	p<0.001	p<0.001	NA
≤6.5%, n (%)	12 (52.2)	17 (65.4)	16 (59.3)	0
p-Value vs placebo	p=0.003	p<0.001	p=0.001	NA
<5.7%, n (%)	1 (4.3)	2 (7.7)	1 (3.7)	0
p-Value vs placebo	p=0.482	p=0.321	p=0.568	NA
FBG (mg/dL)				

Outcome Measure	TZP 15 mg-1 (N=28)	TZP 15 mg-2 (N=28)	TZP 12 mg (N=29)	Placebo (N=26)
LS Mean Change from Baseline	-70.2	-74.2	-60.7	-12.3
Difference from placebo (p-value)	-58.0 (p<0.001)	-61.9 (p<0.001)	-48.5 (p<0.001)	NA
Body Weight (kg)				
LS Mean Change from Baseline	-5.5	-5.7	-5.3	-0.5
Difference from placebo (p-value)	-5.0 (p<0.001)	-5.2 (p<0.001)	-4.8 (p<0.001)	NA

Abbreviations: HbA1c = glycosylated hemoglobin A1c; FBG = fasting blood glucose; LS = least-squares; mITT = modified intent-to-treat; n = number of patients in the specified category; N = number of patients in population; NA = not applicable; TZP = tirzepatide; vs = versus.

LY 15 mg-1 = Escalation dose group of LY3298176 once-weekly of 2.5 mg x 2, 5 mg x 2, 10 mg x 4, 15 mg x 4.

LY 15 mg-2 = Escalation dose group of LY3298176 once-weekly of 2.5 mg x 4, 7.5 mg x 4, 15 mg x 4.

LY 12 mg = Escalation dose group of LY3298176 once-weekly of 4 mg x 4, 8 mg x 4, 12 mg x 4.

Safety results: Treatment emergent adverse events were reported by 77.6% (66 of 85 patients) in the tirzepatide treatment groups and 50% (13 of 26 patients) in the placebo group. Mild to moderate GI events were the most common TEAEs. The combined nausea, vomiting, and diarrhoea AEs of each treatment group suggest that the first exposure to tirzepatide was generally more likely to result in AEs, but the incidence and prevalence may be reduced with lower initial doses. Smaller subsequent dose escalations to higher doses were also more likely to be associated with lower incidences of GI events. There were no reports of severe hypoglycaemia, pancreatitis, cholecystitis, or cholelithiasis.

2.6.5.2. Main study(ies)

Please note: for brevity and ease of reading, key methodological aspects for the five global phase 3 studies are summarised below.

Five phase 3 studies were conducted designed to evaluate the efficacy and safety of once-weekly treatment with injectable tirzepatide at maintenance doses of 5, 10, and 15 mg compared with placebo or active comparators in a broad population of patients with T2DM. Tirzepatide was assessed as monotherapy and as add-on treatment to OAMs or basal insulin.

Key design elements of the five global Phase 3 Studies

	GPGK (SURPASS-1)	GPGL (SURPASS-2)	GPGH (SURPASS-3)	GPGM (SURPASS-4)	GPGI (SURPASS-5)
Study Design	Double-blind	Open-label[a]	Open-label	Open-label	Double-blind
TZP QW Maintenance Doses	5, 10, 15 mg	5, 10, 15 mg	5, 10, 15 mg	5, 10, 15 mg	5, 10, 15 mg
Comparator	PBO	Semaglutide 1 mg	Insulin degludec[b] (titrated)	Insulin glargine[b] (titrated)	PBO
Randomization Scheme	1:1:1:1	1:1:1:1	1:1:1:1	1:1:1:3	1:1:1:1
Treatment Period Duration	40 weeks	40 weeks	52 weeks	52 to 104 weeks	40 weeks
Total # Randomized	478	1878	1437	1995	475

and Treated with Study Drug					
# Randomized and Treated with TZP	363	1409	1077	995	355
Background Medications	None (lifestyle changes only)	Metformin	Metformin ± SGLT-2i	1 to 3 OAMs (± metformin ± SU ± SGLT-2i)	Insulin glargine[b] (titrated) ± metformin
HbA1c Inclusion Criterion	≥7.0 to ≤9.5% (≥53 to ≤80 mmol/mol)	≥7.0 to ≤10.5% (≥53 to ≤91 mmol/mol)	≥7.0 to ≤10.5% (≥53 to ≤91 mmol/mol)	≥7.5 to ≤10.5% (≥58 to ≤91 mmol/mol)	≥7.0 to ≤10.5% (≥53 to ≤91 mmol/mol)

Abbreviations: # = number; ± = with or without; HbA1c = glycosylated hemoglobin A1c; OAM = oral antihyperglycaemic medication; PBO = placebo; QW = once-weekly; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide.

[a] Investigators and patients were blinded to the dose of tirzepatide administered in Study GPGL.

[b] The insulin concentration was 100 units/mL (U100).

The phase 3 studies included both double-blinded and open-label study designs. A double-blind design was possible for studies GPGK and GPGI because tirzepatide and the comparator (placebo) were provided in single-dose pens with the same appearance. Studies GPGL, GPGH, and GPGM were open-label with regard to the assignment of patients to either tirzepatide or the active comparator, due to differences in the devices, differences in the dose-escalation schemes for tirzepatide and semaglutide, and the dose-titration scheme for the insulin comparators, and the inability to obtain a placebo control for semaglutide. Only global Studies GPGH and GPGM were open-label with regard to tirzepatide doses, which enabled dose de-escalation in these studies.

Methods

- **Study Participants**

Patient population

The patient population across the studies included adults with T2DM who varied with regard to their HbA1c requirements, the duration of disease, background therapy, co-morbidities, and complications. Key exclusion criteria included conditions related to special safety topics of pancreatitis, MTC, hepatic function, and diabetic retinopathy.

HbA1c requirements for enrollment

The HbA1c requirements for enrollment in the phase 3 studies varied. The lower limit of the inclusion criterion range was higher in Study GPGM than in the other global phase 3 studies (7.5% instead of 7.0%) to minimize the risk of hypoglycaemia, as some patients enrolled in this study were also taking a sulfonylurea. Additionally, the upper limit of the HbA1c inclusion criterion was lower in placebo-controlled Study GPGK (≤9.5%) than in the other global Phase 3 studies (≤10.5%).

Rescue therapy

Patients enrolled in the clinical trials were tightly monitored for blood glucose during their participation. Rescue therapy could be added to randomized study drug in all studies if patients met the criteria for severe persistent hyperglycaemia. GLP-1 receptor agonists, DPP-4i, and pramlintide were not allowed as rescue

therapy since the mechanism of action of these medications would confound assessment of the efficacy, safety, and tolerability of tirzepatide. For patients randomly assigned to the insulin treatment groups of Studies GPGM and GPGH, the prespecified criteria for initiation of rescue therapy were only applicable after weeks 12 and 16, respectively. During the initial 12 or 16 weeks, the first choice before initiating any rescue therapy with those patients was to increase the dose of basal insulin following the treat-to-target algorithm, which was not considered as rescue therapy.

BMI requirements for enrolment

The majority of the patients in the phase 3 studies had BMI in the obesity or overweight range. Patients were required to be of stable weight for at least 3 months prior to screening. Other than the lifestyle and dietary measures for diabetes treatment, patients were not allowed to initiate a new diet or exercise program with the intent of reducing body weight. The lower limit of the BMI inclusion criteria was lower in the two studies that enrolled patients in Japan compared with the other phase 3 studies: studies GPGL, GPGH, and GPGM required BMI ≥25 kg/m^2 while studies GPGK and GPGI allowed BMI as low as 23 kg/m^2 at screening.

Renal function and CV risk

The inclusion criteria were designed to accommodate country-specific eGFR thresholds for use of some background therapy (for example, metformin). In most phase 3 studies patients with mild to moderate renal impairment were included (lower limit of eGFR 30 ml/min/1.73 m^2), except for study GPGM which had no exclusion criterion based on eGFR.
Study GPGM also included patients with increased risk of CV events, as defined by at least 1 of the following:

- coronary heart disease
- peripheral arterial disease presumed to be of atherosclerotic origin
- cerebrovascular disease presumed to be of atherosclerotic origin
- aged ≥50 years with a history of CKD and eGFR <60 mL/min/1.73 m2, and
- aged ≥50 years with congestive heart failure.

- **Treatments**

Tirzepatide dosing regimen

Dose-escalation scheme and duration of treatment in phase 3 studies

The tirzepatide dose-escalation scheme (increments of 2.5 mg tirzepatide) used in the phase 3 studies is shown in the table below. Patients were treated with the target dose for at least 16 weeks. The 15 mg dose group had the longest dose-escalation period. Treatment durations of 40 weeks (Studies GPGK, GPGL, and GPGI), 52 weeks (Study GPGH), or 52 to 104 weeks (Study GPGM) were planned for the period following study drug initiation.

Tirzepatide Dose-Escalation Scheme in the Phase 3 Studies

Treatment Group	Treatment Period Intervals					
	Weeks 0 to 4	Weeks 4 to 8	Weeks 8 to 12	Weeks 12 to 16	Weeks 16 to 20	Week 20 through End of Treatment Period
Tirzepatide 5 mg	2.5 mg	5 mg	5 mg	5 mg	5 mg	5 mg
Tirzepatide 10 mg	2.5 mg	5 mg	7.5 mg	10 mg	10 mg	10 mg
Tirzepatide 15 mg	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg

Dose de-escalation

Tirzepatide dose de-escalation was allowed during the first 24 weeks of studies Studies GPGH and GPGM. The goal of dose de-escalation was to improve tolerability during study drug initiation and dose escalation for patients with persistent, intolerable GI symptoms and encourage patients to remain in the study on study drug. No dose de-escalation was allowed after week 24. Patients could de-escalate only once to a lower maintenance dose. Those patients who de-escalated remained on that lower maintenance dose throughout the remainder of the study. Patients on tirzepatide 5 mg could not de-escalate to a lower dose and had to discontinue from study drug. Dose de-escalation was used by 14.4% of patients in study GPGH and 15.1% of patients in study GPGM.

Add-On Therapies and Active Comparators

Add-on therapies

Tirzepatide was investigated as monotherapy and as add-on therapy to other glucose-lowering medications, either alone or in combination. The combination therapies reflect the evaluation of tirzepatide throughout disease progression, ranging from metformin alone, to combination therapy with up to 3 commonly used oral medications (metformin ± sulfonylurea ± SGLT-2i), and as add-on to a basal insulin. For the studies in which metformin was allowed, a stable dose (defined as 3 months prior to study entry) was required (≥1500 mg/day).

Active comparators

Insulin degludec, an ultra-long-acting basal insulin, was chosen as the active comparator in study GPGH. Semaglutide 1 mg once-weekly was chosen as the active comparator in study GPGL. The 1 mg dose was the highest marketed dose of semaglutide for the treatment of T2DM available when Study GPGL was initiated.

Both add-on therapy and active comparator

Insulin glargine, a long-acting basal insulin, was chosen as add-on therapy for Study GPGI and as the active comparator in Study GPGM.

- **Outcomes/endpoints**

Efficacy endpoints in Phase 3 studies

The primary endpoint for assessment of efficacy was *change from baseline in HbA1c*. Change from baseline in body weight was a key secondary endpoint (controlled for Type 1 error) in all studies. Additional clinical endpoints included, but were not limited to, proportions of patients reaching glycaemic and body weight loss targets, change from baseline in FSG, 7-point SMBG, waist circumference, change from baseline in lipid profile, and patient-reported outcomes. Two substudies of study GPGH provided data on CGM, change from

baseline in liver fat content, volume of visceral adipose tissue, and volume of abdominal subcutaneous adipose tissue.

Patient reported outcome measures

The following questionnaires were applied in the phase 3 studies:

The *IW-SP questionnaire* contains three items that assessed how often the patients' body weight affects how happy they are with their appearance and how often they feel self-conscious when out in public. Each item was rated on a 5-point scale ranging from 1 "always" to 5 "never." Raw scores were derived by summing the item scores and dividing by the number of items. Scores were then linearly transformed to a range from 0 to 100. Higher IW-SP raw scores and higher transformed scores correspond to better self-perception.

The *APPADL questionnaire* contained seven items that assesses how difficult it was for patients to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs. Items were scored on a 5-point numeric rating scale ranging from 1 "unable to do" to 5 "not at all difficult." Raw scores were derived by summing the item scores and dividing by the number of items. Scores were then linearly transformed to a range from 0 to 100. Higher APPADL raw scores and higher transformed scores correspond to better self-reported ability to perform physical activities of daily living.

An improvement in the *EQ-5D-5L score* indicates better overall health-related quality of life (categorises into five domains: mobility, self-care, usual activities, pain or discomfort, anxiety/depression).

The *DTSQ questionnaire* assesses patient satisfaction with diabetes treatment (e.g. How satisfied are you with your current treatment? Response options: very satisfied to very dissatisfied).

The *IWQOL-Lite-CT* is a 20-item patient-reported outcomes instrument where the instrument assesses three domains of weight-related quality of life: Physical (7 items), Physical Function (comprising 5 of the 7 items included in the Physical domain), and Psychosocial (13 items). Items in the Physical Function composite describe physical limitations related to general and specific physical activities.

- **Statistical methods**

Estimands and efficacy analyses

All efficacy analyses were conducted using all randomly assigned patients who took at least 1 dose of study drug excluding patients who discontinued study drug due to inadvertent enrolment.

Two estimands were specified for evaluating primary and key secondary efficacy objectives (subjected to type I error control).

The "treatment-regimen" estimand represents the efficacy irrespective of adherence to study drug or initiation of rescue antihyperglycaemic therapy. Analyses aligned to the "treatment-regimen" estimand were conducted using all available data obtained up to the primary endpoint visit, regardless of adherence to study drug or initiation of rescue antihyperglycaemic medication. Analyses for mean change from baseline to the primary endpoint visit in HbA1c and other longitudinal continuous variables were conducted utilizing analysis of covariance (ANCOVA). Analysis of the proportion of patients achieving HbA1c reduction targets at the primary endpoint visit was conducted using logistic regression. Analyses were conducted with multiple imputation for missing data at the primary endpoint visit. In Studies GPGL, GPGH, and GPGM imputation of missing data was based on "retrieved dropouts", defined as patients with evaluable data at the primary

endpoint visit in the same treatment arm who prematurely discontinued study drug. In Studies GPGK and GPGI, due to an insufficient number of "retrieved dropouts", missing data were imputed using placebo data.

The "efficacy" estimand represents the efficacy prior to discontinuation of study drug without confounding effects of rescue antihyperglycaemic therapy. Analyses aligned to the "efficacy" estimand were conducted using data obtained up to the primary endpoint visit excluding data after initiation of rescue antihyperglycaemic medication or permanent discontinuation of study drug (last dose date + 7 days). Analyses for mean change from baseline to the primary endpoint visit in HbA1c and other longitudinal continuous variables were conducted utilizing mixed-model repeated measures (MMRM). Analysis of the proportion of patients achieving HbA1c reduction targets at the primary endpoint visit was conducted using logistic regression. Missing data for HbA1c reduction targets at the primary endpoint visit were imputed using the predicted values from MMRM followed by dichotomizing per the cut-off value.

Multiplicity adjustment

No type 1 error rate adjustments were made for conducting analyses relative to "treatment-regimen" and "efficacy" estimands. For analyses within each estimand, graphical multiple testing procedures were used to control the family-wise type 1 error rate at a 2-sided alpha level of 0.05 for evaluating primary and key secondary objectives (subjected to type I error control).

Results

- **Participant flow**

Patient retention

Patient retention in each of the phase 3 studies is shown in the tables below. No differences in patient retention were observed between studies that allowed dose de-escalation (Studies GPGH and GPGM) compared with studies that did not.

Proportions of Patients in the Global Phase 3 Studies Who Completed Study Drug and those how completed the study

	%				
	GPGK (SURPASS-1) (N=478)	**GPGL (SURPASS-2) (N=1878)**	**GPGH (SURPASS-3) (N=1437)**	**GPGM (SURPASS-4) (N=1995)**	**GPGI (SURPASS-5) (N=475)**
Completed Study Drug	86.2	89.3	85.2	85.2	89.3
Completed Study	89.5	94.9	91.8	90.0	94.9

Abbreviations: N = number of patients randomly assigned and treated with at least 1 dose of study drug.

Proportions of Patients Who Completed Study Drug in Each Treatment Group of the Global Phase 3 Studies

Treatment Group	%				
	Study GPGK (SURPASS-1) (N=478)	**Study GPGL (SURPASS-2) (N=1878)**	**Study GPGH (SURPASS-3) (N=1437)**	**Study GPGM (SURPASS-4) (N=1995)**	**Study GPGI (SURPASS-5) (N=475)**
TZP 5 mg	90.9	91.5	88.0	84.5	90.5

TZP 10 mg	90.1	87.6	81.4	86.1	88.2
TZP 15 mg	78.5	86.8	83.6	83.7	81.7
Active Comparator	–	91.3	87.7	85.7	–
Placebo	85.2	–	–	–	96.7

Abbreviations: N = number of patients randomly assigned and treated with at least 1 dose of study drug; TZP = tirzepatide.
Note: The active comparators included semaglutide (Study GPGL), titrated insulin degludec (Study GPGH), and titrated insulin glargine (Study GPGM).

- **Recruitment**
- **Conduct of the study**
- **Baseline data**

Demographics

Across the Phase 3 studies, adult patients with T2DM had at baseline:

- mean HbA1c that ranged from 7.94% to 8.52% (63.3 to 69.7 mmol/mol)
- mean age that ranged from 54.1 to 63.6 years (age groups are detailed under "Studies in special populations of this overview")
- mean weight that ranged from 85.9 to 95.2 kg
- mean BMI that ranged from 31.9 to 34.2 kg/m2
- mean duration of diabetes that ranged from 4.7 to 13.3 years.

Summary of Baseline Clinical Characteristics in Tirzepatide Phase 3 Studies
mITT Population

	Study GPGK N=478	**Study GPGL N=1878**	**Study GPGH N=1437**	**Study GPGM N=1995**	**Study GPGI N=475**
Weight (kg)					
Mean ± SD	85.9 ± 19.77	93.7 ± 21.86	94.3 ± 20.06	90.3 ± 18.66	95.2 ± 21.64
Median	82.9	90.1	91.6	88.3	93.5
Min; Max	44.6; 175.0	50.1; 222.1	53.2; 229.0	51.5; 227.0	43.1; 198.0
BMI (kg/m^2)					
Mean ± SD	31.9 ± 6.59	34.2 ± 6.93	33.5 ± 6.06	32.6 ± 5.54	33.4 ± 6.06
Median	30.4	32.8	32.6	31.7	32.8
Min; Max	21.6; 68.3	22.7; 89.3	21.5; 67.4	21.7; 67.9	22.7; 55.2
BMI Group, n (%)					
<30 kg/m^2	224 (46.9)	552 (29.4)	446 (31.0)	718 (36.0)	152 (32.0)
≥30 to <35 kg/m^2	123 (25.7)	636 (33.9)	496 (34.5)	721 (36.1)	143 (30.1)
≥35 kg/m^2	131 (27.4)	690 (36.7)	495 (34.4)	556 (27.9)	180 (37.9)
Duration of Diabetes (years)					
Mean ± SD	4.7 ± 5.4	8.62 ± 6.46	8.38 ± 6.24	11.78 ± 7.51	13.3 ± 7.3
Median	2.8	7.06	7.27	10.53	11.93
Min; Max	0.0; 32.8	0.3; 42.0	0.0; 59.7	0.3; 48.7	0.6; 39.7
Duration of Diabetes Group, n (%)					
≤5 years	323 (67.6)	643 (34.2)	502 (35.0)	368 (18.4)	58 (12.2)
>5 to ≤10 years	89 (18.6)	599 (31.9)	465 (32.4)	1058 (53.0)	111 (23.4)

>10 years	66 (13.8)	636 (33.9)	469 (32.7)	569 (28.5)	306 (64.4)
Antihyperglycaemic Treatment, n (%)					
No OAM	478 (100.0)	0	0	0	0
1 OAM	0	1878 (100.0)	979 (68.1)	725 (36.3)	0
2 OAMs	0	0	458 (31.9)	1052 (52.7)	0
3 OAMs	0	0	0	217 (10.9)	0
Insulin	0	0	0	0	81 (17.1)
Insulin + metformin	0	0	0	0	394 (82.9)
HbA1c (%)					
Mean ± SD	7.94 ± 0.87	8.28 ± 1.03	8.17 ± 0.91	8.52 ± 0.88	8.31 ± 0.85
Median	7.80	8.10	8.00	8.40	8.20
Min; Max	5.2; 11.5	5.6; 12.2	4.9; 11.5	5.5; 15.8	6.3; 11.0
HbA1c (mmol/mol)					
Mean ± SD	63.3 ± 9.46	67.0 ± 11.25	65.8 ± 9.99	69.7 ± 9.65	67.4 ± 9.31
Median	61.8	65.0	63.9	68.3	66.1
Min; Max	33.3; 102.2	37.7; 109.8	30.1; 102.2	36.6; 149.2	45.4; 96.7
HbA1c (%) Group, n (%)					
≤8.5%	378 (79.1)	1192 (63.5)	1005 (69.9)	1131 (56.7)	N/A[a]
≥8.5%	100 (20.9)	686 (36.5)	432 (30.1)	864 (43.3)	N/A[a]
FSG (mg/dL)					
Mean ± SD	153.6 ± 39.83	172.9 ± 51.46	169.3 ± 45.89	171.2 ± 50.75	162.4 ± 51.27
Median	147.9	163.0	162.1	164.0	151.3
Min; Max	52.2; 329.7	20.0; 394.0	47.0; 485.0	41.0; 549.0	46.0; 505.0
FSG (mmol/L)					
Mean ± SD	8.5 ± 2.21	9.6 ± 2.86	9.4 ± 2.55	9.5 ± 2.82	9.0 ± 2.85
Median	8.2	9.1	9.0	9.1	8.4
Min; Max	2.9; 18.3	1.1; 21.9	2.6; 26.9	2.3; 30.5	2.6; 28.0
eGFR CKD-EPI (mL/min/1.73 m^2)					
Mean ± SD	94.1 ± 19.70	96.0 ± 17.07	94.1 ± 17.04	81.3 ± 21.11	85.5 ± 17.78
Median	96.0	98.0	97.0	86.0	87.0
Min; Max	43.0; 144.0	45.0; 151.0	44.0; 141.0	16.0; 133.0	35.0; 140.0
<60 mL/min/1.73 m^2	28 (5.9)	64 (3.4)	56 (3.9)	342 (17.1)	47 (9.9)
≥60 mL/min/1.73 m^2	450 (94.1)	1814 (96.6)	1381 (96.1)	1653 (82.9)	428 (90.1)

Abbreviations: BMI = body mass index; CKD-EPI = Chronic Kidney Disease-Epidemiology; eGFR = estimated glomerular filtration rate; FSG = fasting serum glucose; HbA1c = glycosylated hemoglobin A1c; Max = maximum; Min = minimum; mITT = modified intent-to-treat; n = number of patients in category; N = number of patients who were randomized and received at least 1 dose of study drug; N/A = not available; OAM = oral antihyperglycaemic medication; SD = standard deviation.

Global population

A total of 6263 patients were randomly assigned and treated with at least one dose of study drug (modified intent-to-treat population) in the phase 3 studies. Patients were recruited globally.

Study GPGK did not include patients from Europe due to restrictions on the duration of placebo-controlled studies (EMA 2018). Overall, 45% of patients were women, 46.6% were Hispanic or Latino, 3.6% were Black or African American, and 6.8% were Asian. By design, Study GPGM had the highest proportion of patients with a history of CV disease at baseline (86.8%).

Summary of Regional Demographics in the 5 Global Phase 3 Tirzepatide Studies mITT Population

Region	n (%)					
	Study GPGK (SURPASS-1) (n=478)	Study GPGL (SURPASS-2) (n=1878)	Study GPGH (SURPASS-3) (n=1437)	Study GPGM (SURPASS-4) (n=1995)	Study GPGI (SURPASS-5) (n=475)	Total (N=6263)
North America	152 (31.8)	534 (28.4)	330 (23.0)	385 (19.3)	46 (9.7)	1447 (23.1)
Central/South America and Mexico	164 (34.3)	1139 (60.6)	224 (15.6)	893 (44.8)	-	2420 (38.6)
Asia (excluding Japan)	73 (15.3)	87 (4.6)	70 (4.9)	59 (3.0)	-	289 (4.6)
Japan	89 (18.6)	-	-	-	82 (17.3)	171 (2.7)
EU/United Kingdom/Ukraine	-	72 (3.8)	813 (56.6)	551 (27.6)	347 (73.1)	1783 (28.5)
Rest of World	-	46 (2.4)	-	107 (5.4)	-	153 (2.4)

Abbreviations: EU = European Union; mITT = modified intent-to-treat; n = number of patients in the specified category; N = number of patients who were randomly assigned and received at least 1 dose of study drug.

Note: North America = United States, including Puerto Rico, and Canada; Central/South America and Mexico = Argentina, Brazil, Mexico; Asia (excluding Japan) = India, Israel, South Korea, and Taiwan; EU/United Kingdom/Ukraine = Austria, Czech Republic, Germany, Greece, Hungary, Italy, Poland, Romania, Slovakia, Spain, Ukraine, and United Kingdom; Rest of World includes Australia and Russian Federation.

- **Outcomes and estimation**

Efficacy Results

This section contains the results of the primary and key secondary objectives of the five global phase 3 studies GPGK, GPGL, GPGH, GPGM, and GPGI and are grouped by:

1. HbA1c measures
2. FSG and 7-point SMBG
3. Body weight measures
4. Lipid parameters, and
5. PRO measures.

Results are provided for the *treatment regimen estimand* (all data irrespective of adherence to study drug or introduction of resue); *for brevity, results for the efficacy estimand (on-treatment without rescue) are not regularily provided in this Overview.*

GPGK Study (SURPASS-1): results

Primary endpoint: mean change from baseline in HbA1c

Tirzepatide 5, 10, and 15 mg were superior to placebo on mean change from baseline in HbA1c at 40 weeks using both estimands (***p<0.001). Additionally, compared with placebo, all three doses of tirzepatide had significantly higher proportions of patients who achieved HbA1c target values of:

- <7.0% (<53 mmol/mol)
- ≤6.5% (≤48 mmol/mol), and
- <5.7% (<39 mmol/mol)

Results (including those on the secondary endpoints responder analyses) are given in the following table for both the treatment-regimen estimand and the efficacy estimand:

Summary of HbA1c Efficacy Endpoints for Study GPGK, mITT Population

	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=120	Placebo N=113
HbA1c (%)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	7.97 → 6.20	7.90 → 6.24	7.85 → 6.25	8.07 → 7.86
Change from baseline at Week 40	-1.75†††	-1.71†††	-1.69†††	-0.09
Difference from placebo (95% CI)	-1.66*** (-1.96, -1.36)	-1.62*** (-1.92, -1.32)	-1.60*** (-1.91, -1.30)	NA
Efficacy Estimand[b]				
Baseline → Week 40	7.97 → 6.08	7.88 → 6.06	7.88 → 5.88	8.08 → 7.99
Change from baseline at Week 40	-1.87†††	-1.89†††	-2.07†††	0.04
Difference from placebo (95% CI)	-1.91*** (-2.18, -1.63)	-1.93*** (-2.21, -1.65)	-2.11*** (-2.39, -1.83)	NA
HbA1c (mmol/mol)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	63.59 → 44.27	62.86 → 44.68	62.34 → 44.86	64.71 → 62.39
Change from baseline at Week 40	-19.09†††	-18.67†††	-18.49†††	-0.96
Difference from placebo (95% CI)	-18.12*** (-21.40, -14.85)	-17.70*** (-20.99, -14.42)	-17.53*** (-20.85, -14.20)	NA
Efficacy Estimand[b]				
Baseline → Week 40	63.6 → 43.0	62.6 → 42.7	62.6 → 40.7	64.8 → 63.8
Change from baseline at Week 40	-20.4†††	-20.7†††	-22.7†††	0.4
Difference from placebo (95% CI)	-20.8*** (-23.9, -17.8)	-21.1*** (-24.1, -18.0)	-23.1*** (-26.2, -20.0)	NA
Percentage of patients with HbA1c <7.0% (<53 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	81.8***	84.5***	78.3***	23.0
Efficacy Estimand[d]	86.8***	91.5***	87.9***	19.6
Percentage of patients with HbA1c ≤6.5% (≤48 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	75.3###	73.8###	72.7###	11.3
Efficacy Estimand[d]	81.8###	81.4###	86.2###	9.8
Percentage of patients with HbA1c <5.7% (<39 mmol/mol) at Week 40 (%)				

	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=120	Placebo N=113
Treatment-Regimen Estimand[c]	30.9***	26.8***	38.4***	1.4
Efficacy Estimand[d]	33.9***	30.5***	51.7***	0.9

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; HbA1c = glycosylated hemoglobin A1c; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the full and efficacy analysis sets; NA = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using placebo imputation; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using retrieved placebo imputation.

d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

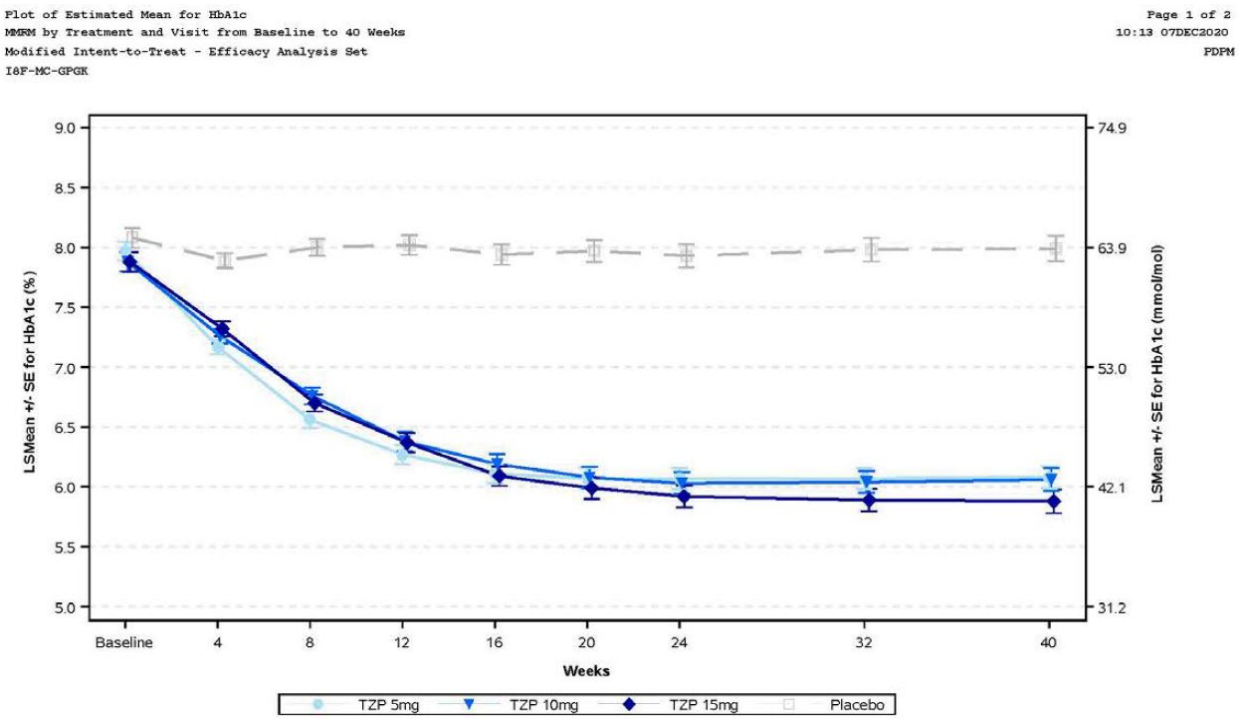
***p-Value <0.001 versus placebo subject to type 1 error rate control.

###Nominal p-value <0.001 versus placebo, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Mean change from baseline in HbA1c *over time* to 40 weeks

All three tirzepatide dose groups had significantly larger mean reductions from baseline in HbA1c compared with placebo beginning with week 4. Maximal reductions from baseline in HbA1c by all tirzepatide doses were reached at around 24 weeks and were maintained through 40 weeks.



Secondary endpoints

All key secondary efficacy objectives were controlled for type 1 error.

Fasting serum glucose

Tirzepatide 5, 10, and 15 mg showed statistically significant reduction in FSG from baseline to 40 weeks compared with placebo.

7-Point SMBG

Tirzepatide 5, 10, and 15 mg significantly reduced SMBG overall daily mean, pre-meal daily mean, and post-meal daily mean from baseline to 40 weeks compared with placebo

Additionally, compared to placebo, all three doses of tirzepatide significantly reduced mean SMBG levels for all 7 timepoints.

Summary of Blood Glucose Efficacy Endpoints for Study GPGK

	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=120	Placebo N=113
FSG (mg/dL)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	153.7 → 114.2	152.6 → 114.0	153.6 → 115.1	155.2 → 157.4
Change from baseline at Week 40	-39.6†††	-39.8†††	-38.6†††	3.7
Difference from placebo (95% CI)	-43.2*** (-54.8, -31.6)	-43.4*** (-55.1, -31.7)	-42.3*** (-54.4, -30.3)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	153.7 → 110.5	152.6 → 108.1	154.6 → 104.8	155.2 → 166.9
Change from baseline at Week 40	-43.6†††	-45.9†††	-49.3†††	12.9††
Difference from placebo (95% CI)	-56.5*** (-66.8, -46.1)	-58.8*** (-69.2, -48.4)	-62.1*** (-72.7, -51.5)	N/A
FSG (mmol/L)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	8.5 → 6.3	8.5 → 6.3	8.5 → 6.4	8.6 → 8.7
Change from baseline at Week 40	-2.2†††	-2.2†††	-2.1†††	0.2
Difference from placebo (95% CI)	-2.4*** (-3.0, -1.8)	-2.4*** (-3.1, -1.8)	-2.3*** (-3.0, -1.7)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	8.5 → 6.1	8.5 → 6.0	8.6 → 5.8	8.6 → 9.3
Change from baseline at Week 40	-2.4†††	-2.6†††	-2.7†††	0.7††
Difference from placebo (95% CI)	-3.1*** (-3.71, -2.56)	-3.3*** (-3.84, -2.69)	-3.5*** (-4.04, -2.86)	N/A
Daily Mean 7-Point SMBG (mg/mL)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 40	182.9 → 125.3	178.6 → 126.7	183.2 → 125.6	180.9 → 173.4
Change from baseline at Week 40	-55.7†††	-54.3†††	-55.4†††	-7.6†
Difference from placebo (95% CI)	-48.1### (-56.5, -39.7)	-46.7### (-55.1, -38.3)	-47.8### (-56.4, -39.2)	N/A
Premeal daily mean				
Baseline → Week 40	163.6 → 116.8	159.4 → 116.8	165.1 → 118.4	161.2 → 156.8
Change from baseline at Week 40	-45.3†††	-45.3†††	-43.6†††	-5.3

	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=120	Placebo N=113
Difference from placebo (95% CI)	-40.0### (-47.1, -32.8)	-40.0### (-47.2, -32.8)	-38.4### (-45.7, -31.0)	N/A
2-Hour postmeal daily mean				
Baseline → Week 40	200.7 → 132.6	195.6 → 136.7	198.7 → 132.9	198.7 → 187.1
Change from baseline at Week 40	-65.3†††	-61.3†††	-65.0†††	-10.8††
Difference from placebo (95% CI)	-54.5### (-64.6, -44.4)	-50.5### (-60.6, -40.3)	-54.2### (-64.6, -43.9)	N/A
Daily Mean 7-Point SMBG (mmol/L)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 40	10.15 → 6.95	9.92 → 7.03	10.17 → 6.97	10.04 → 9.62
Change from baseline at Week 40	-3.1†††	-3.0†††	-3.1†††	-0.4†
Difference from placebo (95% CI)	-2.7### (-3.14, -2.21)	-2.6### (-3.06, -2.13)	-2.7### (-3.13, -2.18)	N/A
Premeal daily mean				
Baseline → Week 40	9.1 → 6.5	8.9 → 6.5	9.2 → 6.6	9.0 → 8.7
Change from baseline at Week 40	-2.5†††	-2.5†††	-2.4†††	-0.3
Difference from placebo (95% CI)	-2.2### (-2.62, -1.82)	-2.2### (-2.62, -1.82)	-2.1### (-2.54, -1.72)	N/A
2-Hour postmeal daily mean				
Baseline → Week 40	11.1 → 7.4	10.9 → 7.6	11.0 → 7.4	11.0 → 10.4
Change from baseline at Week 40	-3.6†††	-3.4†††	-3.6†††	-0.6††
Difference from placebo (95% CI)	-3.0### (-3.58, -2.46)	-2.8### (-3.36, -2.24)	-3.0### (-3.59, -2.44)	N/A

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; FSG = fasting serum glucose; MAR = missing at random; MMRM = mixed model repeated measures; mITT = modified intent-to-treat; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; SMBG = self-monitored blood glucose; TZP = tirzepatide.

a ANCOVA with multiple imputation of missing data at the primary endpoint visit using placebo imputation; ANOVA used at baseline.

b MMRM analysis assuming MAR; ANOVA used at baseline.

Note: Shown are the least-squares means.

***p-Value <0.001 versus placebo subject to type 1 error rate control.

##Nominal p-values <0.01, ###nominal p-values <0.001 versus placebo, not included in graphical testing procedure.

†p-Value <0.05, ††p-value <0.01, †††p-Value <0.001 versus baseline.

Body weight

Tirzepatide 5, 10, and 15 mg demonstrated statistically significant reductions in body weight from baseline to 40 weeks compared with placebo. Additionally, compared to placebo, all 3 doses of tirzepatide had significantly higher proportions of patients who achieved body weight reductions of ≥5%, ≥10%, and ≥15%. Results on body weight change are given in the following table:

Summary of Body Weight Measures for Study GPGK, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=120	Placebo N=113
Body Weight (kg)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	87.0 → 79.5	86.2 → 78.8	85.5 → 78.0	84.5 → 84.8
Change from baseline at Week 40	-6.3†††	-7.0†††	-7.8†††	-1.0
Difference from placebo (95% CI)	-5.3*** (-6.8, -3.9)	-6.0*** (-7.4, -4.6)	-6.8*** (-8.3, -5.4)	NA
Efficacy Estimand[b]				
Baseline → Week 40	87.0 → 79.2	85.7 → 78.4	85.9 → 76.7	84.4 → 85.5
Change from baseline at Week 40	-7.0†††	-7.8†††	-9.5†††	-0.7
Difference from placebo (95% CI)	-6.3*** (-7.8, -4.7)	-7.1*** (-8.6, -5.5)	-8.8*** (-10.3, -7.2)	NA
Percentage of patients with Weight Loss ≥5% at Week 40 (%)				
Treatment-Regimen Estimand[c]	60.97###	70.50###	61.68###	11.29
Efficacy Estimand[d]	66.94###	77.97###	76.72###	14.29
Percentage of patients with Weight Loss ≥10% at Week 40 (%)				
Treatment-Regimen Estimand[c]	27.28##	33.98###	37.66###	0.09
Efficacy Estimand[d]	30.58###	39.83###	47.41###	0.89
Percentage of patients with Weight Loss ≥15% at Week 40 (%)				
Treatment-Regimen Estimand[e]	11.57###	15.70###	23.33###	0
Efficacy Estimand[d]	13.22#	16.95##	26.72##	0

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; MAR = missing at random; MMRM = mixed model repeated measures; N = number of in the efficacy analysis set and full analysis set; NA = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using placebo imputation; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using placebo imputation.

d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

e Fisher's exact test with placebo multiple imputation.

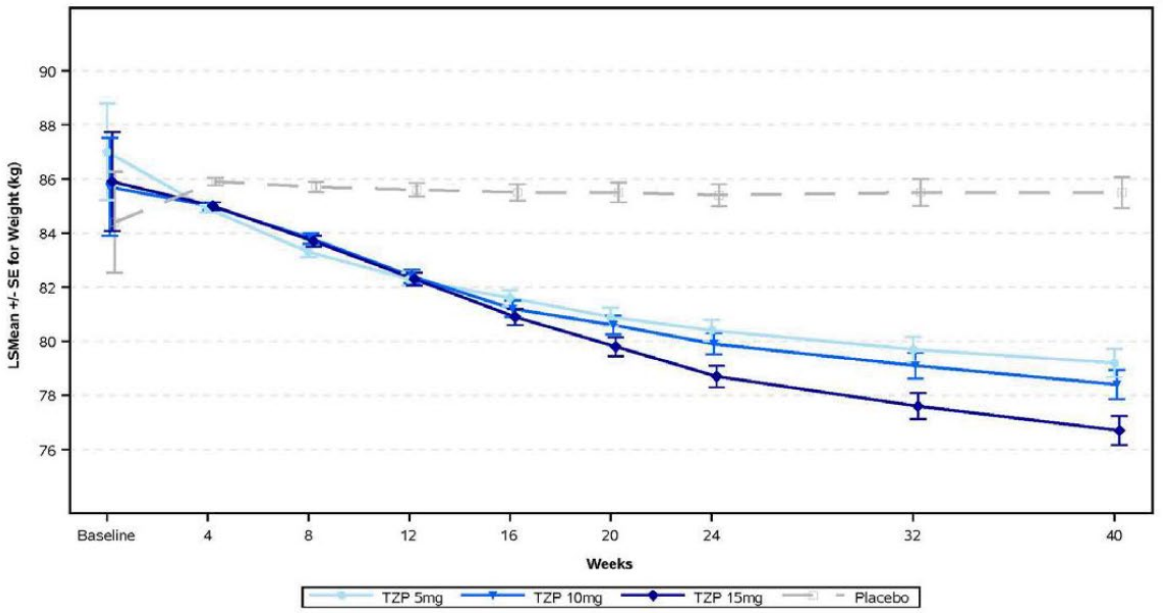
***p-Value <0.001 versus placebo subject to type 1 error rate control.

#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus placebo, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Mean change from baseline in body weight over time to 40 weeks

All three tirzepatide dose groups had significantly greater mean reductions from baseline in body weight compared with placebo beginning at week4. Mean weight reductions continued through 40 weeks and did not appear to plateau.



Lipid parameter results

At 40 weeks, all tirzepatide groups significantly reduced triglycerides, total cholesterol, LDL-C, and VLDL-C and increased HDL-C from baseline. Additionally, all 3 doses of tirzepatide significantly reduced triglycerides, total cholesterol, and VLDL-C and significantly increased HDL-C at 40 weeks compared with placebo. Tirzepatide 15mg also significantly reduced LDL-C compared with placebo. Results on lipid parameters are summarized in the following:

Summary of Lipid Parameters for Study GPGK, mITT Population – Efficacy Analysis Set

Parameters		TZP 5 mg (N=121)	TZP 10 mg (N=121)	TZP 15 mg (N=120)	Placebo (N=113)
Triglycerides					
Baseline → Week 40	(mg/dL)	154.2 → 123.3	149.0 → 123.8	149.4 → 119.5	152.4 → 158.5
	(mmol/L)	1.74 → 1.39	1.68 → 1.40	1.69 → 1.35	1.72 → 1.79
Change from baseline at 40 weeks	(mg/dL)	-28.0	-27.6	-31.8	7.1
	(mmol/L)	-0.32	-0.31	-0.36	0.08
Percent change from baseline at 40 weeks (%)		-18.5†††	-18.2†††	-21.0†††	4.7
Placebo-adjusted percent change at 40 weeks (%) (95% CI)		-22.2### (-30.5, -12.8)	-21.9### (-30.3, -12.4)	-24.6### (-32.8, -15.3)	N/A
Total cholesterol					
Baseline → Week 40	(mg/dL)	181.2 → 171.2	180.4 → 169.6	184.1 → 165.8	177.5 → 179.7
	(mmol/L)	4.69 → 4.43	4.66 → 4.39	4.76 → 4.29	4.59 → 4.65
Change from baseline at 40 weeks	(mg/dL)	-9.9	-11.5	-15.2	-1.4
	(mmol/L)	-0.26	-0.30	-0.39	-0.04
Percent change from baseline at 40 weeks (%)		-5.5†††	-6.3†††	-8.4†††	-0.8

Parameters		TZP 5 mg (N=121)	TZP 10 mg (N=121)	TZP 15 mg (N=120)	Placebo (N=113)
Placebo-adjusted percent change at 40 weeks (%) (95% CI)		-4.8# (-9.0, -0.3)	-5.6# (-9.9, -1.2)	-7.7### (-11.9, -3.3)	N/A
HDL-C					
Baseline → Week 40	(mg/dL)	42.7 → 45.1	43.4 → 44.4	42.5 → 46.2	43.0 → 41.4
	(mmol/L)	1.10 → 1.17	1.12 → 1.15	1.10 → 1.20	1.11 → 1.07
Change from baseline at 40 weeks	(mg/dL)	2.1	1.4	3.2	-1.6
	(mmol/L)	0.05	0.04	0.08	-0.04
Percent change from baseline at 40 weeks (%)		4.8††	3.2†	7.5†††	-3.8†
Placebo-adjusted percent change at 40 weeks (%) (95% CI)		9.0### (4.2, 14.0)	7.3## (2.6, 12.2)	11.7### (6.8, 16.9)	N/A
LDL-C					
Baseline → Week 40	(mg/dL)	101.3 → 94.7	101.4 → 93.8	104.9 → 88.9	97.4 → 99.8
	(mmol/L)	2.62 → 2.45	2.62 → 2.43	2.71 → 2.30	2.52 → 2.58
Change from baseline at 40 weeks	(mg/dL)	-6.7	-7.7	-12.6	-1.7
	(mmol/L)	-0.17	-0.20	-0.33	-0.04
Percent change from baseline at 40 weeks (%)		-6.7††	-7.6††	-12.4†††	-1.6
Placebo-adjusted percent change at 40 weeks (%) (95% CI)		-5.1 (-11.9, 2.2)	-6.0 (-12.8, 1.3)	-11.0## (-17.5, -4.0)	N/A
VLDL-C					
Baseline → Week 40	(mg/dL)	30.5 → 24.5	29.6 → 24.7	29.4 → 24.1	30.3 → 31.3
	(mmol/L)	0.79 → 0.63	0.76 → 0.64	0.76 → 0.62	0.78 → 0.81
Change from baseline at 40 weeks	(mg/dL)	-5.5	-5.2	-5.9	1.3
	(mmol/L)	-0.14	-0.14	-0.15	0.03
Percent change from baseline at 40 weeks (%)		-18.3†††	-17.5†††	-19.8†††	4.3
Placebo-adjusted percent change at 40 weeks (%) (95% CI)		-21.7### (-30.0, -12.4)	-20.9### (-29.3, -11.5)	-23.1### (-31.4, -13.7)	N/A

Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide; VLDL-C = very-low-density lipoprotein cholesterol.

Note: MMRM analysis on log-transformed data then converted back to original scale.

Note: Shown are the estimated means.

#Nominal p-value <0.05, ##nominal p-value <0.01, ### nominal p-value <0.001 versus placebo, not included in graphical testing procedure.

†p-Value <0.05, ††p-value <0.01, †††p-Value <0.001 versus baseline.

PRO measures *(methods are summarized in section 2.6.5.2)*

Tirzepatide seemed to improve patient`s self-perception related to the psychological burden of overweight (IWSP) and overall health-related QoL (EQ VAS). No significant effects in favour of tirzepatide were seen on self-reported ability to perform physical activities of daily living (APPALD) and the UK EQ-5D-5L, measuring health related QoL.

Summary of PRO Efficacy Endpoints for Study GPGK, mITT Population – Efficacy Analysis Set

	TZP 5 mg N=121	TZP 10 mg N=121	TZP 15 mg N=120	Placebo N=113
IW-SP (Transformed Scores)[a]				
n	108	104	94	71
Baseline	65.7	67.6	68.2	67.5
Change from baseline at 40 weeks (LOCF)	10.5†††	14.5†††	13.8†††	5.9††
Change difference from placebo (95% CI)	4.7 (-0.9, 10.2)	8.6## (3.0, 14.2)	7.9## (2.2, 13.7)	N/A
APPADL (Transformed Scores)[a]				
n	108	104	94	71
Baseline	70.7	79.4	79.7	77.1
Change from baseline at 40 weeks (LOCF)	4.5†††	4.8†††	5.9†††	1.8
Change difference from placebo (95% CI)	2.7 (-1.4, 6.8)	3.0 (-1.1, 7.1)	4.0 (-0.2, 8.2)	N/A
EQ-5D-5L (UK)[a]				
n	108	104	93	70
Baseline	0.84	0.88	0.88	0.87
Change from baseline at 40 weeks (LOCF)	0.03†	0.03†	0.04††	0
Change difference from placebo (95% CI)	0.03 (-0.01, 0.07)	0.03 (-0.01, 0.07)	0.04 (0.00, 0.08)	N/A
EQ VAS[a]				
n	108	104	93	70
Baseline	80.4	82.8	83.8	83.4
Change from baseline at 40 weeks (LOCF)	4.2†††	5.3†††	6.4†††	0.2
Change difference from placebo (95% CI)	4.0# (0.8, 7.2)	5.1## (2.0, 8.3)	6.2### (3.0, 9.5)	N/A

Abbreviations: ANCOVA = analysis of covariance; APPADL = Ability to Perform Physical Activities of Daily Living; CI = confidence interval; EAS = efficacy analysis set; EQ VAS = EQ visual analog scale; IW-SP = Impact of Weight on Self-Perception; LOCF = last observation carried forward; mITT = modified intent-to-treat; n = number of patients in the mITT efficacy analysis set with baseline and at least 1 postbaseline values; N = number of patients in EAS; N/A = not applicable; PRO = patient-reported outcome; TZP = tirzepatide.

a ANCOVA, LOCF. Only the nonmissing postbaseline observation prior to rescue or study drug discontinuation was carried forward.

Note: Shown are the least-squares means.

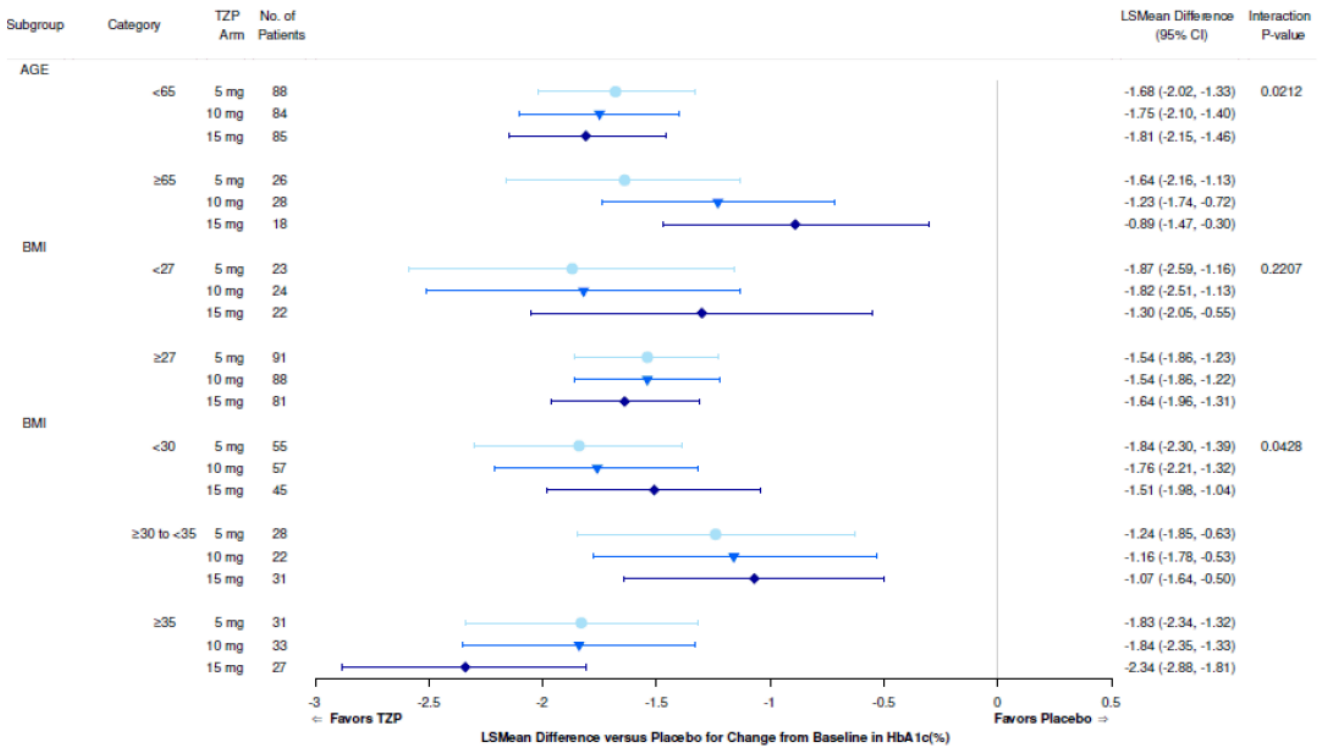
#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus placebo, not included in graphical testing procedure.

†p-Value <0.05, ††p-value <0.01, †††p-value <0.001 versus baseline.

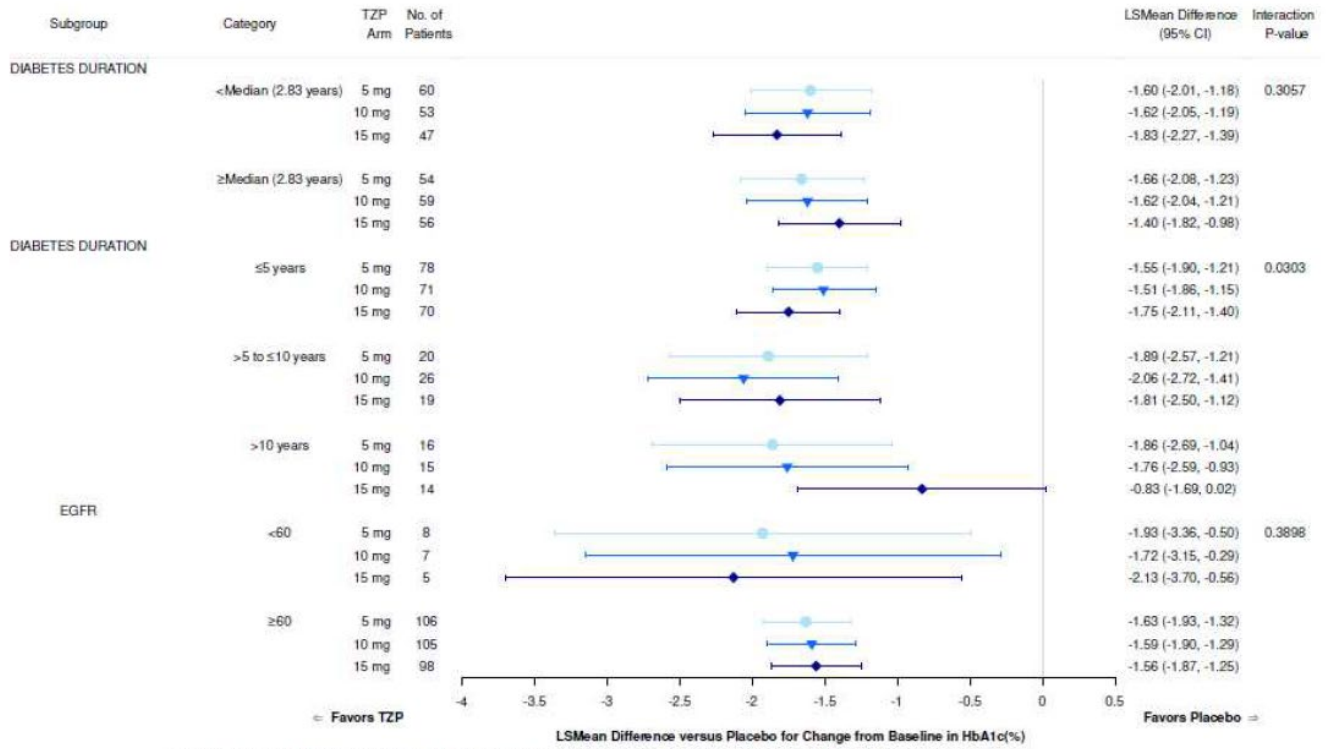
Subgroup analyses of the primary endpoint

Analyses of change from baseline in the HbA1c at 40 weeks (primary endpoint) across patient characteristic subgroups were consistent with the primary results, with the treatment difference favouring all three doses of tirzepatide compared with placebo. Forest plots are presented below:

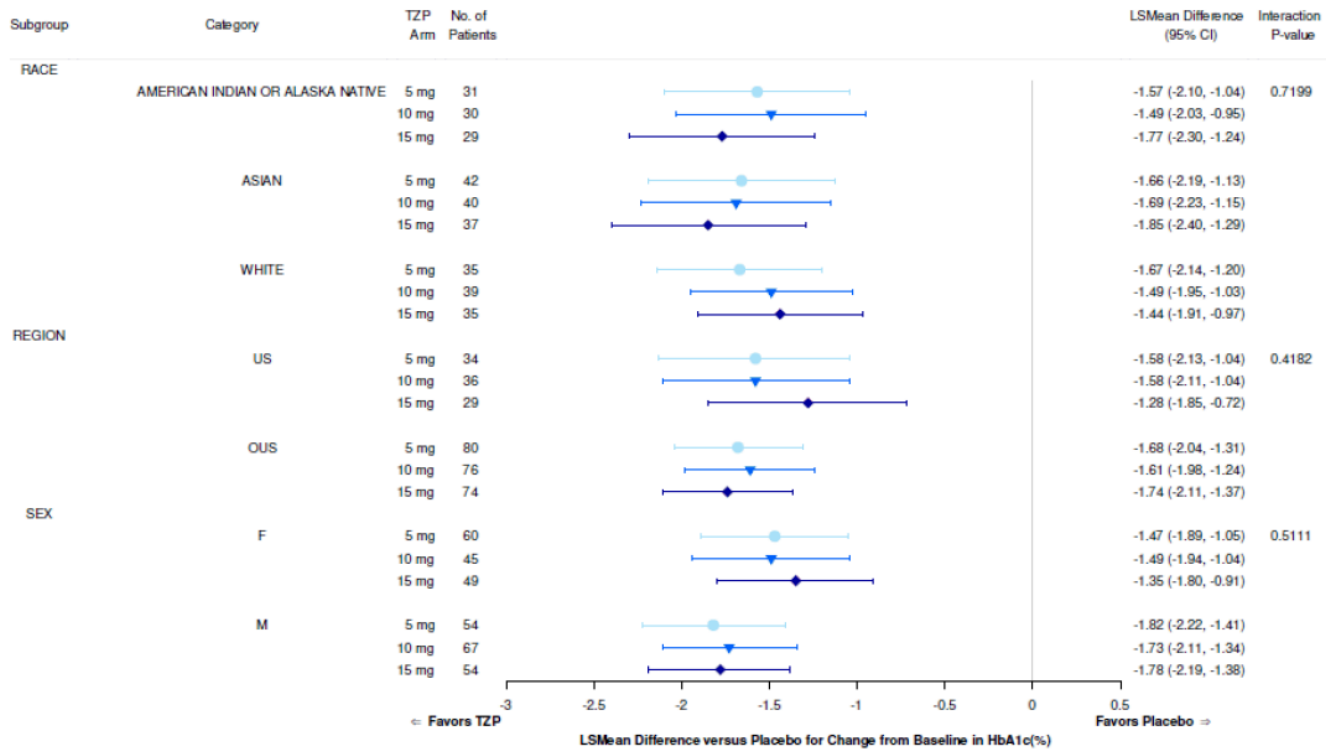
Subgroup Analysis of HbA1c(%) - Change from Baseline at Week 40
Modified Intent-to-Treatment Population - Treatment-Regimen (ANCOVA)
ANCOVA with Imputation Method: Placebo Imputation
I8F-MC-GPGK



Footnote: ANCOVA model for postbaseline measures. Units for Age, BMI and eGFR are years, kg/m2, and mL/min/1.73m2, respectively.
Abbreviations: ANCOVA – analysis of covariance; CI – confidence interval; LSMean – least squares mean; TZP – tirzepatide.



Footnote: ANCOVA model for postbaseline measures. Units for Age, BMI and eGFR are years, kg/m2, and mL/min/1.73m2, respectively.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSMean = least squares mean; TZP = tirzepatide.



Footnote: ANCOVA model for postbaseline measures. Units for Age, BMI and eGFR are years, kg/m2, and mL/min/1.73m2, respectively.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSMean = least squares mean; TZP = tirzepatide.

GPGL Study (SURPASS-2) results:

Primary endpoint: mean change from baseline in HbA1c

At 40 weeks, tirzepatide 5, 10, and 15 mg demonstrated statistically significant reductions in HbA1c from baseline to 40 weeks compared with semaglutide 1 mg.

Additionally, for the efficacy estimand, compared to semaglutide 1 mg, all 3 doses of tirzepatide had significantly higher proportions of patients who achieved HbA1c target values of

<7.0% (<53 mmol/mol)

≤6.5% (≤48 mmol/mol), and

<5.7% (<39 mmol/mol)

Results (including those on the secondary endpoints responder analyses) are given in the following table for both estimands.

Summary of HbA1c Efficacy Endpoints for Study GPGL, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
HbA1c (%)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	8.32 → 6.27	8.30 → 6.04	8.26 → 5.98	8.25 → 6.42
Change from baseline at Week 40	-2.01†††	-2.24†††	-2.30†††	-1.86†††
Difference from semaglutide (95% CI)	-0.15* (-0.28, -0.03)	-0.39*** (-0.51, -0.26)	-0.45*** (-0.57, -0.32)	NA
Efficacy Estimand[b]				
Baseline → Week 40	8.33 → 6.19	8.31 → 5.91	8.25 → 5.82	8.24 → 6.42
Change from baseline at Week 40	-2.09†††	-2.37†††	-2.46†††	-1.86†††
Difference from semaglutide (95% CI)	-0.23*** (-0.36, -0.10)	-0.51*** (-0.64, -0.38)	-0.60*** (-0.73, -0.47)	NA
HbA1c (mmol/mol)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	67.5 → 45.1	67.2 → 42.5	66.8 → 41.8	66.7 → 46.7
Change from baseline at Week 40	-22.0†††	-24.5†††	-25.2†††	-20.3†††
Difference from semaglutide (95% CI)	-1.6* (-3.0, -0.3)	-4.2*** (-5.6, -2.8)	-4.9*** (-6.3, -3.5)	NA
Efficacy Estimand[b]				
Baseline → Week 40	67.5 → 44.2	67.3 → 41.1	66.7 → 40.1	66.6 → 46.7
Change from baseline at Week 40	-22.8†††	-25.9†††	-26.9†††	-20.3†††
Difference from semaglutide (95% CI)	-2.5*** (-3.9, -1.1)	-5.6*** (-7.0, -4.1)	-6.6*** (-8.0, -5.1)	NA
Percentage of patients with HbA1c <7.0% (<53 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	82.0	85.6**	86.2**	79.0
Efficacy Estimand[d]	85.5*	88.9***	92.2***	81.1
Percentage of patients with HbA1c ≤6.5% (≤48 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	68.8	77.1###	79.7###	63.6
Efficacy Estimand[d]	74.0##	82.1###	87.1###	66.2
Percentage of patients with HbA1c <5.7% (<39 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	27.1###	39.8***	45.7***	18.9
Efficacy Estimand[d]	29.3###	44.7***	50.9***	19.7

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; HbA1c = glycosylated hemoglobin A1c; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; NA = not applicable; SEMA = semaglutide; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts.

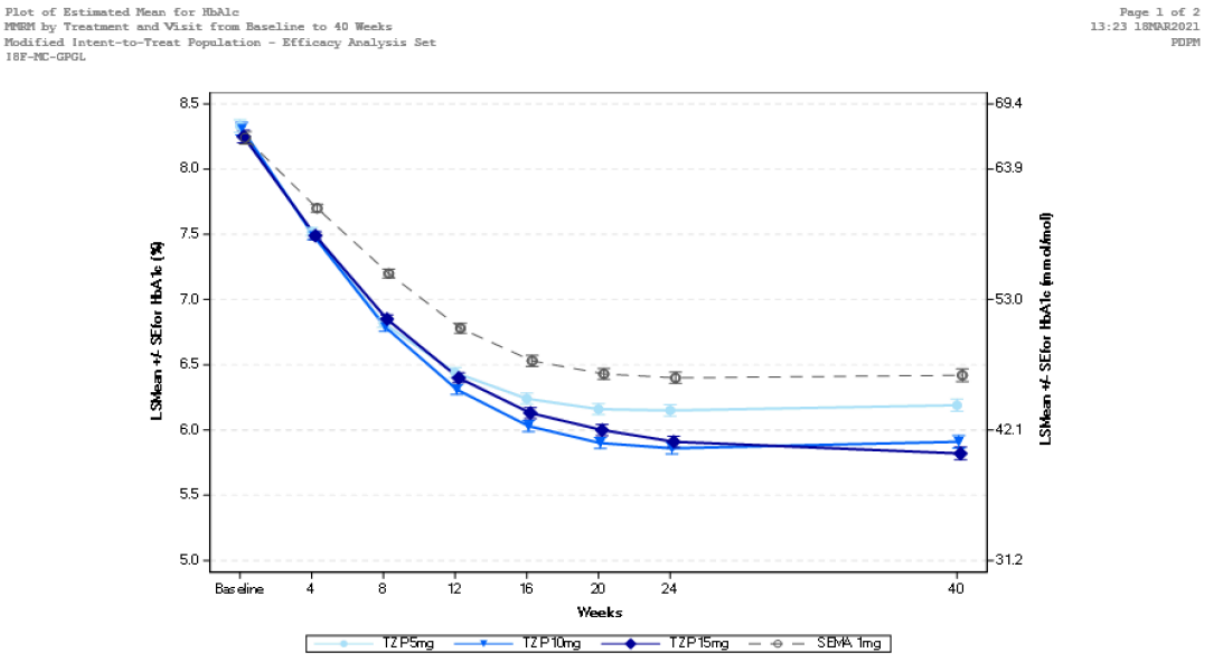
d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

*p-Value <0.05, **p-values <0.01, ***p-value <0.001 versus semaglutide subject to type 1 error control.

##Nominal p-value <0.01, ###nominal p-value <0.001 versus semaglutide, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Mean change from baseline in HbA1c over time to 40 weeks



Secondary endpoints

All key secondary efficacy objectives were controlled for type 1 error. *Fasting serum glucose:* tirzepatide 5, 10, and 15 mg showed statistically significant reductions in FSG from baseline to 40 weeks compared with semaglutide 1mg. *7-Point SMBG*: tirzepatide 5, 10, and 15 mg significantly reduced SMBG overall daily mean, pre-meal daily mean, and postmeal daily mean from baseline to 40 weeks compared with semaglutide 1 mg.

Summary of Blood Glucose Efficacy Endpoints for Study GPGL, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
FSG (mg/dL)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	173.8 → 118.1	174.2 → 113.9	172.4 → 112.7	171.2 → 123.5
Change from baseline at Week 40	-54.8†††	-59.1†††	-60.2†††	-49.4†††
Difference from semaglutide (95% CI)	-5.4# (-9.7, -1.1)	-9.7### (-14.1, -5.2)	-10.8### (-15.1, -6.5)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	174.2 → 117.0	174.6 → 111.3	172.3 → 109.6	170.9 → 124.4
Change from baseline at Week 40	-56.0†††	-61.6†††	-63.4†††	-48.6†††
Difference from semaglutide (95% CI)	-7.3## (-11.7, -3.0)	-13.0### (-17.4, -8.6)	-14.7### (-19.1, -10.3)	N/A
FSG (mmol/L)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	9.65 → 6.55	9.67 → 6.32	9.57 → 6.26	9.50 → 6.86

	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
Change from baseline at Week 40	-3.04†††	-3.28†††	-3.34†††	-2.74†††
Difference from semaglutide (95% CI)	-0.30# (-0.54, -0.06)	-0.54### (-0.78, -0.29)	-0.60### (-0.84, -0.36)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	9.67 → 6.50	9.69 → 6.18	9.56 → 6.09	9.49 → 6.90
Change from baseline at Week 40	-3.11†††	-3.42†††	-3.52†††	-2.70†††
Difference from semaglutide (95% CI)	-0.41## (-0.65, -0.16)	-0.72### (-0.97, -0.48)	-0.82### (-1.06, -0.57)	N/A
Daily Mean 7-Point SMBG (mg/mL)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 40	194.8 → 125.9	192.5 → 120.6	192.0 → 117.0	186.2 → 129.8
Change from baseline at Week 40	-65.4†††	-70.6†††	-74.3†††	-61.4†††
Difference from semaglutide (95% CI)	-4.0## (-6.9, -1.1)	-9.2### (-12.1, -6.3)	-12.9### (-15.8, -10.0)	N/A
Premeal daily mean				
Baseline → Week 40	180.0 → 119.7	178.0 → 115.6	177.8 → 112.4	173.7 → 123.0
Change from baseline at Week 40	-57.5†††	-61.6†††	-64.8†††	-54.2†††
Difference from semaglutide (95% CI)	-3.3# (-6.1, -0.5)	-7.4### (-10.2, -4.6)	-10.6### (-13.4, -7.9)	N/A
2-Hour postmeal daily mean				
Baseline → Week 40	208.1 → 131.9	204.9 → 125.4	204.5 → 121.6	197.8 → 136.3
Change from baseline at Week 40	-71.6†††	-78.2†††	-81.9†††	-67.2†††
Difference from semaglutide (95% CI)	-4.4## (-7.7, -1.1)	-10.9### (-14.2, -7.6)	-14.7### (-18.0, -11.4)	N/A
Daily Mean 7-Point SMBG (mmol/L)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 40	10.81 → 6.99	10.69 → 6.70	10.66 → 6.49	10.34 → 7.21
Change from baseline at Week 40	-3.63†††	-3.92†††	-4.12†††	-3.41†††
Difference from semaglutide (95% CI)	-0.22## (-0.38, -0.06)	-0.51### (-0.67, -0.35)	-0.71### (-0.87, -0.55)	N/A
Premeal daily mean				
Baseline → Week 40	9.99 → 6.65	9.88 → 6.42	9.87 → 6.24	9.64 → 6.83
Change from baseline at Week 40	-3.19†††	-3.42†††	-3.60†††	-3.01†††
Difference from semaglutide (95% CI)	-0.18# (-0.34, -0.03)	-0.41### (-0.56, -0.26)	-0.59### (-0.74, -0.44)	N/A
2-Hour postmeal daily mean				
Baseline → Week 40	11.55 → 7.32	11.37 → 6.96	11.35 → 6.75	10.98 → 7.57
Change from baseline at Week 40	-3.98†††	-4.34†††	-4.55†††	-3.73†††
Difference from semaglutide (95% CI)	-0.24## (-0.43, -0.06)	-0.61### (-0.79, -0.42)	-0.81### (-1.00, -0.63)	N/A

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; FSG = fasting serum glucose; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; SMBG = self-monitored blood glucose; SEMA = semaglutide; TZP = tirzepatide.

a ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b MMRM analysis assuming MAR; ANOVA used at baseline.

Note: Shown are the least-squares means.

#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus semaglutide, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Body weight

Tirzepatide 5, 10, and 15 mg demonstrated statistically significant reductions in body weight from baseline to 40 weeks compared with semaglutide. Additionally, compared to semaglutide, all 3 doses of tirzepatide had significantly higher proportions of patients who achieved body weight reductions of ≥5%, ≥10%, and ≥15%.

Summary of Body Weight Measures for Study GPGL, mITT Population – Full Analysis Set; Efficacy Analysis Set

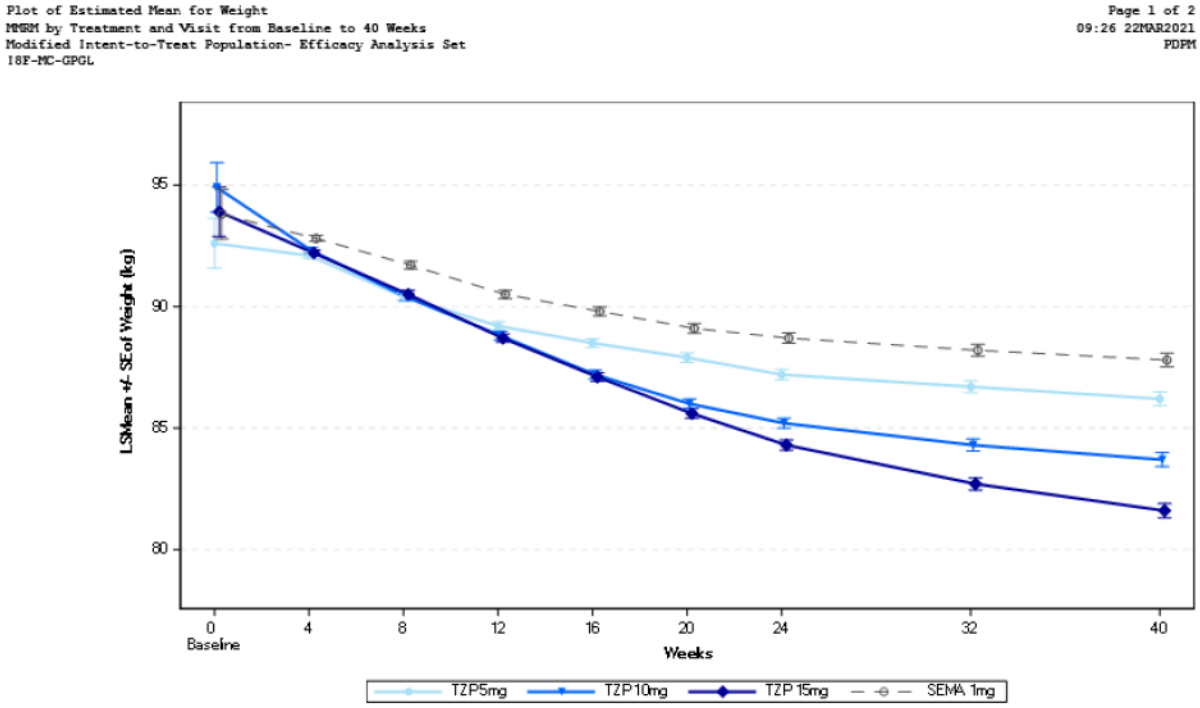
	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
Body Weight (kg)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	92.5 → 86.1	94.8 → 84.4	93.8 → 82.5	93.7 → 88.0
Change from baseline at Week 40	-7.6†††	-9.3†††	-11.2†††	-5.7†††
Difference from semaglutide (95% CI)	-1.9*** (-2.8, -1.0)	-3.6*** (-4.5, -2.7)	-5.5*** (-6.4, -4.6)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	92.6 → 86.2	94.9 → 83.7	93.9 → 81.6	93.8 → 87.8
Change from baseline at Week 40	-7.8†††	-10.3†††	-12.4†††	-6.2†††
Difference from semaglutide (95% CI)	-1.7*** (-2.6, -0.7)	-4.1*** (-5.0, -3.2)	-6.2*** (-7.1, -5.3)	N/A
Percentage of patients with Weight Loss ≥5% at Week 40 (%)				
Treatment-Regimen Estimand[c]	65.3###	76.2###	79.7###	54.0
Efficacy Estimand[d]	68.6##	82.4###	86.2###	58.4
Percentage of patients with Weight Loss ≥10% at Week 40 (%)				
Treatment-Regimen Estimand[c]	34.5###	46.7###	56.9###	23.9
Efficacy Estimand[d]	35.8###	52.9###	64.9###	25.3
Percentage of patients with Weight Loss ≥15% at Week 40 (%)				
Treatment-Regimen Estimand[c]	14.7##	23.9###	35.8###	8.0
Efficacy Estimand[d]	15.2##	27.7###	39.9###	8.7

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; SEMA = semaglutide; TZP = tirzepatide.

[a] Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.
[b] Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.
[c] Logistic regression with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts.
[d] Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.
***p-Value <0.001 versus semaglutide subject to type 1 error rate control.
##Nominal p-value <0.01, ###nominal p-value <0.001 versus semaglutide, not included in graphical testing procedure.
†††p-Value <0.001 versus baseline.

Mean change from baseline in body weight over time to 40 weeks

All three tirzepatide dose groups had significantly greater mean reductions from baseline in body weight compared with semaglutide beginning at Week 4. Weight reductions continued through 40 weeks for all treatment groups and did not appear to plateau.



Lipid parameter results

All treatment groups significantly reduced triglycerides, total cholesterol, LDL-C, and VLDL-C and increased HDL-C from baseline. Additionally, all 3 doses of tirzepatide had significant reductions in triglycerides and VLDL-C and significant increases in HDL-C at 40 weeks compared with semaglutide 1 mg.

Summary of Lipid Parameters for Study GPGL, mITT Population – Efficacy Analysis Set

Parameters	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
Triglycerides				

Parameters		TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
Baseline → Week 40	(mg/dL)	165.9 → 134.1	167.4 → 125.5	163.6 → 124.4	165.2 → 146.4
	(mmol/L)	1.87 → 1.51	1.89 → 1.42	1.85 → 1.40	1.87 → 1.65
Change from baseline at 40 weeks	(mg/dL)	-31.4	-40.0	-41.1	-19.1
	(mmol/L)	-0.35	-0.45	-0.46	-0.22
Percent change from baseline at 40 weeks (%)		-19.0†††	-24.1†††	-24.8†††	-11.5†††
SEMA 1-mg-adjusted percent change at 40 weeks (%) (95% CI)		-8.4### (-13.1, -3.5)	-14.2### (-18.6, -9.6)	-15.0### (-19.3, -10.4)	N/A
Total cholesterol					
Baseline → Week 40	(mg/dL)	171.5 → 161.1	171.3 → 160.3	168.6 → 159.8	170.9 → 162.3
	(mmol/L)	4.44 → 4.17	4.43 → 4.15	4.36 → 4.13	4.42 → 4.20
Change from baseline at 40 weeks	(mg/dL)	-9.4	-10.2	-10.7	-8.2
	(mmol/L)	-0.24	-0.26	-0.28	-0.21
Percent change from baseline at 40 weeks (%)		-5.5†††	-6.0†††	-6.3†††	-4.8†††
SEMA 1-mg-adjusted percent change at 40 weeks (%) (95% CI)		-0.74 (-3.15, 1.72)	-1.24 (-3.65, 1.23)	-1.55 (-3.95, 0.91)	N/A
HDL-C					
Baseline → Week 40	(mg/dL)	42.9 → 45.6	42.7 → 46.1	42.9 → 45.8	42.7 → 44.6
	(mmol/L)	1.11 → 1.18	1.10 → 1.19	1.11 → 1.18	1.10 → 1.15
Change from baseline at 40 weeks	(mg/dL)	2.9	3.4	3.0	1.9
	(mmol/L)	0.08	0.09	0.08	0.05
Percent change from baseline at 40 weeks (%)		6.8†††	7.9†††	7.1†††	4.4†††
SEMA 1-mg-adjusted percent change at 40 weeks (%) (95% CI)		2.3# (0.19,4.41)	3.3## (1.18,5.47)	2.5# (0.42,4.67)	N/A
LDL-C					
Baseline → Week 40	(mg/dL)	88.2 → 81.0	88.4 → 82.8	86.4 → 83.2	88.2 → 82.1
	(mmol/L)	2.28 → 2.09	2.29 → 2.14	2.23 → 2.15	2.28 → 2.12
Change from baseline at 40 weeks	(mg/dL)	-6.7	-4.9	-4.5	-5.6
	(mmol/L)	-0.17	-0.13	-0.12	-0.14
Percent change from baseline at 40 weeks (%)		-7.7†††	-5.6†††	-5.2†††	-6.4†††
SEMA 1-mg-adjusted percent change at 40 weeks (%) (95% CI)		-1.4 (-5.59, 3.02)	0.9 (-3.50, 5.39)	1.3 (-3.04, 5.87)	N/A
VLDL-C					
Baseline → Week 40	(mg/dL)	32.5 → 26.8	32.8 → 25.0	32.3 → 24.8	32.7 → 28.9
	(mmol/L)	0.84 → 0.69	0.85 → 0.65	0.83 → 0.64	0.84 → 0.75
Change from baseline at 40 weeks	(mg/dL)	-5.7	-7.5	-7.7	-3.6
	(mmol/L)	-0.15	-0.19	-0.20	-0.09
Percent change from baseline at 40 weeks (%)		-17.5†††	-23.1†††	-23.7†††	-11.1†††
SEMA 1-mg-adjusted percent change at 40 weeks (%) (95% CI)		-7.2## (-11.8, -2.4)	-13.5### (-17.9, -9.0)	-14.2### (-18.5, -9.6)	N/A

Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; N/A = not applicable; SEMA = semaglutide; TZP = tirzepatide; VLDL-C = very-low-density lipoprotein cholesterol.
Note: MMRM analysis on log-transformed data then converted back to original scale.
Note: Shown are the estimated means.
#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus semaglutide, not included in graphical testing procedure.
†††p-Value <0.001 versus baseline.

PRO measures *(the methodology of the questionaires is summarized in section 2.6.5.2 of this overview)*

IWQOL-Lite-CT

Study GPGL was the only study in the Phase 3 program that measured the IWQOL-Lite-CT.
There was a greater improvement in physical impact experienced by patients due to their weight. There were also significant differences for tirzepatide 10 and 15 mg compared to semaglutide in IWQOL-Lite-CT total scores (meaning there was a greater improvement in overall health-related quality of life and functioning associated with weight) and physical scores (indicating there was a greater improvement in physical impact experienced by patients due to their weight). There was also a significant difference for tirzepatide 15 mg compared to semaglutide in psychosocial scores, meaning there was a greater improvement in the emotional and social impact experienced by patients due to their weight.

Summary of Results for IWQOL-Lite-CT at Baseline and 40 Weeks (LOCF)
mITT Population – Efficacy Analysis Set

	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
Composite Scores of Physical[a]				
n	417	401	395	414
Baseline	65.8	64.3	62.8	66.8
Change from baseline at 40 weeks (LOCF)	9.4†††	9.9†††	11.3†††	7.3†††
Change difference from semaglutide 1 mg (95% CI)	2.1 (-0.1, 4.4)	2.6# (0.4, 4.9)	4.0### (1.8, 6.3)	NA
Composite Scores of Physical Function[a]				
n	417	401	395	414
Baseline	65.5	63.9	62.4	67.0
Change from baseline at 40 weeks (LOCF)	10.4†††	10.6†††	12.2†††	7.9†††
Change difference from semaglutide 1 mg (95% CI)	2.6# (0.2, 5.0)	2.8# (0.4, 5.2)	4.4### (1.9, 6.8)	NA
Composite Scores of Psychosocial[a]				
n	417	401	395	414
Baseline	72.0	71.8	69.5	74.1
Change from baseline at 40 weeks (LOCF)	9.0†††	9.2†††	10.2†††	7.6†††

Change difference from semaglutide 1 mg (95% CI)	1.5 (-0.5, 3.5)	1.6 (-0.4, 3.7)	2.7# (0.6, 4.7)	NA
Total Score of IWQOL-Lite-CT[a]				
n	417	401	394	414
Baseline	69.8	69.2	67.3	71.5
Change from baseline at 40 weeks (LOCF)	9.2†††	9.4†††	10.6†††	7.4†††
Change difference from semaglutide 1 mg (95% CI)	1.7 (-0.2, 3.6)	2.0# (0.0, 3.9)	3.1## (1.2, 5.1)	NA

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; mITT = modified intent-to-treat; n = number of patients in the mITT efficacy analysis set with baseline and at least 1 postbaseline values; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; LOCF = last observation carried forward; NA = not applicable; SEMA = semaglutide; TZP = tirzepatide.

a ANCOVA, LOCF. Only the nonmissing postbaseline observation prior to rescue or study drug discontinuation was carried forward.

Note: Shown are the least-squares means.

#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus semaglutide, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

IW-SP

There was a significant difference in the total transformed IW-SP score for the tirzepatide 15-mg group compared with semaglutide 1 mg at 40 weeks, indicating better self-perception.

APPADL

There was a significant difference in the total transformed APPADL score for the tirzepatide 15-mg group compared with semaglutide 1 mg at 40 weeks, indicating better self-reported ability to perform physical activities of daily living.

DTSQs and DTSQc

There was no significant difference in the total treatment satisfaction score from baseline to 40 weeks for any tirzepatide group compared to semaglutide, indicating similar overall treatment satisfaction. Patients in the tirzepatide 15-mg group had a statistically significant lower perceived frequency of hyperglycaemia compared with the semaglutide 1-mg group.

EQ-5D-5L

There was no statistically significant difference on the change of the EQ VAS scores and EQ-5D-5L Health State Index scores (UK) from baseline to 40 weeks for any tirzepatide group compared with semaglutide, indicating similar overall health-related quality of life.

Summary of PRO Efficacy Endpoints for Study GPGL, mITT Population – Efficacy Analysis Set

	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
IW-SP (Transformed Scores)[a]				

	TZP 5 mg (N=470)	TZP 10 mg (N=469)	TZP 15 mg (N=469)	SEMA 1 mg (N=468)
n	422	405	400	416
Baseline	69.7	69.0	66.9	70.4
Change from baseline at 40 weeks (LOCF)	11.5†††	11.2†††	12.6†††	8.7†††
Change difference from semaglutide (95% CI)	2.8 (0.0, 5.7)	2.6 (-0.3, 5.4)	3.9## (1.1, 6.8)	N/A
APPADL (Transformed Scores)[a]				
n	422	403	400	416
Baseline	69.8	69.2	68.8	68.5
Change from baseline at 40 weeks (LOCF)	5.7†††	6.6†††	7.9†††	5.4†††
Change difference from semaglutide (95% CI)	0.3 (-1.9, 2.4)	1.2 (-1.0, 3.4)	2.6# (0.4, 4.7)	N/A
DTSQs and DTSQc[a]				
Total[b]				
n	419	399	398	411
DTSQs at baseline	27.2 (0.37)	27.8 (0.38)	27.9 (0.38)	27.6 (0.38)
DTSQc at Week 40	15.7 (0.18)	15.6 (0.19)	16.1 (0.19)	15.8 (0.19)
Change difference from semaglutide (95% CI)	-0.10 (-0.62, 0.41)	-0.25 (-0.78, 0.27)	0.26 (-0.26, 0.79)	N/A
Hyperglycaemia[c]				
n	418	399	398	411
DTSQs at baseline	3.9 (0.09)	3.9 (0.09)	3.8 (0.09)	3.6 (0.09)
DTSQc at Week 40	-1.3 (0.10)	-1.4 (0.10)	-1.5 (0.10)	-1.1 (0.10)
Change difference from semaglutide (95% CI)	-0.24 (-0.50, 0.03)	-0.27 (-0.54, 0.00)	-0.39## (-0.66, -0.12)	N/A
Hypoglycaemia[d]				
n	416	398	398	412
DTSQs at baseline	1.2 (0.08)	1.1 (0.08)	1.2 (0.08)	1.1 (0.08)
DTSQc at Week 40	-0.7 (0.10)	-0.7 (0.10)	-0.8 (0.10)	-0.7 (0.10)
Change difference from semaglutide (95% CI)	-0.06 (-0.33, 0.22)	-0.02 (-0.29, 0.26)	-0.13 (-0.40, 0.15)	N/A
EQ-5D-5L (UK)[a]				
n	415	401	395	413
Baseline	0.82	0.82	0.82	0.82
Change from baseline at 40 weeks (LOCF)	0.04†††	0.04†††	0.04†††	0.04†††
Change difference from semaglutide (95% CI)	0.0 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0.0 (-0.02, 0.02)	N/A
EQ VAS[a]				
n	418	402	395	414
Baseline	74.3	75.3	75.8	74.6
Change from baseline at 40 weeks (LOCF)	8.3†††	8.8†††	8.7†††	7.8†††
Change difference from semaglutide (95% CI)	0.5 (-1.2, 2.2)	1.1 (-0.7, 2.8)	1.0 (-0.8, 2.7)	N/A

Abbreviations: ANCOVA = analysis of covariance; APPADL = Ability to Perform Physical Activities of Daily Living; CI = confidence interval; DTSQc = Diabetes Treatment Satisfaction Questionnaire (change); DTSQs = Diabetes Treatment Satisfaction Questionnaire (status); EAS = efficacy analysis set; EQ VAS = EQ visual analog scale; IW-SP = Impact of Weight on Self-Perception; LOCF = last observation carried forward; mITT = modified intent -to-treat; n = number of patients in the mITT efficacy analysis set with baseline and at least 1 postbaseline values; N = number of patients in EAS; N/A = not applicable; PRO = patient-reported outcome; SEMA = semaglutide; TZP = tirzepatide.

[a] ANCOVA, LOCF. Only the nonmissing postbaseline observation prior to rescue or study drug discontinuation was carried forward.

[b] A greater score indicates greater patient satisfaction with treatment.

[c] Represents the following question on the instrument answered by patients: "How often have you felt that your blood sugars have been unacceptably high recently?" Lower scores indicate blood glucose levels closer to the ideal. Higher scores indicate problems.

[d] Represents the following question on the instrument answered by patients: "How often have you felt that your blood sugars have been unacceptably low recently?" Lower scores indicate blood glucose levels closer to the ideal. Higher scores indicate problems.

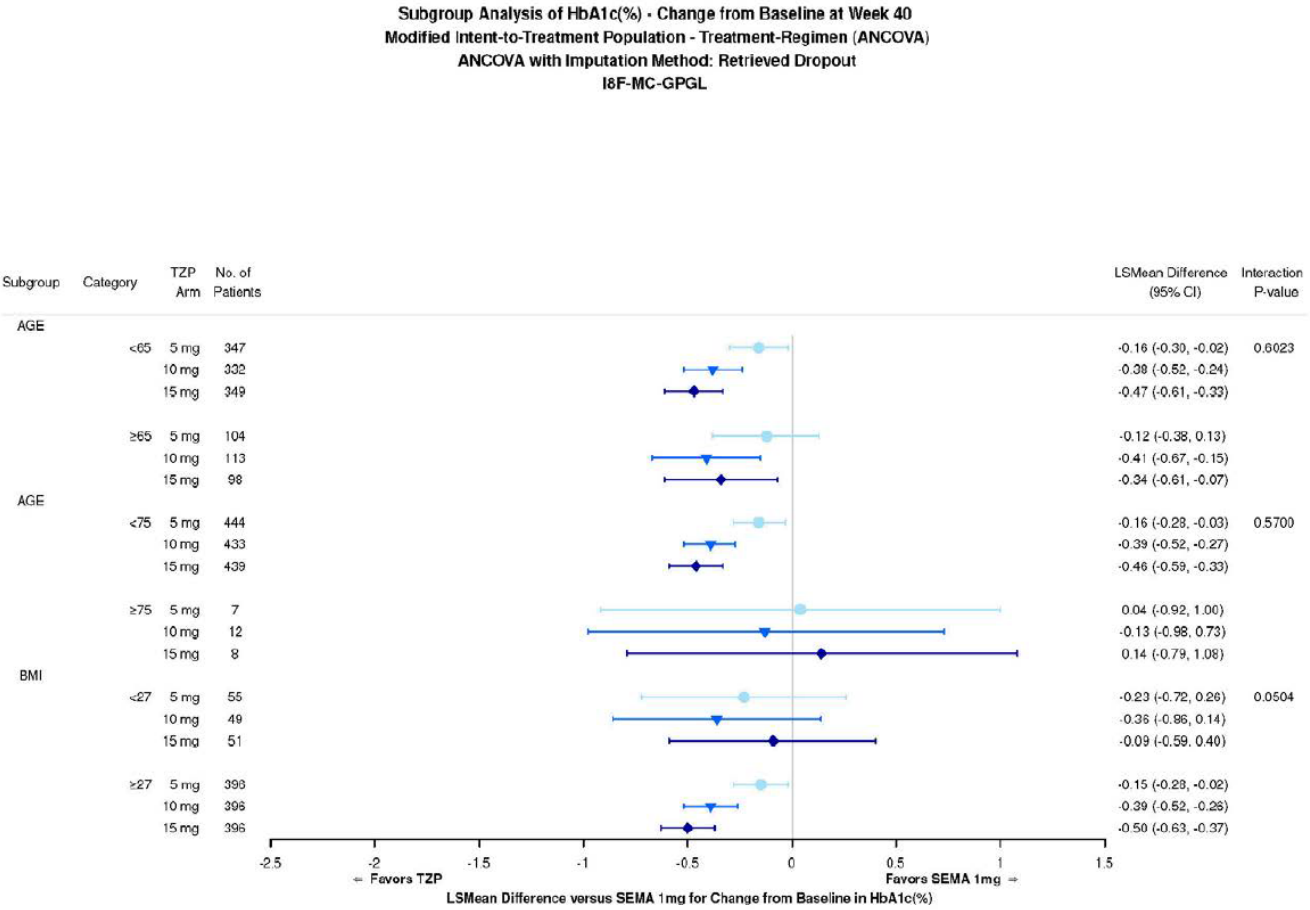
Note: Shown are the least-squares means.

#Nominal p-value <0.05, ##nominal p-value <0.01versus semaglutide, not included in graphical testing procedure.

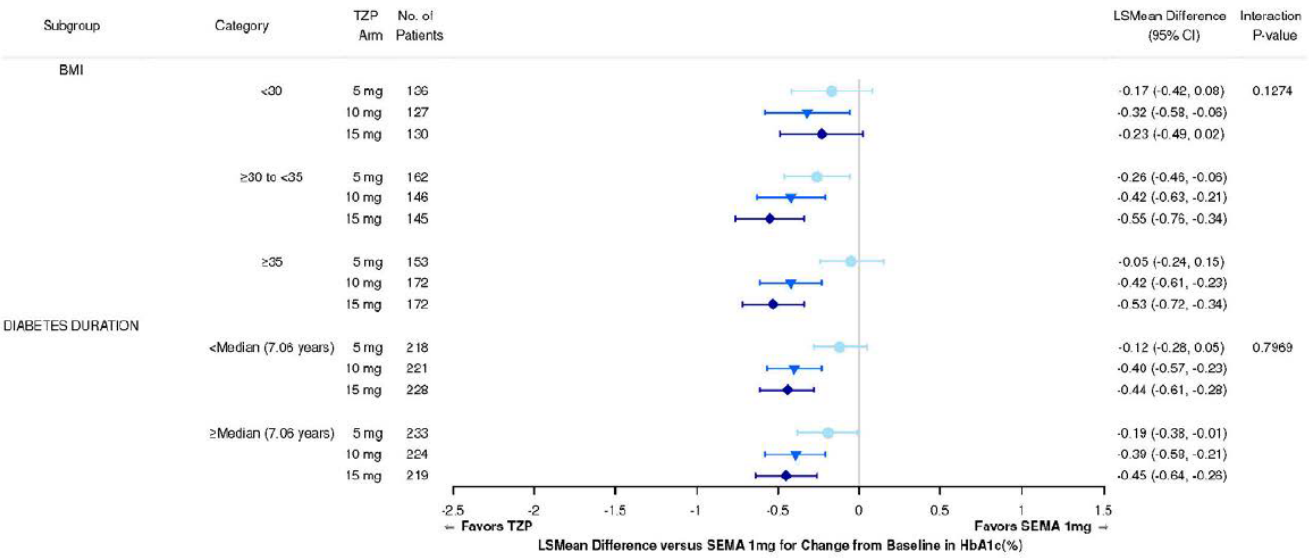
†††p-Value <0.001 versus baseline.

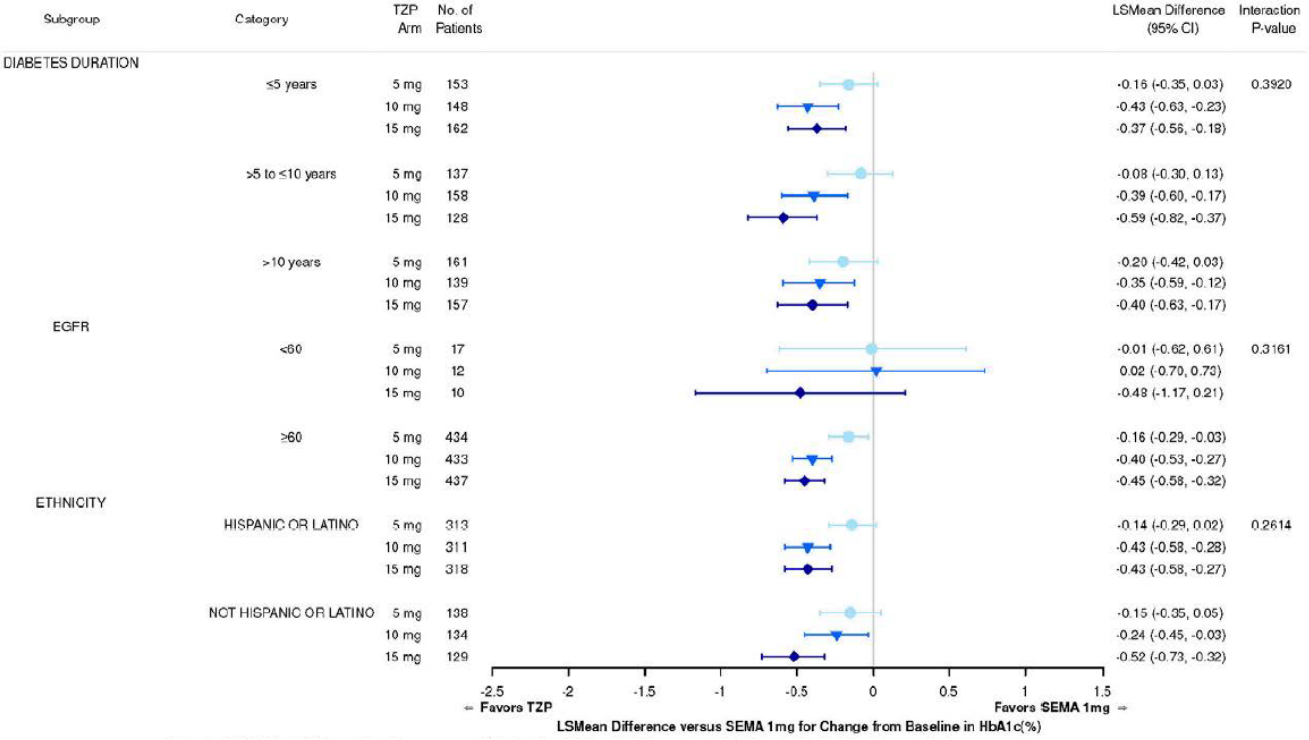
Subgroup analyses of the primary endpoint

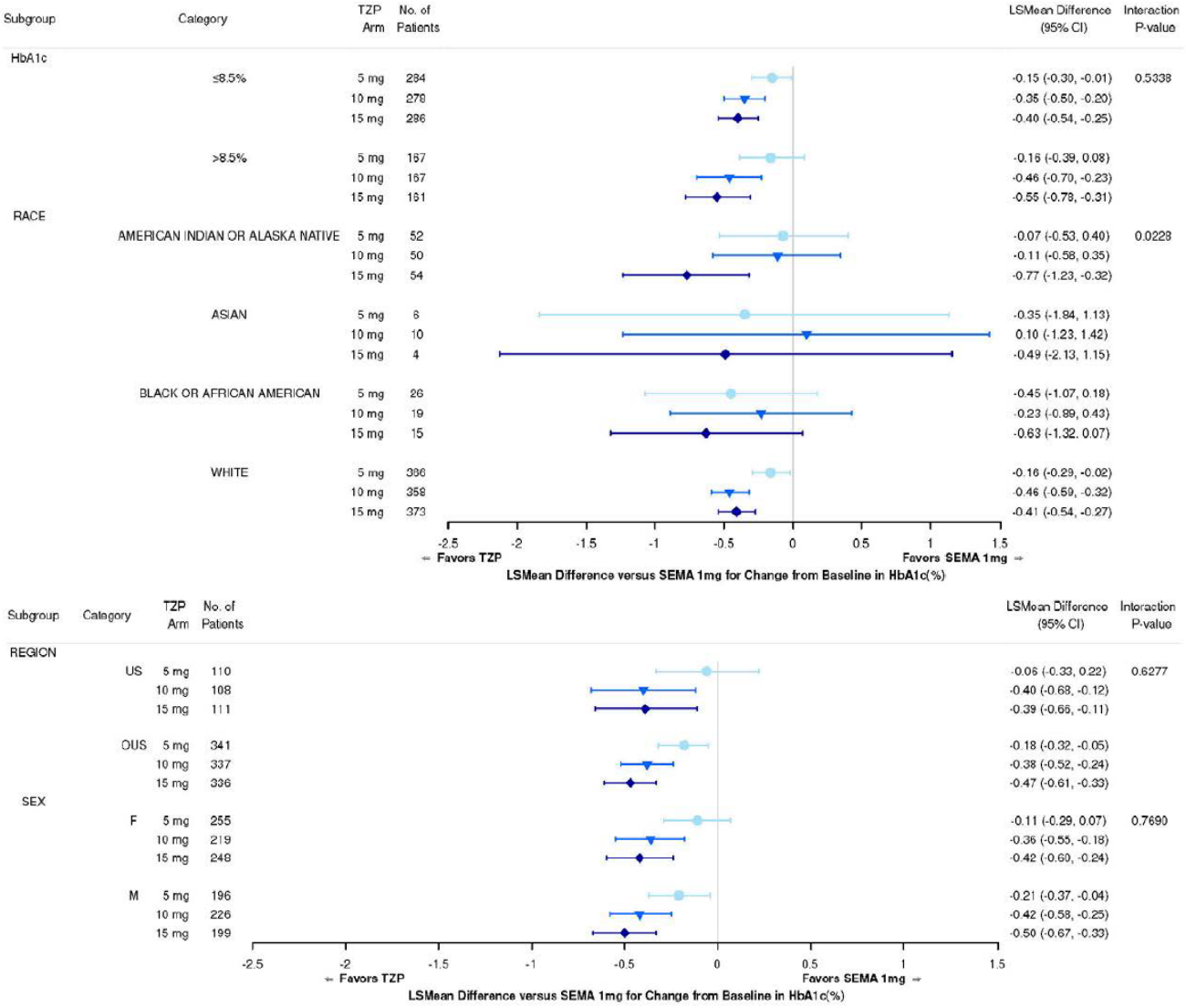
The results of the subgroup analyses (age, BMI, diabetes duration, eGFR, region and gender) using the treatment-regimen estimand are presented as forest plots below.



Footnote: ANCOVA model for postbaseline measures. Units for Age, BMI and eGFR are years, kg/m2, and mL/min/1.73m2, respectively.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSMean = least squares mean; TZP = tirzepatide; SEMA = semaglutide.


Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
BMI
<30
5 mg 106 -0.17 (-0.42, 0.08) 0.1274
10 mg 127 -0.32 (-0.58, -0.06)
15 mg 130 -0.23 (-0.49, 0.02)
≥30 to <35
5 mg 162 -0.26 (-0.46, -0.06)
10 mg 146 -0.42 (-0.63, -0.21)
15 mg 145 -0.55 (-0.75, -0.34)
≥35
5 mg 153 -0.05 (-0.24, 0.15)
10 mg 172 -0.42 (-0.61, -0.23)
15 mg 172 -0.53 (-0.72, -0.34)
DIABETES DURATION
<Median (7.06 years)
5 mg 218 -0.12 (-0.28, 0.05) 0.7969
10 mg 221 -0.40 (-0.57, -0.23)
15 mg 228 -0.44 (-0.61, -0.28)
≥Median (7.06 years)
5 mg 233 -0.19 (-0.38, -0.01)
10 mg 224 -0.39 (-0.59, -0.21)
15 mg 219 -0.45 (-0.64, -0.26)
-2.5 -2 -1.5 -1 -0.5 0 0.5 1 1.5
← Favors TZP
Favors SEMA 1mg →
LSMean Difference versus SEMA 1mg for Change from Baseline in HbA1c(%)


Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
DIABETES DURATION
≤5 years
5 mg 153 -0.16 (-0.35, 0.03) 0.3920
10 mg 148 -0.43 (-0.63, -0.23)
15 mg 162 -0.37 (-0.56, -0.18)
>5 to ≤10 years
5 mg 137 -0.08 (-0.30, 0.13)
10 mg 158 -0.39 (-0.60, -0.17)
15 mg 128 -0.59 (-0.82, -0.37)
>10 years
5 mg 161 -0.20 (-0.42, 0.03)
10 mg 139 -0.35 (-0.59, -0.12)
15 mg 157 -0.40 (-0.63, -0.17)
EGFR
<60
5 mg 17 -0.01 (-0.62, 0.61) 0.3161
10 mg 12 0.02 (-0.70, 0.73)
15 mg 10 -0.48 (-1.17, 0.21)
≥60
5 mg 434 -0.16 (-0.29, -0.03)
10 mg 433 -0.40 (-0.53, -0.27)
15 mg 437 -0.45 (-0.58, -0.32)
ETHNICITY
HISPANIC OR LATINO
5 mg 313 -0.14 (-0.29, 0.02) 0.2614
10 mg 311 -0.43 (-0.58, -0.28)
15 mg 318 -0.43 (-0.58, -0.27)
NOT HISPANIC OR LATINO
5 mg 138 -0.15 (-0.35, 0.05)
10 mg 134 -0.24 (-0.45, -0.03)
15 mg 129 -0.52 (-0.73, -0.32)
-2.5 -2 -1.5 -1 -0.5 0 0.5 1 1.5
← Favors TZP
Favors SEMA 1mg →
LSMean Difference versus SEMA 1mg for Change from Baseline in HbA1c(%)



GPGH Study (SURPASS-3) results

Primary endpoint: mean change from baseline in HbA1c

Tirzepatide 5, 10, and 15 mg demonstrated statistically significant reductions in HbA1c from baseline to 52 weeks compared with insulin degludec. Additionally, compared to insulin degludec, all three doses of tirzepatide had significantly higher proportions of patients who achieved HbA1c target values of <7.0%, ≤6.5%, and <5.7%.

Summary of HbA1c Efficacy Endpoints for Study GPGH, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
HbA1c (%)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	8.17 → 6.32	8.18 → 6.16	8.21 → 6.03	8.11 → 6.92
Change from baseline at Week 52	-1.85†††	-2.01†††	-2.14†††	-1.25†††
Difference from insulin degludec (95% CI)	-0.60*** (-0.74, -0.45)	-0.76*** (-0.90, -0.61)	-0.89*** (-1.03, -0.74)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	8.17 → 6.26	8.19 → 5.99	8.21 → 5.81	8.13 → 6.85
Change from baseline at Week 52	-1.93†††	-2.20†††	-2.37†††	-1.34†††
Difference from insulin degludec (95% CI)	-0.59*** (-0.73, -0.45)	-0.86*** (-1.00, -0.72)	-1.04*** (-1.17, -0.90)	N/A
HbA1c (mmol/mol)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	65.8 → 45.6	65.9→ 43.8	66.2 → 42.4	65.2 → 52.1
Change from baseline at Week 52	-20.2†††	-21.9†††	-23.4†††	-13.7†††
Difference from insulin degludec (95% CI)	-6.5*** (-8.1, -4.9)	-8.3*** (-9.9, -6.6)	-9.7*** (-11.3, -8.1)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	65.8 → 44.9	66.0 → 41.9	66.3 → 40.0	65.4 → 51.3
Change from baseline at Week 52	-21.1†††	-24.0†††	-26.0†††	-14.6†††
Difference from insulin degludec (95% CI)	-6.4*** (-7.9, -4.9)	-9.4*** (-10.9, -7.9)	-11.3*** (-12.8, -9.8)	N/A
Percentage of patients with HbA1c <7.0% (<53 mmol/mol) at Week 52 (%)				
Treatment-Regimen Estimand[c]	79.2***	81.5***	83.5***	58.0
Efficacy Estimand[d]	82.4***	89.7***	92.6***	61.3
Percentage of patients with HbA1c ≤6.5% (≤48 mmol/mol) at Week 52 (%)				
Treatment-Regimen Estimand[c]	67.5###	71.5###	74.5###	42.2
Efficacy Estimand[d]	71.4###	80.3###	85.3###	44.4
Percentage of patients with HbA1c <5.7% (<39 mmol/mol) at Week 52 (%)				
Treatment-Regimen Estimand[c]	23.6###	33.9###	40.7###	5.1
Efficacy Estimand[d]	25.8###	38.6###	48.4###	5.4

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; HbA1c = glycosylated hemoglobin A1c; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts.

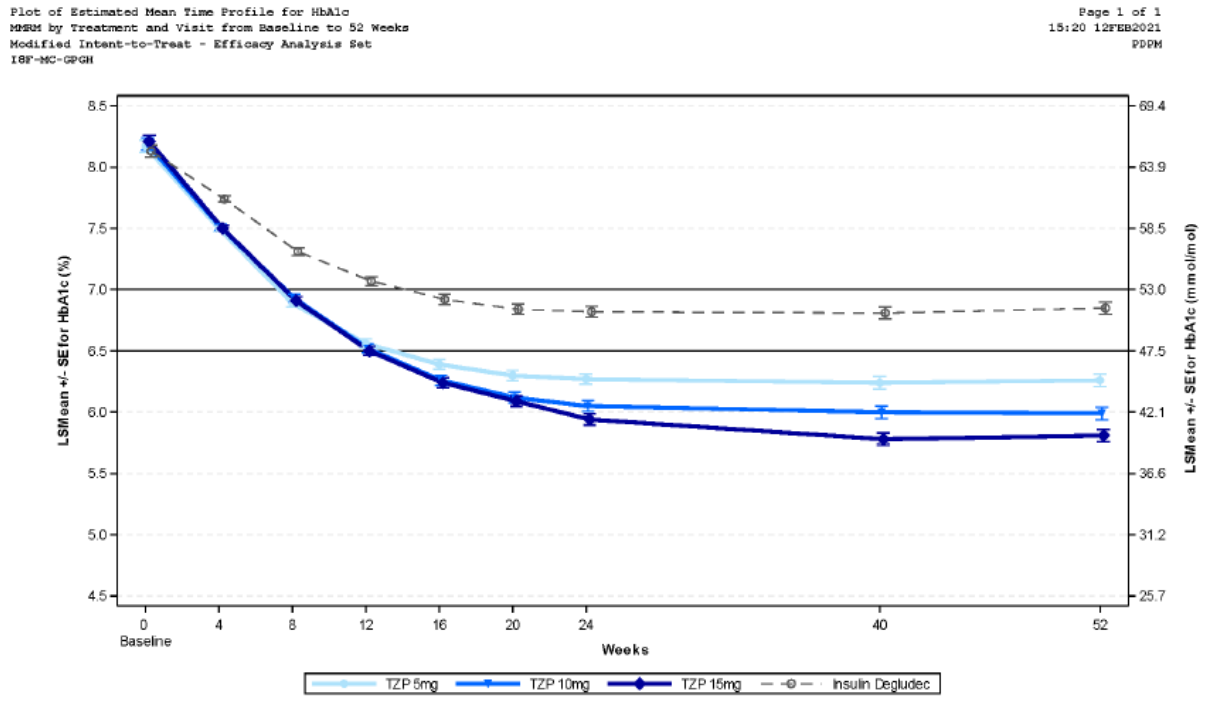
d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

***p-Value <0.001 versus insulin degludec under graphical testing procedure.

###Nominal p-value <0.001 versus insulin degludec, not included in graphical testing procedure.
†††p-Value <0.001 versus baseline.

Mean change from baseline in HbA1c over time to 52 weeks

All three tirzepatide dose groups had significantly larger mean reductions from baseline in HbA1c compared with insulin degludec beginning at week 4. Near maximal reductions from baseline in HbA1c by all tirzepatide doses were reached around 24 weeks and were maintained through 52 weeks.



Secondary endpoints

All key secondary efficacy objectives were controlled for type 1 error.

Fasting serum glucose

Significant mean changes from baseline in FSG at Week 52 were observed in all four treatment groups. Insulin degludec had a significantly larger mean reduction in FSG compared to tirzepatide 5 mg. Tirzepatide 10 and 15 mg showed similar mean reductions to insulin degludec in FSG.

Insulin degludec was titrated throughout the study to achieve an FSG <90 mg/dL (<5 mmol/L). At week 52, significantly higher proportions of patients in the insulin degludec group compared to all 3 tirzepatide groups achieved the FSG target of <90 mg/dL (<5 mmol/L): tirzepatide 5 mg: 6.9%, tirzepatide 10 mg: 14.6%, tirzepatide 15 mg: 16.3%, and insulin degludec: 25.7%.

7-Point SMBG

All doses of tirzepatide significantly reduced the SMBG overall daily mean and 2-hour postmeal daily mean assessed at 52 weeks compared with insulin degludec. Tirzepatide 10 and 15 mg also significantly reduced the pre-meal daily mean compared to insulin degludec.

Summary of Blood Glucose Efficacy Endpoints for Study GPGH, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
FSG (mg/dL)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	171.7 → 122.3	170.4 → 119.1	168.4 → 115.1	166.6 → 118.8
Change from baseline at Week 52	-47.0†††	-50.1†††	-54.2†††	-50.5†††
Difference from insulin degludec (95% CI)	3.5 (-2.8, 9.7)	0.3 (-6.0, 6.6)	-3.8 (-9.9, 2.4)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	171.8 → 121.6	170.7→114.9	168.4 → 110.5	166.4 → 114.1
Change from baseline at Week 52	-48.2†††	-54.8†††	-59.2†††	-55.7†††
Difference from insulin degludec (95% CI)	7.5## (2.4, 12.5)	0.8 (-4.3, 5.9)	-3.6 (-8.7, 1.5)	N/A
FSG (mmol/L)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	9.53 → 6.79	9.46 → 6.61	9.35 → 6.39	9.25 → 6.60
Change from baseline at Week 52	-2.61†††	-2.78†††	-3.01†††	-2.80†††
Difference from insulin degludec (95% CI)	0.19 (-0.15, 0.54)	0.02 (-0.33, 0.37)	-0.21 (-0.55, 0.14)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	9.54 → 6.75	9.48→ 6.38	9.35→ 6.13	9.24 → 6.33
Change from baseline at Week 52	-2.68†††	-3.04†††	-3.29†††	-3.09†††
Difference from insulin degludec (95% CI)	0.41## (0.14, 0.69)	0.05 (-0.24, 0.33)	-0.20 (-0.48, 0.08)	N/A
Daily Mean 7-Point SMBG (mg/mL)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 52	179.2 → 125.7	180.1 → 118.5	181.4→ 117.6	173.2 → 130.2
Change from baseline at Week 52	-52.6†††	-59.7†††	-60.6†††	-48.0†††
Difference from insulin degludec (95% CI)	-4.6## (-7.8, -1.3)	-11.7### (-15.0, -8.4)	-12.6### (-15.9, -9.3)	N/A
Premeal daily mean				
Baseline → Week 52	165.5 → 119.6	165.3 → 113.0	167.6 → 112.0	159.8 → 118.1
Change from baseline at Week 52	-44.7†††	-51.3†††	-52.3†††	-46.2†††
Difference from insulin degludec (95% CI)	1.5 (-1.5, 4.6)	-5.1## (-8.2, -2.0)	-6.1### (-9.2, -3.1)	N/A
2-Hour postmeal daily mean				
Baseline → Week 52	192.8 → 131.6	194.1 → 124.7	195.2 → 123.7	186.7 → 141.7
Change from baseline at Week 52	-60.3†††	-67.2†††	-68.2†††	-50.2†††
Difference from insulin degludec (95% CI)	-10.0### (-14.1, -6.0)	-17.0### (-21.0, -12.9)	-17.9### (-22.0, -13.9)	N/A

	TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
Daily Mean 7-Point SMBG (mmol/L)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 52	9.95 → 6.98	10.00 → 6.58	10.07 → 6.53	9.62 → 7.23
Change from baseline at Week 52	-2.92†††	-3.32†††	-3.37†††	-2.67†††
Difference from insulin degludec (95% CI)	-0.25## (-0.44, -0.07)	-0.65### (-0.83,-0.46)	-0.70### (-0.88,-0.52)	N/A
Premeal daily mean				
Baseline → Week 52	9.19 → 6.64	9.17 → 6.27	9.30 → 6.22	8.87 → 6.56
Change from baseline at Week 52	-2.48†††	-2.85†††	-2.90†††	-2.56†††
Difference from insulin degludec (95% CI)	0.09 (-0.08, 0.25)	-0.28## (-0.45, -0.11)	-0.34### (-0.51, -0.17)	N/A
2-Hour postmeal daily mean				
Baseline → Week 52	10.70 → 7.31	10.78 → 6.92	10.83 → 6.87	10.36 → 7.86
Change from baseline at Week 52	-3.35†††	-3.73†††	-3.78†††	-2.79†††
Difference from insulin degludec (95% CI)	-0.56### (-0.78, -0.33)	-0.94### (-1.17, -0.72)	-0.99### (-1.22, -0.77)	N/A

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; FSG = fasting serum glucose; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; SMBG = self-monitored blood glucose; TZP = tirzepatide.

a ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b MMRM analysis assuming MAR; ANOVA used at baseline.

Note: Shown are the least-squares means.

##Nominal p-value <0.01, ###nominal p-value <0.001 versus insulin degludec, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Continuous Glucose Monitoring (CGM) substudy

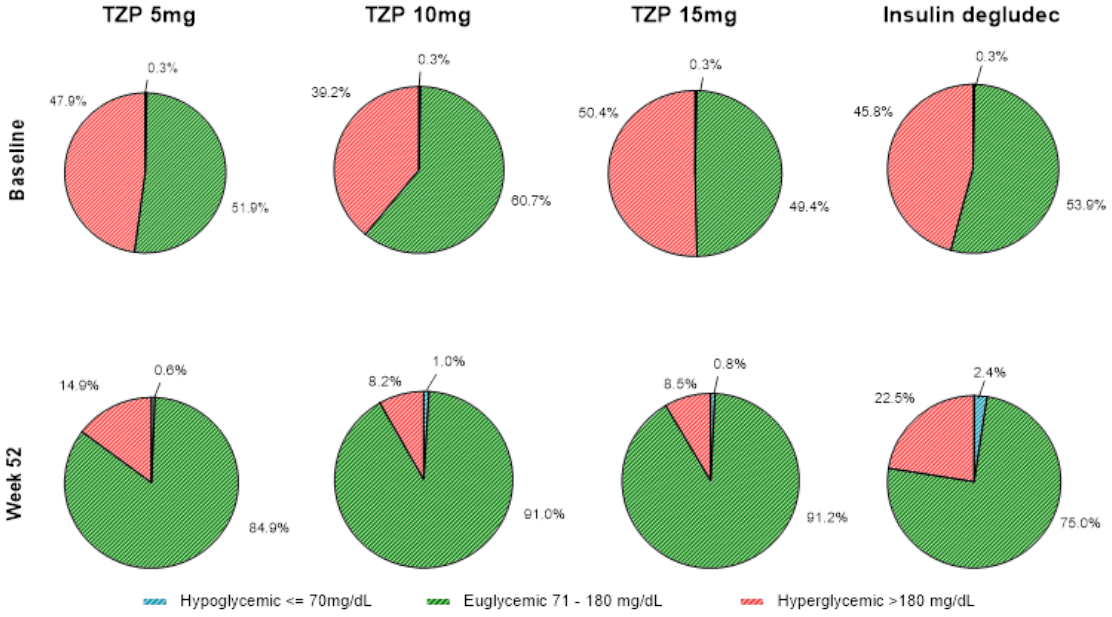
Percentage and Duration of Time in euglycaemic range of 71 to 140 mg/dL (3.9 to 7.8 mmol/L)

A subset of patients in Study GPGH (N=243) participated in an evaluation of the 24-hour glucose profiles captured with blinded CGM. All three doses of tirzepatide (5 mg, 10 mg, and 15 mg) presented a significantly greater mean percentage of time with glucose in the euglycaemic range of 71 to 140 mg/dL (3.9 to 7.8 mmol/L) within a 24-hour period at 52 weeks compared with insulin degludec. Thus, the duration of time in the euglycaemic range for tirzepatide increased by 167.39 to 353.93 minutes (approximately 3 to 6 hours) more than insulin degludec at 52 weeks. Once weekly tirzepatide 10 mg and 15 mg presented a significantly greater mean percentage of time with glucose in the euglycaemic range of 71 to 140 mg/dL (3.9 to 7.8 mmol/L) within a 24-hour period at 24 weeks compared with insulin degludec. This was equivalent to an increase of 276.22 to 304.85 minutes (approximately 4 to 5 hours) in euglycaemic range for tirzepatide 10 mg and 15 mg when compared to insulin degludec. Once weekly tirzepatide 5 mg achieved a numerically but

not significantly greater mean percentage of time within euglycaemic range at 24 weeks compared with insulin degludec, with a difference of 119.89 minutes (approximately 2 hours) longer spent in euglycaemic range of 71 to 140mg/dL (3.9 to 7.8 mmol/L).

According to the international CGM consensus guidelines ADA (Battelino 2019), the goal for hypoglycaemia is to spend less than 4% of time <70mg/dL (<3.9 mmol/L), for TIR 70-180mg/dL (3.9 to 10.0 mmol/L) to be 70% of time, and for hyperglycaemia >180mg/dL (>10.0 mmol/L) to be less than 25% of time within a 24-hour period. A numerically higher percentage of tirzepatide treated patients achieved all three of these goals in comparison to insulin degludec, as illustrated in the following figure:

Actual values in percentage of time with sensor glucose within target ranges of ≤70 mg/dL (≤3.9 mmol/L), 71 to 180 mg/dL (3.9 to 10.0 mmol/L), and >180 (>10.0 mmol/L) during a 24-hour period at baseline and 52 weeks: CGM analysis set.



Abbreviations: TZP = tirzepatide.

Note: Actual values do not add up to 100% due to separate analysis models for each endpoint.

Baseline percentage and duration of time with glucose in the *hyperglycaemic* range of >180 mg/dL (>10.0 mmol/L), baseline percentage and duration of time with CGM glucose in the *hypoglycaemic* ranges of ≤70 mg/dL and <54 mg/dL within a 24-hour period did not significantly differ across the treatment groups. Tirzepatide 10 mg and 15 mg presented a numerically but not significantly lower incidence of patients with *at least 1 nocturnal episode of hypoglycaemia* <70mg/dL (≤3.9 mmol/L) at both 24 and 52 weeks when compared with insulin degludec (number of events tirzepatide 5 mg 8, tirepatide 10 mg 9, tirzepatide 15 mg 12, insulin 14).

Baseline within day glucose SD variability during a 24-hour period did not significantly differ across the treatment groups. All 3 doses of tirzepatide achieved a significant decrease in within day glucose SD variability as measured by SD from baseline at both 24 weeks and 52 weeks compared to insulin degludec. Insulin degludec presented limited improvement from baseline in glycaemic variability as measured by SD at 24 and 52 weeks.

Liver fat content (LFC) and adipose tissue, MRI substudy

A subset of patients (N = 296) participated in an evaluation of LFC, visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) assessed through magnetic resonance imaging. At 52 weeks, patients treated with tirzepatide (10 mg and 15 mg pooled) demonstrated statistically significantly greater mean reductions in LFC compared to insulin degludec, -8.09 % versus -3.38 % respectively, from baselines of 15.67 % and 16.58 %. Patients treated with tirzepatide 5 mg, 10 mg and 15 mg had significantly greater reductions in volume of VAT (-1.10, -1.53 and -1.65 L respectively) and ASAT (-1.40, -2.25 and -2.05 L respectively) from overall baselines of 6.6 L and 10.4 L respectively at 52 weeks compared with an increase in the insulin degludec group (0.38 and 0.63 L).

Body Weight

Tirzepatide 5, 10, and 15 mg showed significant reductions in body weight from baseline to 52 weeks. Conversely, patients in the insulin degludec group showed an increase in mean body weight. Additionally, compared to insulin degludec, all three doses of tirzepatide had significantly higher proportions of patients who achieved body weight reductions of ≥5%, ≥10%, and ≥15%.

Summary of Body Weight Measures for Study GPGH,
mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
Body Weight (kg)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	94.4 → 87.2	93.8 → 84.7	94.9 → 83.0	94.0 → 96.2
Change from baseline at Week 52	-7.0†††	-9.6†††	-11.3†††	1.9†††
Difference from insulin degludec (95% CI)	-8.9*** (-10.0, -7.8)	-11.5*** (-12.6, -10.4)	-13.2*** (-14.3, -12.1)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	94.5 → 87.3	94.3 → 84.2	94.9 → 81.9	94.2 → 97.1
Change from baseline at Week 52	-7.5†††	-10.7†††	-12.9†††	2.3†††
Difference from insulin degludec (95% CI)	-9.8*** (-10.8, -8.8)	-13.0*** (-14.0, -11.9)	-15.2*** (-16.2, -14.2)	N/A
Percentage of patients with Weight Loss ≥5% at Week 52 (%)				
Treatment-Regimen Estimand[c]	60.6###	74.0###	78.7###	8.4
Efficacy Estimand[d]	66.0###	83.7###	87.8###	6.3
Percentage of patients with Weight Loss ≥10% at Week 52 (%)				
Treatment-Regimen Estimand[c]	35.1###	49.5###	57.9###	3.0
Efficacy Estimand[d]	37.4###	55.7###	69.4###	2.9
Percentage of patients with Weight Loss ≥15% at Week 52 (%)				
Treatment-Regimen Estimand[c]	11.8##	25.4###	35.1###	0.4
Efficacy Estimand[d]	12.5###	28.3###	42.5###	0.0

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts.

d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

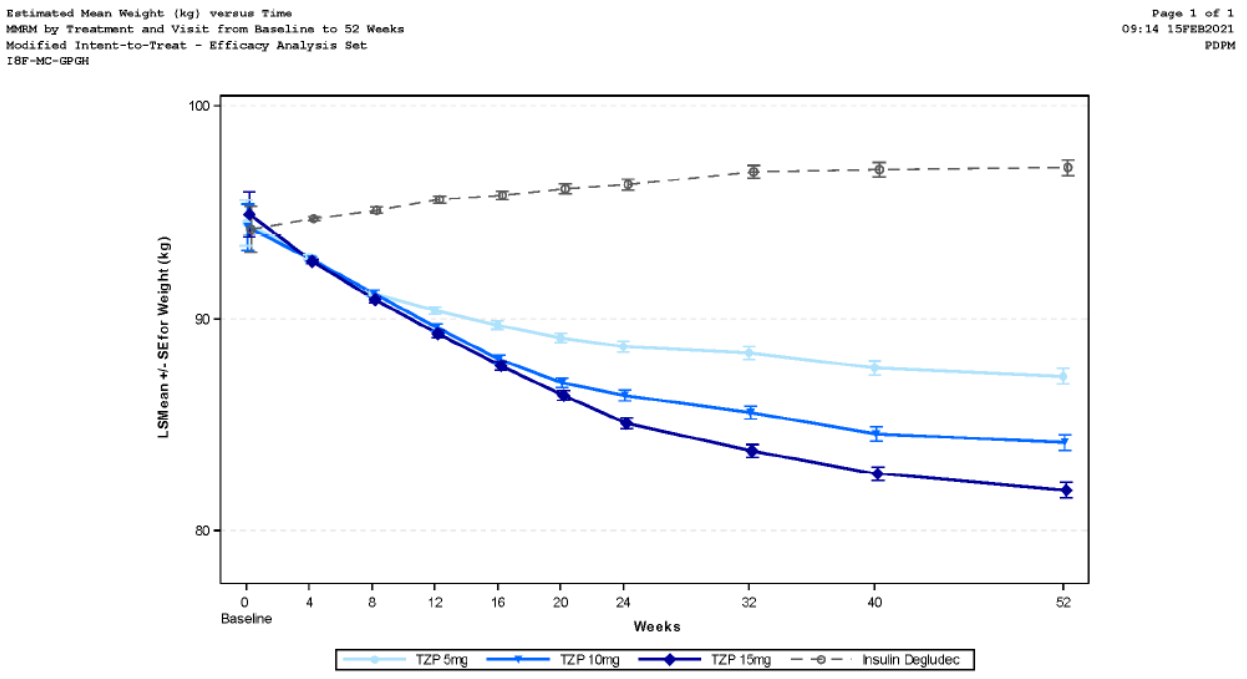
***p-Value <0.001 versus insulin degludec under graphical testing procedure.

##Nominal p-value <0.01, ###nominal p-value <0.001 versus insulin degludec, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Mean change from baseline in body weight over time to 52 weeks

All three tirzepatide dose groups had significant mean reductions from baseline in body weight starting at Week 4. Steady decreases in weight continued through 52 weeks and did not appear to plateau by the end of the treatment period. Conversely, the mean body weight in the insulin degludec group increased from baseline starting at Week 12.



Lipid parameter results

At 52 weeks, all tirzepatide groups significantly reduced triglycerides, total cholesterol, LDL-C, and VLDL-C and increased HDL-C from baseline. Tirzepatide 10 and 15 mg significantly reduced triglycerides and VLDL-C compared with insulin degludec. Additionally, all 3 doses of tirzepatide significantly increased HDL-C at 52

weeks compared with insulin degludec. There was no difference in LDL-C and total cholesterol between any of the tirzepatide groups and the insulin degludec group.

Summary of Lipid Parameters for Study GPGH, mITT Population – Efficacy Analysis Set

Parameters		TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
Triglycerides					
Baseline → Week 52	(mg/dL)	158.8 → 138.4	169.8 → 119.9	168.4 → 122.3	157.7 → 143.5
	(mmol/L)	1.79 → 1.56	1.92 → 1.35	1.90 → 1.38	1.78 → 1.62
Change from baseline at 52 weeks	(mg/dL)	-25.1	-43.6	-41.2	-20.0
	(mmol/L)	-0.28	-0.49	-0.46	-0.23
Percent change from baseline at 52 weeks (%)		-15.4†††	-26.7†††	-25.2†††	-12.2†††
Insulin degludec adjusted change difference at 52 weeks (%) (95% CI)		-3.6 (-9.4, 2.7)	-16.4### (-21.6, -11.0)	-14.8### (-20.0, -9.2)	N/A
Total Cholesterol					
Baseline → Week 52	(mg/dL)	166.1 → 162.4	171.1 → 159.8	170.4 → 160.0	171.7 → 164.7
	(mmol/L)	4.30 → 4.20	4.42 → 4.13	4.41 → 4.14	4.44 → 4.26
Change from baseline at 52 weeks	(mg/dL)	-7.2	-9.9	-9.7	-5.0
	(mmol/L)	-0.19	-0.26	-0.25	-0.13
Percent change from baseline at 52 weeks (%)		-4.25†††	-5.81†††	-5.69†††	-2.92††
Insulin degludec adjusted change difference at 52 weeks (%) (95% CI)		-1.37 (-4.32, 1.67)	-2.98 (-5.92, 0.06)	-2.85 (-5.80, 0.19)	N/A
HDL-C					
Baseline → Week 52	(mg/dL)	42.8 → 45.2	42.1 → 47.3	42.4 → 47.2	44.4 → 43.3
	(mmol/L)	1.11 → 1.17	1.09 → 1.22	1.10 → 1.22	1.15 → 1.12
Change from baseline at 52 weeks	(mg/dL)	2.4	4.4	4.4	0.4
	(mmol/L)	0.06	0.11	0.11	0.01
Percent change from baseline at 52 weeks (%)		5.49†††	10.22†††	10.20†††	1.03
Insulin degludec adjusted change difference at 52 weeks (%) (95% CI)		4.42### (1.86, 7.03)	9.10### (6.39, 11.88)	9.08### (6.37, 11.85)	N/A
LDL-C					
Baseline → Week 52	(mg/dL)	85.4 → 82.4	88.5 → 82.7	87.6 → 82.0	89.7 → 85.3
	(mmol/L)	2.21 → 2.13	2.29 → 2.14	2.27 → 2.12	2.32 → 2.21
Change from baseline at 52 weeks	(mg/dL)	-5.3	-5.0	-5.7	-2.4
	(mmol/L)	-0.14	-0.13	-0.15	-0.06
Percent change from baseline at 52 weeks (%)		-6.01†††	-5.70††	-6.55†††	-2.71
Insulin degludec adjusted change difference at 52 weeks (%) (95% CI)		-3.39 (-8.19, 1.66)	-3.07 (-7.96, 2.07)	-3.94 (-8.78, 1.15)	N/A
VLDL-C					
Baseline → Week 52	(mg/dL)	31.2 → 27.4	33.0 → 23.9	33.0 → 24.3	30.7 → 28.5
	(mmol/L)	0.81 → 0.71	0.85 → 0.62	0.85 → 0.63	0.79 → 0.74

Parameters		TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
Change from baseline at 52 weeks	(mg/dL)	-4.5	-8.1	-7.6	-3.4
	(mmol/L)	-0.12	-0.21	-0.20	-0.09
Percent change from baseline at 52 weeks (%)		-14.2†††	-25.2†††	-23.8†††	-10.6†††
Insulin degludec adjusted change difference at 52 weeks (%) (95% CI)		-4.1 (-9.7, 1.9)	-16.4### (-21.4, -11.1)	-14.7### (-19.8, -9.3)	N/A

Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide; VLDL-C = very-low-density lipoprotein cholesterol.

Note: MMRM analysis on log-transformed data then converted back to original scale.

Note: Shown are the estimated means.

###Nominal p-value <0.001 versus insulin degludec, not included in graphical testing procedure.

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

PRO results *(questionnaires are briefly described in section 2.6.5.2 of this overview)*

IW-SP

There was a significant difference in the total transformed IW-SP score for all three doses of tirzepatide compared with insulin degludec at 52 weeks, indicating better self-perception.

APPADL

All three doses of tirzepatide significantly improved the APPADL transformed scores from baseline to 52 weeks compared with insulin degludec, indicating better self-reported ability to perform physical activities of daily living.

DTSQs and DTSQc

Each of the three tirzepatide groups had a significantly higher total DTSQc scores, indicating greater improvement in treatment satisfaction, compared with insulin degludec. The tirzepatide 15-mg group had a statistically significant lower perceived frequency of hyperglycaemia compared with the insulin degludec group. The tirzepatide 5-mg group had a statistically significant lower perceived frequency of hypoglycaemia compared with the insulin degludec group.

EQ-5D-5L

There were significant differences in the EQ VAS score for all 3 doses of tirzepatide compared with insulin degludec at 52 weeks, indicating better overall health-related quality of life. No significant differences were seen in the EQ-5D-5L Index scores for all 3 doses of tirzepatide compared to insulin degludec from baseline to 52 weeks.

Summary of PRO Efficacy Endpoints for Study GPGH, mITT Population – Efficacy Analysis Set

	TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
IW-SP (Transformed Scores)[a]				
n	312	297	297	321
Baseline	67.9	68.9	67.8	69.5
Change from baseline at 52 weeks (LOCF)	7.3†††	11.8†††	10.3†††	-1.4
Change difference from insulin degludec (95% CI)	8.7### (5.3, 12.1)	13.2### (9.8, 16.7)	11.7### (8.2, 15.1)	N/A
APPADL (Transformed Scores)[a]				
n	312	297	297	320
Baseline	71.3	69.8	71.1	70.5
Change from baseline at 52 weeks (LOCF)	3.0†††	5.5†††	6.3†††	-1.0
Change difference from insulin degludec (95% CI)	4.0## (1.6, 6.4)	6.5### (4.1, 8.9)	7.3### (4.9, 9.7)	N/A
DTSQs and DTSQc[a]				
Total[b]				
n	305	293	292	313
DTSQs at baseline	27.7	28.1	28.0	27.8
DTSQc at Week 52	15.6	15.5	15.6	12.6
Change difference from insulin degludec (95% CI)	3.01### (2.26, 3.75)	2.90### (2.15, 3.65)	2.99### (2.24, 3.74)	N/A
Hyperglycaemia[c]				
n	306	293	292	312
DTSQs at baseline	3.6	3.5	3.5	3.3
DTSQc at Week 52	-1.4	-1.4	-1.6	-1.1
Change difference from insulin degludec (95% CI)	-0.26 (-0.57, 0.05)	-0.25 (-0.57, 0.06)	-0.47## (-0.78, -0.16)	N/A
Hypoglycaemia[d]				
n	306	293	292	313
DTSQs at baseline	0.9	0.8	0.9	0.9
DTSQc at Week 52	-1.1	-0.9	-1.0	-0.7
Change difference from insulin degludec (95% CI)	-0.41# (-0.74, -0.08)	-0.18 (-0.51, 0.15)	-0.26 (-0.59, 0.07)	N/A
EQ-5D-5L (UK)[a]				
n	309	295	294	318
Baseline	0.85	0.83	0.85	0.83
Change from baseline at 52 weeks (LOCF)	0.02†	0.03†††	0.03†††	0.01
Change difference from insulin degludec (95% CI)	0.01 (-0.01, 0.03)	0.02 (0.00, 0.04)	0.02 (0.00, 0.04)	N/A
EQ VAS[a]				

	TZP 5 mg (N=358)	TZP 10 mg (N=360)	TZP 15 mg (N=358)	Insulin Degludec (N=359)
n	310	296	295	318
Baseline	76.9	77.3	78.1	76.7
Change from baseline at 52 weeks (LOCF)	6.0†††	6.6†††	6.4†††	2.3†††
Change difference from insulin degludec (95% CI)	3.7### (1.8, 5.5)	4.3### (2.4, 6.2)	4.1### (2.2, 6.0)	N/A

Abbreviations: ANCOVA = analysis of covariance; APPADL = Ability to Perform Physical Activities of Daily Living; CI = confidence interval; DTSQc = Diabetes Treatment Satisfaction Questionnaire (change); DTSQs = Diabetes Treatment Satisfaction Questionnaire (status); EAS = efficacy analysis set; EQ VAS = EQ visual analog scale; IW-SP = Impact of Weight on Self-Perception; LOCF = last observation carried forward; mITT = modified intent-to-treat; n = number of patients in the mITT efficacy analysis set with baseline and at least 1 postbaseline values; N = number of patients in EAS; N/A = not applicable; PRO = patient-reported outcome; TZP = tirzepatide.

a ANCOVA, LOCF. Only the nonmissing postbaseline observation prior to rescue or study drug discontinuation was carried forward.

b A greater score indicates greater patient satisfaction with treatment.

c Represents the following question on the instrument answered by patients: "How often have you felt that your blood sugars have been unacceptably high recently?" Lower scores indicate blood glucose levels closer to the ideal. Higher scores indicate problems.

d Represents the following question on the instrument answered by patients: "How often have you felt that your blood sugars have been unacceptably low recently?" Lower scores indicate blood glucose levels closer to the ideal. Higher scores indicate problems.

Note: Shown are the least-squares means.

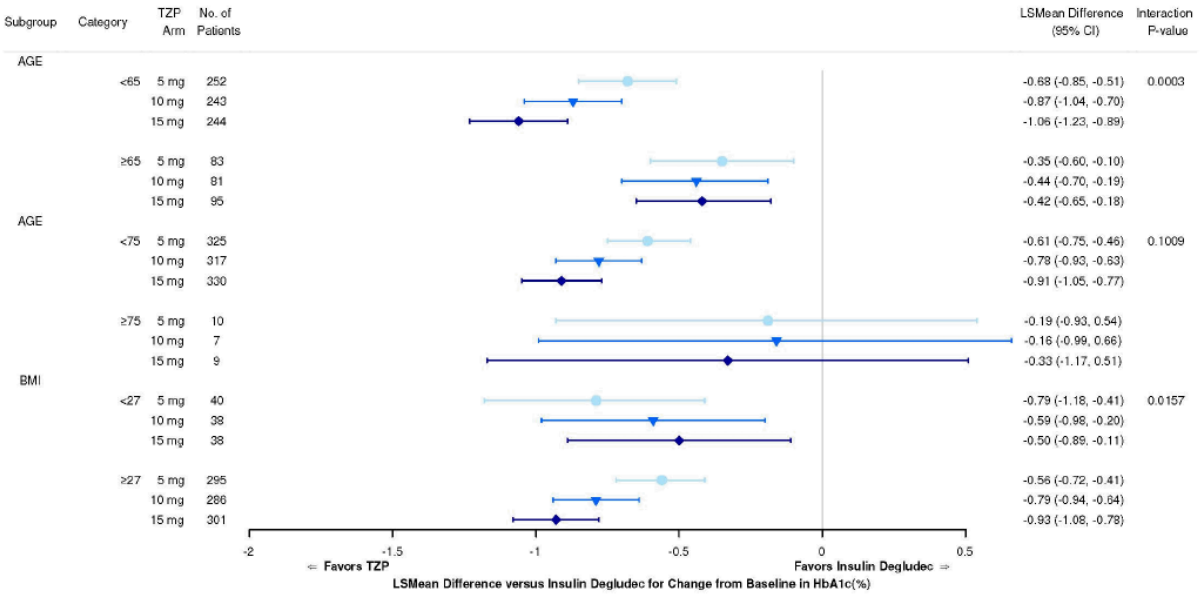
#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus insulin degludec, not included in graphical testing procedure.

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

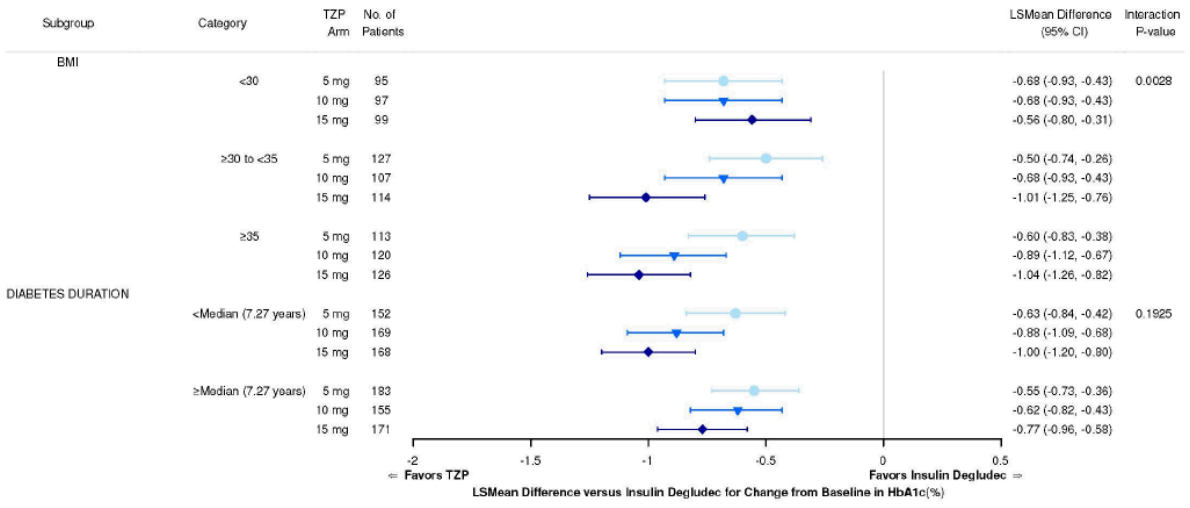
Subgroup analyses of the primary endpoint

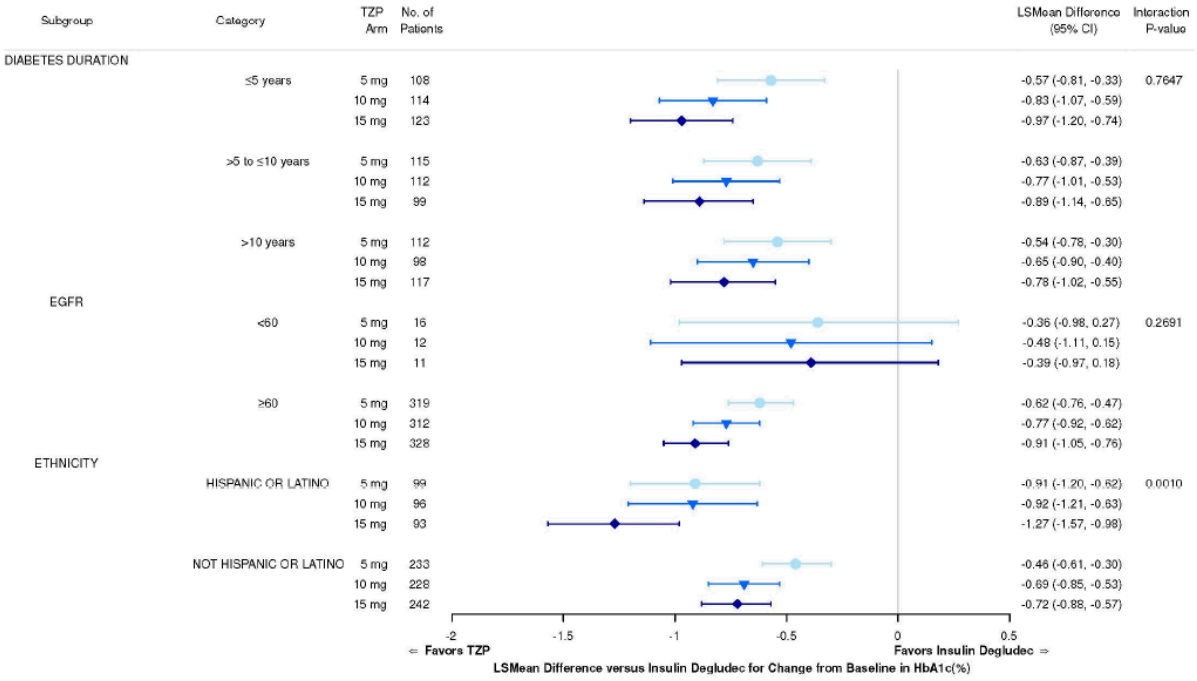
Subgroup analyses were conducted to assess treatment interaction with important factors affecting the change from baseline in HbA1c of patients of the mITT Population using treatment regimen and efficacy estimands. Forest plots are presented below:

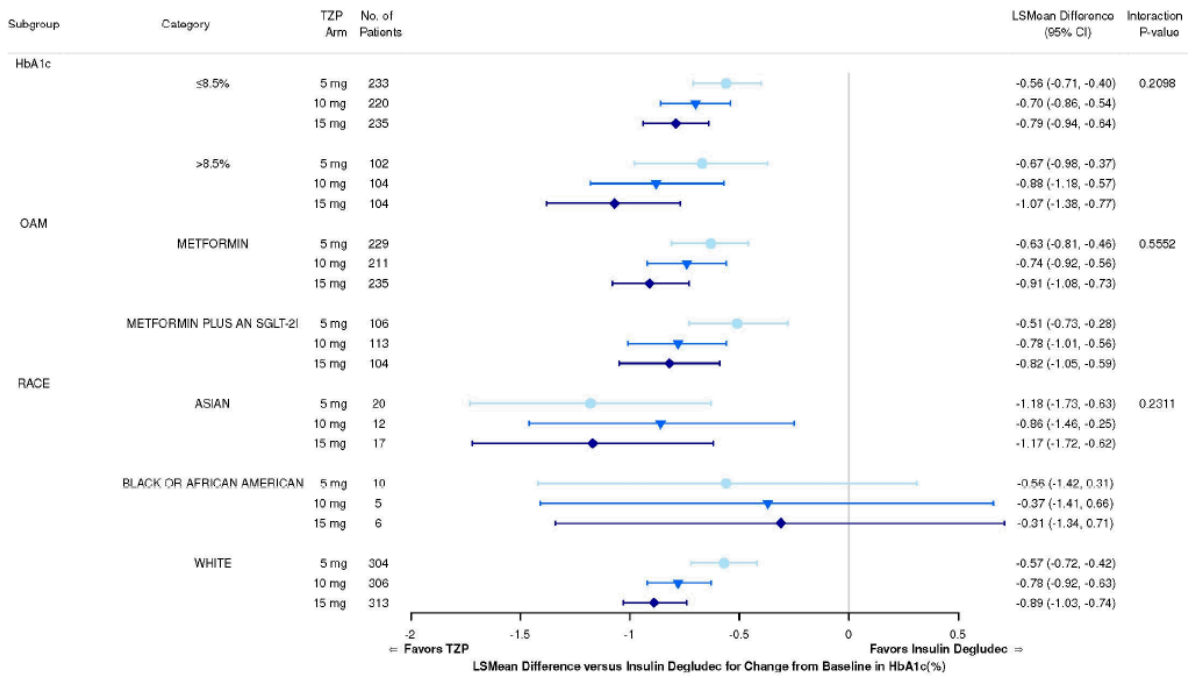
Subgroup Analysis of HbA1c(%) - Change from Baseline at Week 52
Modified Intent-to-Treatment Population - Treatment-Regimen (ANCOVA)
ANCOVA with Imputation Method: Retrieved Dropout
I8F-MC-GPGH

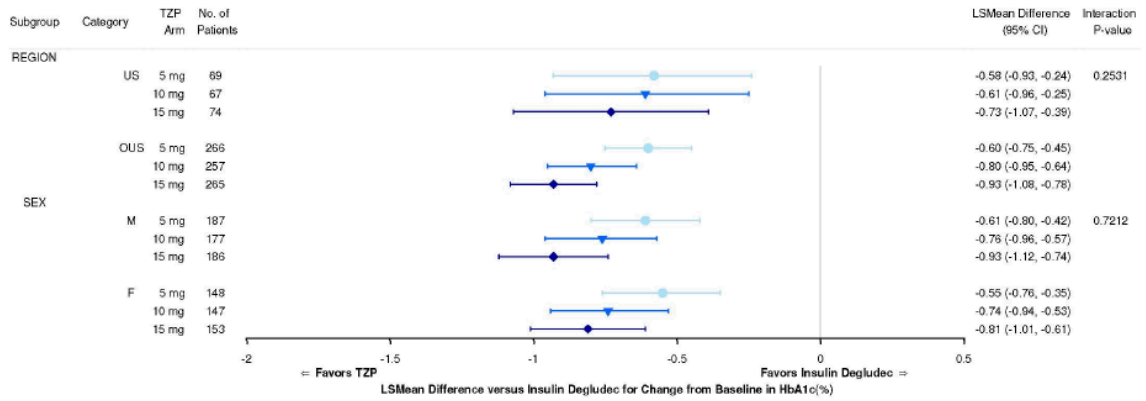


Footnote: ANCOVA model for postbaseline measures. Units for Age, BMI and eGFR are years, kg/m2, and mL/min/1.73m2, respectively.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSMean = least squares mean; TZP = tirzepatide.




Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
DIABETES DURATION
≤5 years
5 mg 108 -0.57 (-0.81, -0.33) 0.7647
10 mg 114 -0.83 (-1.07, -0.59)
15 mg 123 -0.97 (-1.20, -0.74)
>5 to ≤10 years
5 mg 115 -0.63 (-0.87, -0.39)
10 mg 112 -0.77 (-1.01, -0.53)
15 mg 99 -0.89 (-1.14, -0.65)
>10 years
5 mg 112 -0.54 (-0.78, -0.30)
10 mg 98 -0.65 (-0.90, -0.40)
15 mg 117 -0.78 (-1.02, -0.55)
EGFR
<60
5 mg 16 -0.36 (-0.98, 0.27) 0.2691
10 mg 12 -0.48 (-1.11, 0.15)
15 mg 11 -0.39 (-0.97, 0.18)
≥60
5 mg 319 -0.62 (-0.76, -0.47)
10 mg 312 -0.77 (-0.92, -0.62)
15 mg 328 -0.91 (-1.05, -0.76)
ETHNICITY
HISPANIC OR LATINO
5 mg 99 -0.91 (-1.20, -0.62) 0.0010
10 mg 96 -0.92 (-1.21, -0.63)
15 mg 93 -1.27 (-1.57, -0.98)
NOT HISPANIC OR LATINO
5 mg 233 -0.46 (-0.61, -0.30)
10 mg 228 -0.69 (-0.85, -0.53)
15 mg 242 -0.72 (-0.88, -0.57)
-2
-1.5
-1
-0.5
0
0.5
⇐ Favors TZP
Favors Insulin Degludec ⇒
LSMean Difference versus Insulin Degludec for Change from Baseline in HbA1c(%)


Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
HbA1c
≤8.5%
5 mg 233 -0.56 (-0.71, -0.40) 0.2098
10 mg 220 -0.70 (-0.86, -0.54)
15 mg 235 -0.79 (-0.94, -0.64)
>8.5%
5 mg 102 -0.67 (-0.98, -0.37)
10 mg 104 -0.88 (-1.18, -0.57)
15 mg 104 -1.07 (-1.38, -0.77)
OAM
METFORMIN
5 mg 229 -0.63 (-0.81, -0.46) 0.5552
10 mg 211 -0.74 (-0.92, -0.56)
15 mg 235 -0.91 (-1.08, -0.73)
METFORMIN PLUS AN SGLT-2I
5 mg 106 -0.51 (-0.73, -0.28)
10 mg 113 -0.78 (-1.01, -0.56)
15 mg 104 -0.82 (-1.05, -0.59)
RACE
ASIAN
5 mg 20 -1.18 (-1.73, -0.63) 0.2311
10 mg 12 -0.86 (-1.46, -0.25)
15 mg 17 -1.17 (-1.72, -0.62)
BLACK OR AFRICAN AMERICAN
5 mg 10 -0.56 (-1.42, 0.31)
10 mg 5 -0.37 (-1.41, 0.66)
15 mg 6 -0.31 (-1.34, 0.71)
WHITE
5 mg 304 -0.57 (-0.72, -0.42)
10 mg 306 -0.78 (-0.92, -0.63)
15 mg 313 -0.89 (-1.03, -0.74)
-2
-1.5
-1
-0.5
0
0.5
⇐ Favors TZP
Favors Insulin Degludec ⇒
LSMean Difference versus Insulin Degludec for Change from Baseline in HbA1c(%)



GPGM Study (SURPASS-4): results

Primary endpoint: mean change from baseline in HbA1c

Tirzepatide 5, 10, and 15 mg demonstrated statistically significant reduction in HbA1c from baseline to 52 weeks compared with insulin glargine. Additionally, compared to insulin glargine, all 3 doses of tirzepatide had significantly higher proportions of patients who achieved HbA1c target values of <7.0%, ≤6.5% and <5.7%.

Summary of HbA1c Efficacy Endpoints for Study GPGM, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
HbA1c (%)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	8.52 → 6.41	8.60 → 6.22	8.52 → 6.11	8.50 → 7.13
LS mean change from baseline at Week 52	-2.11[†††]	-2.30[†††]	-2.41[†††]	-1.39[†††]
LS mean difference from insulin glargine (95% CI)	-0.72*** (-0.86, -0.58)	-0.91*** (-1.05, -0.77)	-1.02*** (-1.15, -0.89)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	8.52 → 6.29	8.60 → 6.09	8.52 → 5.95	8.51 → 7.09
LS mean change from baseline at Week 52	-2.24[†††]	-2.43[†††]	-2.58[†††]	-1.44[†††]
LS mean difference from insulin glargine (95% CI)	-0.80*** (-0.92, -0.68)	-0.99*** (-1.11, -0.87)	-1.14*** (-1.26, -1.02)	N/A
HbA1c (mmol/mol)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	69.6 → 46.6	70.5 → 44.5	69.6 → 43.3	69.4 → 54.4
LS mean change from baseline at Week 52	-23.1[†††]	-25.2[†††]	-26.4[†††]	-15.2[†††]
LS mean difference from insulin glargine (95% CI)	-7.8*** (-9.4,-6.3)	-10.0*** (-11.5,-8.4)	-11.2*** (-12.5,-9.8)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	69.6 → 45.3	70.5 → 43.1	69.6 → 41.5	69.5 → 54.0

	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
LS mean change from baseline at Week 52	-24.5†††	-26.6†††	-28.2†††	-15.7†††
LS mean difference from insulin glargine (95% CI)	-8.8*** (-10.1, -7.4)	-10.9*** (-12.3, -9.6)	-12.5*** (-13.8,-11.2)	N/A
Percentage of patients with HbA1c <7.0% (<53 mmol/mol) at Week 52 (%)				
Treatment-Regimen Estimand[c]	75.1***	82.9***	84.9***	48.8
Efficacy Estimand[d]	81.0***	88.2***	90.7***	50.7
Percentage of patients with HbA1c ≤6.5% (≤48 mmol/mol) at Week 52 (%)				
Treatment-Regimen Estimand[c]	61.9###	69.8###	74.0###	31.0
Efficacy Estimand[d]	66.0###	76.0###	81.1###	31.7
Percentage of patients with HbA1c <5.7% (<39 mmol/mol) at Week 52 (%)				
Treatment-Regimen Estimand[c]	21.7###	31.1###	38.0###	3.5
Efficacy Estimand[d]	23.0###	32.7###	43.1###	3.4

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; HbA1c = glycosylated hemoglobin A1c; LS = least-squares; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts.

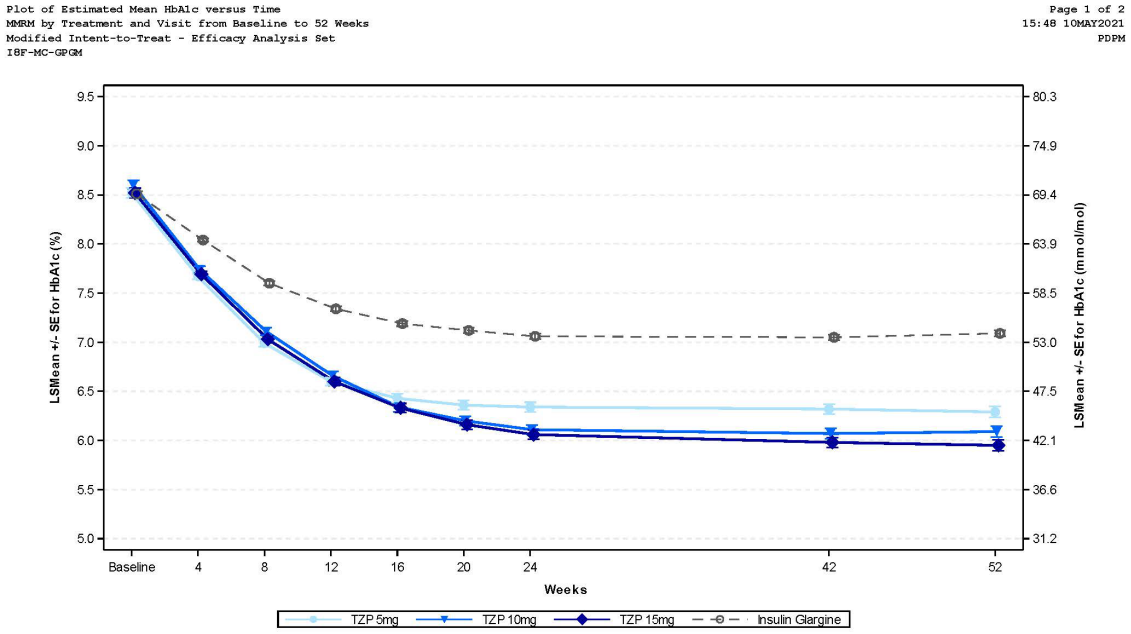
d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

***p-Value <0.001 versus insulin glargine under graphical testing procedure.

###Nominal p-value <0.001 versus insulin glargine, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Mean change from baseline in HbA1c over time to 52 weeks



Abbreviations: ANOVA = analysis of variance; HbA1c= hemoglobin A1c; LSMean = least squares mean; MMRM = mixed model repeated measures; SE = standard error; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; TZP = tirzepatide.
Note 1: MMRM model for post-baseline measures: Actual Value = Baseline + Pooled Country + Baseline SGLT-2i use (Yes, No) + Treatment + Time + Treatment*Time (Type III sum of squares). Variance-Covariance structure (Actual Value) = Unstructured.
Note 2: ANOVA model for baseline measures: Actual Value = Treatment (Type III sum of squares).

Fasting serum glucose

Tirzepatide 5 and 10 mg showed similar mean reductions in FSG compared with insulin glargine, while tirzepatide 15 mg had a significantly larger mean reduction compared with insulin glargine.

7-Point SMBG

All doses of tirzepatide significantly reduced the SMBG overall daily mean, premeal daily mean, and 2-hour postmeal daily mean assessed at 52 weeks compared with insulin glargine for the efficacy estimand. At 52 weeks, all daily mean SMBG values were <140 mg/dL across all 3 tirzepatide groups, while only the premeal daily mean SMBG value was <140 mg/dL in the insulin glargine group.

Summary of Blood Glucose Efficacy Endpoints for Study GPGM, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
FSG (mg/dL)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	172.3 → 127.0	175.7 → 120.9	174.1 → 116.7	168.4 → 122.4
Change from baseline at Week 52	-44.3[†††]	-50.3[†††]	-54.5[†††]	-48.8[†††]
Difference from insulin glargine (95% CI)	4.5 (-1.7, 10.8)	-1.5 (-7.3, 4.3)	-5.7[#] (-11.3, -0.1)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	172.3 → 121.0	175.7 → 116.4	174.2 → 112.0	168.7 → 120.0
Change from baseline at Week 52	-50.4[†††]	-54.9[†††]	-59.3[†††]	-51.4[†††]

	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
Difference from insulin glargine (95% CI)	1.0 (-3.7, 5.7)	-3.6 (-8.2, 1.1)	-8.0### (-12.6, -3.4)	N/A
FSG (mmol/L)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	9.57 → 7.05	9.75 → 6.71	9.67 → 6.48	9.35 → 6.80
Change from baseline at Week 52	-2.46†††	-2.79†††	-3.02†††	-2.71†††
Difference from insulin glargine (95% CI)	0.25 (-0.09, 0.60)	-0.08 (-0.40, 0.24)	-0.32# (-0.63, 0.00)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	9.57 → 6.71	9.75 → 6.46	9.67 → 6.23	9.37 → 6.67
Change from baseline at Week 52	-2.80†††	-3.06†††	-3.29†††	-2.84†††
Difference from insulin glargine (95% CI)	0.04 (-0.22, 0.30)	-0.21 (-0.48, 0.05)	-0.44### (-0.71, -0.18)	N/A
Daily Mean 7-Point SMBG (mg/mL)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 52	186.8 → 128.5	189.8 → 125.9	190.3 → 120.9	185.9 → 140.9
Change from baseline at Week 52	-58.4†††	-61.1†††	-66.1†††	-46.1†††
Difference from insulin glargine (95% CI)	-12.4### (-16.1, -8.6)	-15.0### (-18.8, -11.3)	-20.0### (-23.7, -16.2)	N/A
Premeal daily mean				
Baseline → Week 52	170.4 → 122.0	174.0 → 118.6	177.5 → 114.4	170.1 → 126.2
Change from baseline at Week 52	-49.6†††	-53.0†††	-57.2†††	-45.4†††
Difference from insulin glargine (95% CI)	-4.2# (-7.7, -0.8)	-7.6### (-11.1, -4.1)	-11.8### (-15.2, -8.3)	N/A
2-Hour postmeal daily mean				
Baseline → Week 52	201.6 → 134.7	204.1 → 133.2	205.5 → 128.0	200.8 → 152.7
Change from baseline at Week 52	-67.4†††	-68.9†††	-74.1†††	-49.4†††
Difference from insulin glargine (95% CI)	-18.0### (-22.4, -13.6)	-19.5### (-23.9, -15.1)	-24.8### (-29.1, -20.4)	N/A
Daily Mean 7-Point SMBG (mmol/L)				
Efficacy Estimand[b]				
Overall daily mean				
Baseline → Week 52	10.37 → 7.13	10.53 → 6.99	10.57 → 6.71	10.32 → 7.82
Change from baseline at Week 52	-3.24†††	-3.39†††	-3.67†††	-2.56†††
Difference from insulin glargine (95% CI)	-0.69### (-0.89, -0.48)	-0.83### (-1.04, -0.63)	-1.11### (-1.32, -0.90)	N/A
Premeal daily mean				
Baseline → Week 52	9.46 → 6.77	9.66 → 6.58	9.85 → 6.35	9.44 → 7.00
Change from baseline at Week 52	-2.75†††	-2.94†††	-3.17†††	-2.52†††

	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
Difference from insulin glargine (95% CI)	-0.23# (-0.43, -0.04)	-0.42### (-0.62, -0.23)	-0.65### (-0.85, -0.46)	N/A
2-Hour postmeal daily mean				
Baseline → Week 52	11.19 → 7.48	11.33 → 7.39	11.41 → 7.10	11.15 → 8.48
Change from baseline at Week 52	-3.74†††	-3.83†††	-4.12†††	-2.74†††
Difference from insulin glargine (95% CI)	-1.00### (-1.24, -0.76)	-1.08### (-1.33, -0.84)	-1.37### (-1.62, -1.13)	N/A

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; FSG = fasting serum glucose; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; SMBG = self-monitored blood glucose; TZP = tirzepatide.

a ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b MMRM analysis assuming MAR; ANOVA used at baseline.

Note: Shown are the least-squares means.

#Nominal p-value <0.05, ###nominal p-value <0.001 versus insulin glargine, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Body weight

Tirzepatide 5, 10, and 15 mg showed significant reduction in body weight from baseline to 52 weeks. Conversely, the insulin glargine group showed an increase in mean body weight.

Summary of Body Weight Efficacy Endpoints for Study GPGM, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
Body Weight (kg)				
Treatment-Regimen Estimand[a]				
Baseline → Week 52	90.3 → 83.8	90.6 → 81.3	90.0 → 79.7	90.2 → 91.9
Change from baseline at Week 52	-6.4†††	-8.9†††	-10.6†††	1.7†††
Difference from insulin glargine (95% CI)	-8.1*** (-8.9, -7.3)	-10.6*** (-11.4, -9.8)	-12.2*** (-13.0,-11.5)	N/A
Efficacy Estimand[b]				
Baseline → Week 52	90.3 → 83.4	90.7 → 81.1	90.0 → 78.9	90.3 → 92.4
Change from baseline at Week 52	-7.1†††	-9.5†††	-11.7†††	1.9†††
Difference from insulin glargine (95% CI)	-9.0*** (-9.8, -8.3)	-11.4*** (-12.1, -10.6)	-13.5*** (-14.3, -12.8)	N/A
Percentage of patients with Weight Loss ≥5% at Week 52 (%)				
Treatment-Regimen Estimand[c]	57.3###	74.2###	77.5###	9.2
Efficacy Estimand[d]	62.9###	77.6###	85.3###	8.0
Percentage of patients with Weight Loss ≥10% at Week 52 (%)				
Treatment-Regimen Estimand[c]	31.9###	49.8###	59.3###	1.8
Efficacy Estimand[d]	35.9###	53.0###	65.6###	1.5
Percentage of patients with Weight Loss ≥15% at Week 52 (%)				
Treatment-Regimen Estimand[c]	13.2###	22.8###	32.9###	0.5
Efficacy Estimand[d]	13.8###	24.0###	36.5###	0.5

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR ; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using retrieved dropouts.

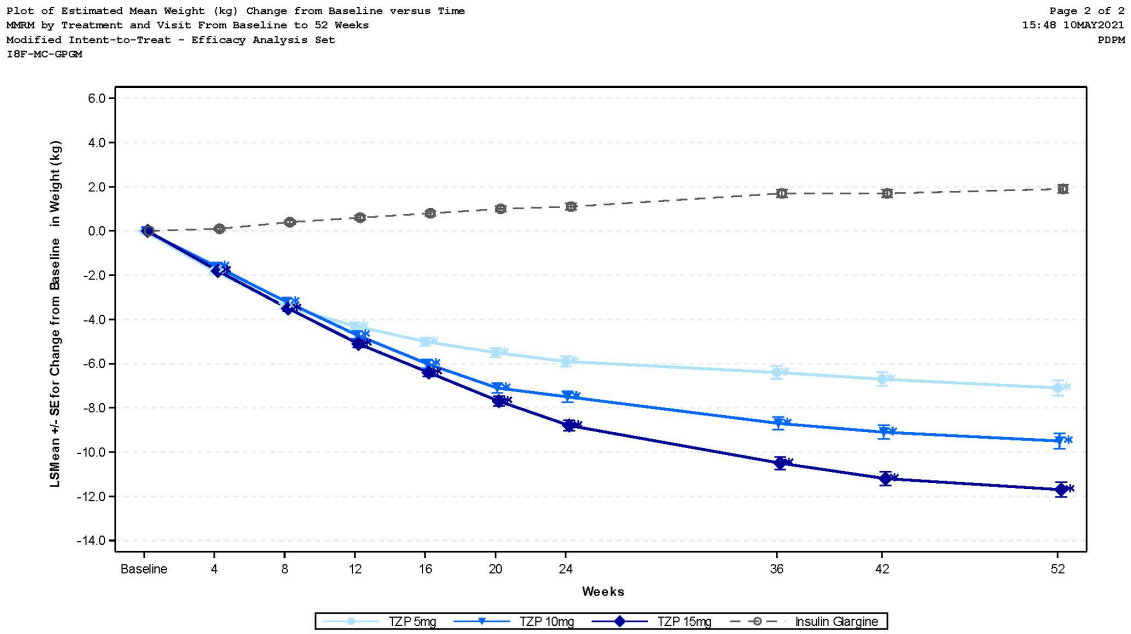
d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

***p-value <0.001 versus insulin degludec under graphical testing procedure.

###Nominal p-value <0.001 versus insulin degludec, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Mean change from baseline in body weight over time to 52 weeks



Abbreviations: ANOVA = analysis of variance; HbA1c= hemoglobin A1c; LSMean = least squares mean; MMRM = mixed model repeated measures; SE = standard error; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; TZP = tirzepatide.
Note 1: MMRM model for post-baseline measures: Change from Baseline = Baseline + Pooled Country + Baseline HbA1c Group (<=8.5%, >8.5%) + Baseline SGLT-2i use (Yes, No) + Treatment + Time + Treatment*Time (Type III sum of squares). Variance-Covariance structure (Change from Baseline) = Unstructured.
Note 2: If p-value for TZP versus Insulin Glargine comparison is less than 0.05, then marked with *.

Lipid parameter results

At 52 weeks, all three doses of tirzepatide significantly reduced triglycerides, total cholesterol, LDL-C, and VLDL-C and increased HDL-C both from baseline and compared with insulin glargine.

Summary of Lipid Parameters for Study GPGM, mITT Population – Efficacy Analysis Set

Parameters		TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
Triglycerides					
Baseline → Week 52	(mg/dL)	167.7 → 134.4	161.7 → 128.1	161.2 → 124.2	158.4 → 150.2
	(mmol/L)	1.89 → 1.52	1.83 → 1.45	1.82 → 1.40	1.79 → 1.70
Change from baseline at 52 weeks	(mg/dL)	-25.9	-32.2	-36.2	-10.1
	(mmol/L)	-0.29	-0.36	-0.41	-0.11
Percent change from baseline at 52 weeks (%)		-16.1†††	-20.0†††	-22.5†††	-6.3†††
Insulin glargine adjusted change difference at 52 weeks (%) (95% CI)		-10.5### (-15.1, -5.7)	-14.7### (-19.0, -10.1)	-17.3### (-21.5, -12.9)	N/A
Total Cholesterol					
Baseline → Week 52	(mg/dL)	158.5 → 146.7	152.0 → 145.9	155.1 → 145.8	154.7 → 154.5
	(mmol/L)	4.10 → 3.79	3.93 → 3.77	4.01 → 3.77	4.00 → 4.00
	(mg/dL)	-7.8	-8.6	-8.7	0

Parameters		TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
Change from baseline at 52 weeks	(mmol/L)	-0.20	-0.22	-0.22	0
Percent change from baseline at 52 weeks (%)		-5.0†††	-5.5†††	-5.6†††	0.02
Insulin glargine adjusted change difference at 52 weeks (%) (95% CI)		-5.0$^{\#\#\#}$ (-7.6, -2.4)	-5.6$^{\#\#\#}$ (-8.1, -2.9)	-5.6$^{\#\#\#}$ (-8.2, -3.0)	N/A
HDL-C					
Baseline → Week 52	(mg/dL)	41.3 → 43.3	40.2 → 44.5	40.4 → 45.0	40.6 → 41.7
	(mmol/L)	1.07 → 1.12	1.04 → 1.15	1.04 → 1.16	1.05 → 1.08
Change from baseline at 52 weeks	(mg/dL)	2.8	4.0	4.4	1.2
	(mmol/L)	0.07	0.10	0.11	0.03
Percent change from baseline at 52 weeks (%)		6.8†††	9.8†††	10.9†††	2.9†††
Insulin glargine adjusted change difference at 52 weeks (%) (95% CI)		3.8$^{\#\#\#}$ (1.6, 6.0)	6.7$^{\#\#\#}$ (4.4 9.0)	7.8$^{\#\#\#}$ (5.5, 10.1)	N/A
LDL-C					
Baseline → Week 52	(mg/dL)	77.2 → 69.9	72.9 → 68.7	74.9 → 69.0	75.5 → 75.9
	(mmol/L)	2.00 → 1.81	1.88 → 1.78	1.94 → 1.78	1.95 → 1.96
Change from baseline at 52 weeks	(mg/dL)	-5.1	-6.3	-6.0	0.9
	(mmol/L)	-0.13	-0.16	-0.15	0.02
Percent change from baseline at 52 weeks (%)		-6.7†††	-8.4†††	-8.0†††	1.3
Insulin glargine adjusted change difference at 52 weeks (%) (95% CI)		-7.9$^{\#\#\#}$ (-12.1, -3.4)	-9.5$^{\#\#\#}$ (-13.7, -5.1)	-9.1$^{\#\#\#}$ (-13.2, -4.8)	N/A
VLDL-C					
Baseline → Week 52	(mg/dL)	33.1 → 26.6	31.9 → 25.4	31.6 → 24.7	31.1 → 29.7
	(mmol/L)	0.85 → 0.69	0.83 → 0.66	0.82 → 0.64	0.80 → 0.77
Change from baseline at 52 weeks	(mg/dL)	-4.9	-6.2	-6.9	-1.8
	(mmol/L)	-0.13	-0.16	-0.18	-0.05
Percent change from baseline at 52 weeks (%)		-15.6†††	-19.5†††	-21.8†††	-5.6†††
Insulin glargine adjusted change difference at 52 weeks (%) (95% CI)		-10.6$^{\#\#\#}$ (-15.0, -5.9)	-14.7$^{\#\#\#}$ (-18.8, -10.3)	-17.1$^{\#\#\#}$ (-21.1, -12.9)	N/A

Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide; VLDL-C = very-low-density lipoprotein cholesterol.

Note: MMRM analysis on log-transformed data then converted back to original scale.

Note: Shown are the estimated means.

###p-Value <0.001 versus insulin glargine, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

PRO measures (*questionaires are briefly described in section 2.6.5.2 of this overview*)

DTSQs and DTSQc

Each of the 3 tirzepatide groups had a significantly higher total DTSQc score, indicating greater improvement in treatment satisfaction compared with insulin glargine. The tirzepatide 10- and 15 mg groups had a statistically significant lower score, indicating lower perceived frequency of hyperglycaemia compared with the insulin glargine group. All 3 tirzepatide dose groups had statistically significant lower scores, indicating lower perceived frequency of hypoglycaemia compared with the insulin glargine group.

IW-SP

There were significant differences in the total transformed IW-SP scores for all three doses of tirzepatide compared with insulin glargine at 52 weeks, indicating better weight-related self-perception.

APPADL

All 3 doses of tirzepatide significantly improved the APPADL transformed scores from baseline to 52 weeks compared with insulin glargine, indicating better self-reported ability to perform physical activities of daily living.

EQ-5D-5L

There were significant differences in the EQ VAS and EQ-5D Index scores for all 3 doses of tirzepatide compared with insulin glargine at 52 weeks, indicating better overall health-related quality of life.

Summary of PRO Efficacy Endpoints for Study GPGM, mITT Population – Efficacy Analysis Set

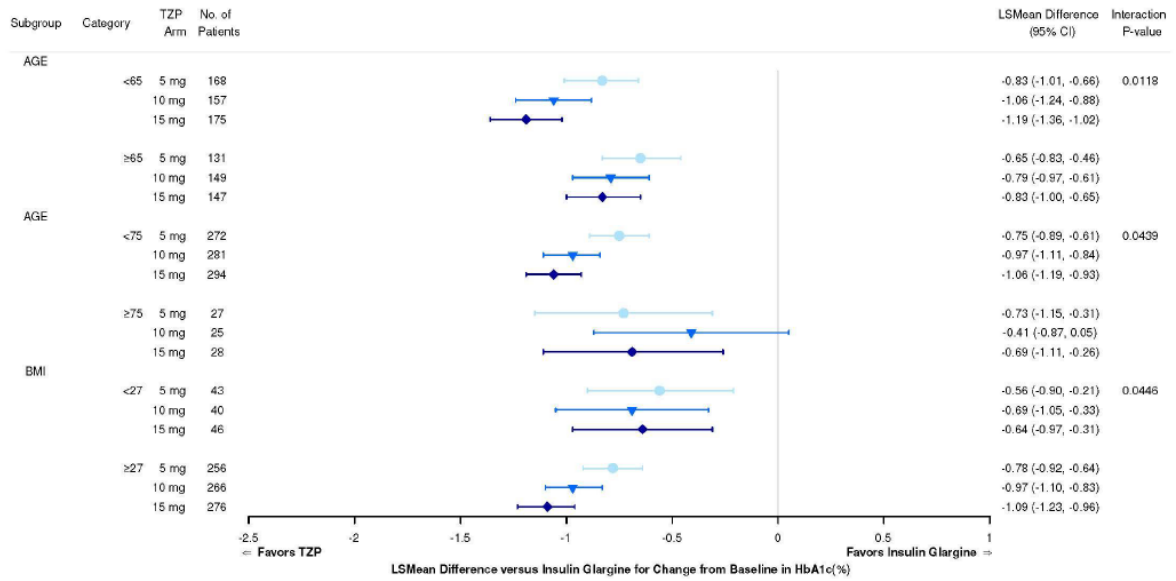
	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
IW-SP (Transformed Scores)[a]				
n	285	290	295	903
Baseline	70.5	68.6	70.5	72.5
Change from baseline at 52 weeks (LOCF)	10.4†††	12.5†††	11.6†††	2.9†††
Change difference from insulin glargine (95% CI)	7.5### (4.7, 10.3)	9.7### (6.9, 12.5)	8.8### (6.0, 11.5)	N/A
APPADL (Transformed Scores)[a]				
n	285	291	296	903
Baseline	63.8	61.4	61.5	63.4
Change from baseline at 52 weeks (LOCF)	5.9†††	5.6†††	6.1†††	-1.1
Change difference from insulin glargine (95% CI)	7.0### (4.6, 9.4)	6.7### (4.3, 9.1)	7.2### (4.8, 9.5)	N/A

	TZP 5 mg (N=328)	TZP 10 mg (N=326)	TZP 15 mg (N=337)	Insulin Glargine (N=998)
DTSQs and DTSQc[a]				
Total[b]				
n	278	286	290	884
DTSQs at baseline	28.5	27.8	27.7	27.9
DTSQc at Week 52	15.3	15.7	15.3	13.7
Change difference from insulin glargine (95% CI)	1.63### (0.99, 2.26)	1.98### (1.35, 2.62)	1.63### (1.00, 2.26)	N/A
Hyperglycaemia[c]				
n	278	287	291	883
DTSQs at baseline	3.4	3.6	3.7	3.4
DTSQc at Week 52	-0.9	-1.2	-1.5	-0.9
Change difference from insulin glargine (95% CI)	-0.03 (-0.30, 0.25)	-0.29# (-0.56, -0.02)	-0.62### (-0.89, -0.35)	N/A
Hypoglycaemia[d]				
n	278	286	289	881
DTSQs at baseline	0.9	1.1	1.0	1.0
DTSQc at Week 52	-0.9	-0.7	-0.8	-0.4
Change difference from insulin glargine (95% CI)	-0.50### (-0.77, -0.23)	-0.33# (-0.60, -0.06)	-0.38## (-0.65, -0.12)	N/A
EQ-5D-5L (UK)[a]				
n	282	289	295	887
Baseline	0.80	0.76	0.77	0.79
Change from baseline at 52 weeks (LOCF)	0.04†††	0.04†††	0.04†††	0.00
Change difference from insulin glargine (95% CI)	0.04 ### (0.02, 0.07)	0.04## (0.01, 0.06)	0.04## (0.01, 0.06)	N/A
EQ VAS[a]				
n	284	290	296	897
Baseline	75.4	73.8	74.5	75.3
Change from baseline at 52 weeks (LOCF)	8.1†††	6.5†††	6.3†††	3.0†††
Change difference from insulin glargine (95% CI)	5.1### (3.3, 6.9)	3.5### (1.7, 5.3)	3.3### (1.6, 5.1)	N/A

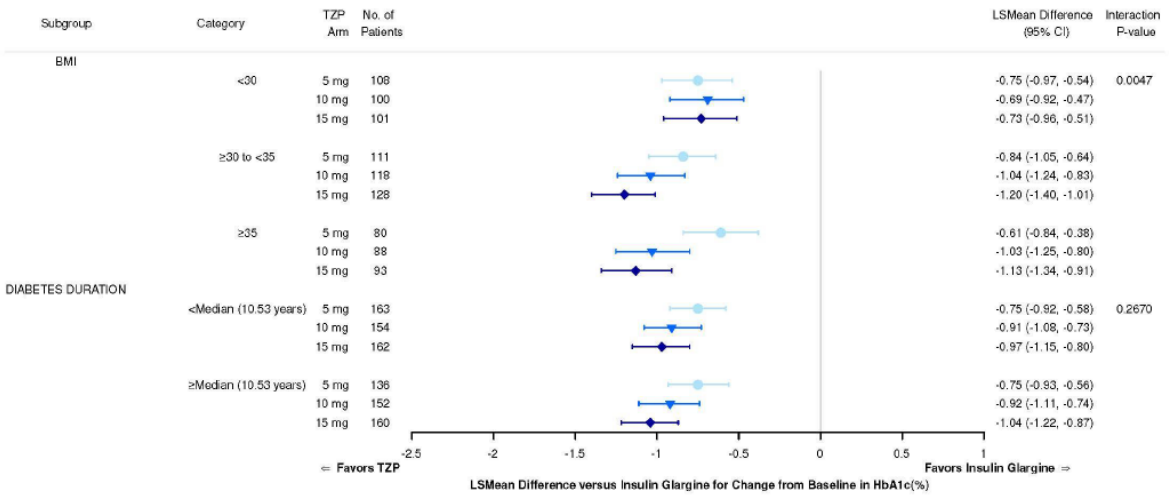
Subgroup analyses of the primary endpoint

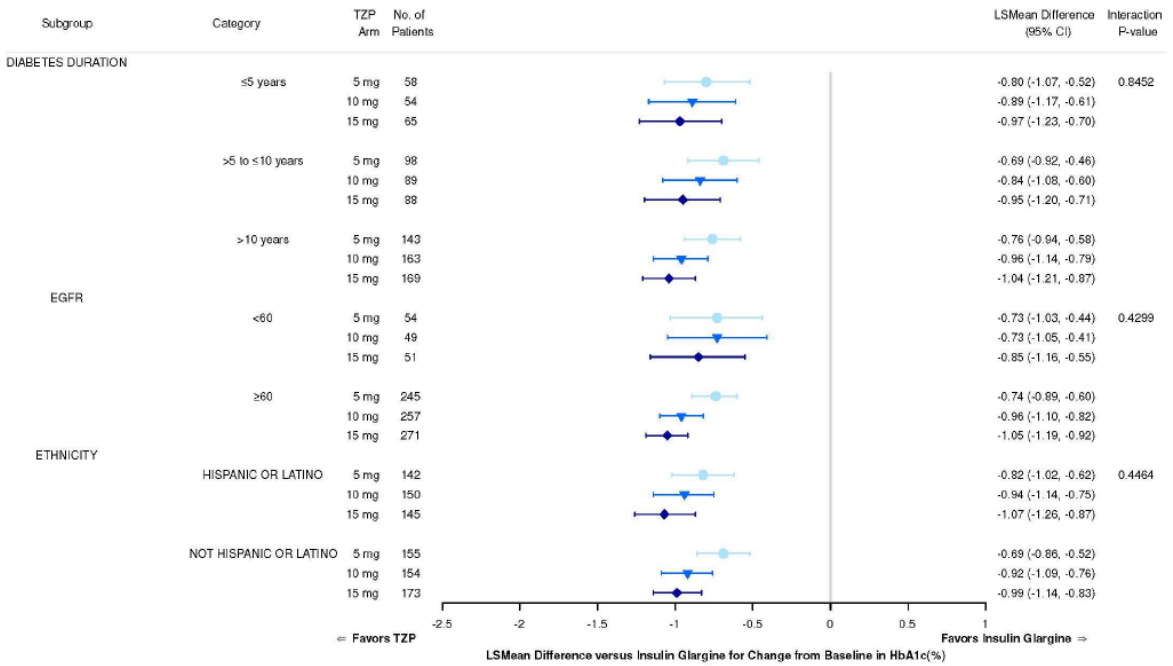
Analyses of change from baseline in the HbA1c at 52 weeks (primary endpoint) across patient characteristic subgroups were consistent with the primary results, with the treatment difference favouring all three doses of tirzepatide compared with Insulin glargine. Forest plots are given in the following:

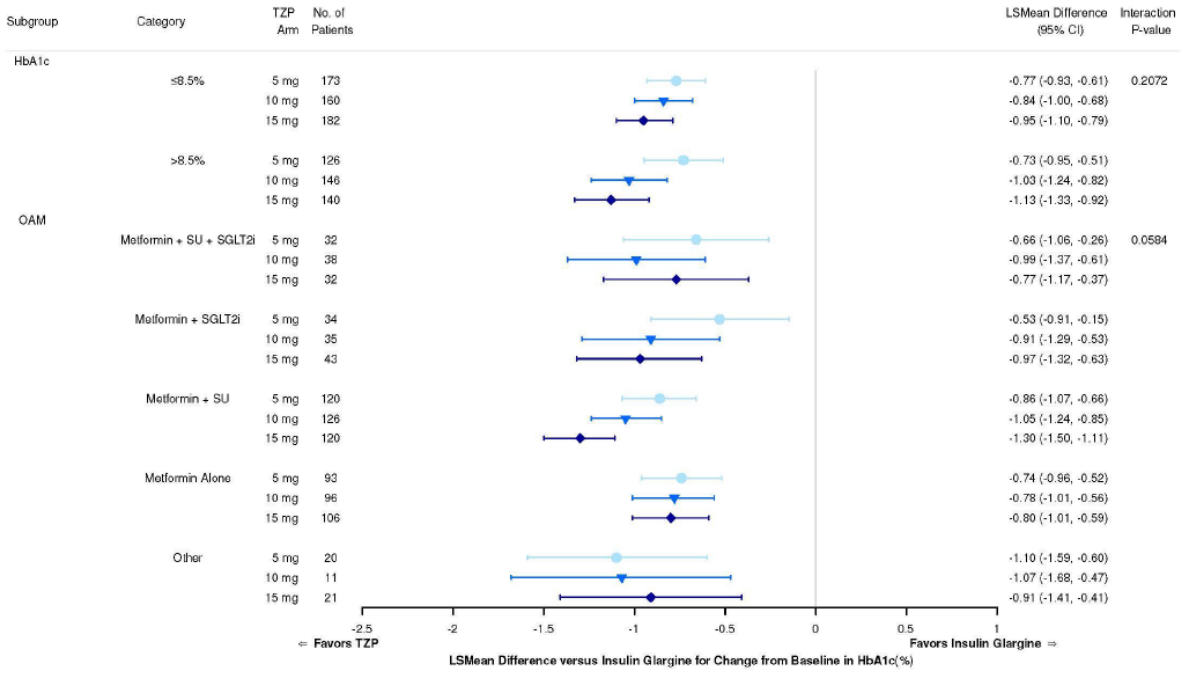
Subgroup Analysis of HbA1c(%) - Change from Baseline at Week 52
Modified Intent-to-Treatment Population - Treatment-Regimen (ANCOVA)
ANCOVA with Imputation Method: Retrieved Dropout
I8F-MC-GPGM

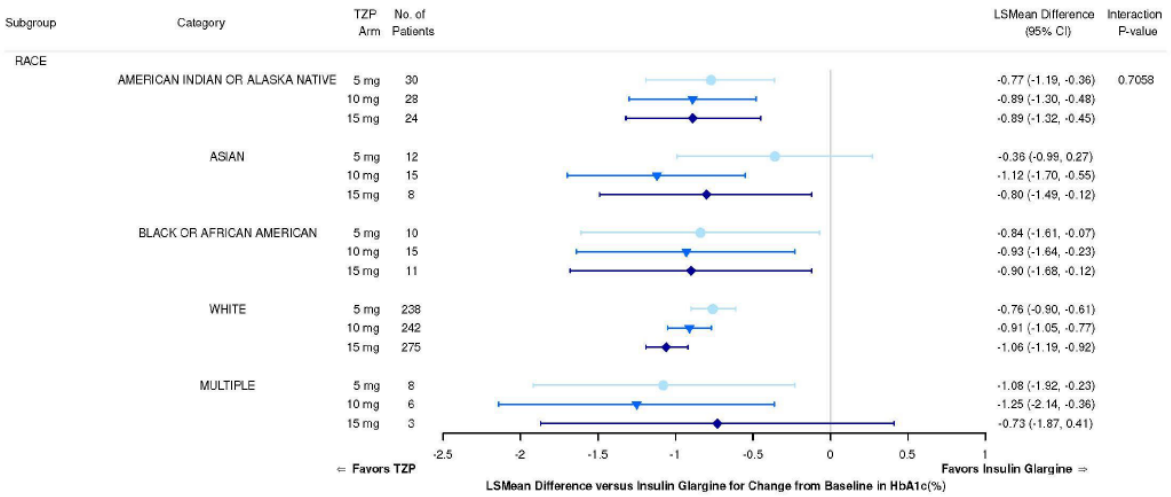


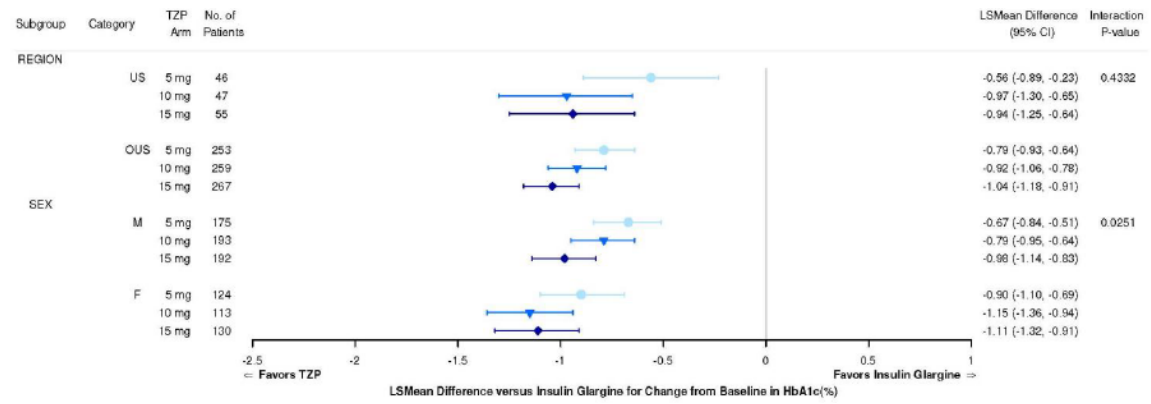
Footnote: ANCOVA model for postbaseline measures. Units for Age, BMI and eGFR are years, kg/m2, and mL/min/1.73m2, respectively.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSMean = least squares mean; OAM = Oral Antihyperglycemic Medication; TZP = tirzepatide.




Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
DIABETES DURATION
≤5 years
5 mg 58 -0.80 (-1.07, -0.52) 0.8452
10 mg 54 -0.89 (-1.17, -0.61)
15 mg 65 -0.97 (-1.23, -0.70)
>5 to ≤10 years
5 mg 98 -0.69 (-0.92, -0.46)
10 mg 89 -0.84 (-1.08, -0.60)
15 mg 88 -0.95 (-1.20, -0.71)
>10 years
5 mg 143 -0.76 (-0.94, -0.58)
10 mg 163 -0.96 (-1.14, -0.79)
15 mg 169 -1.04 (-1.21, -0.87)
EGFR
<60
5 mg 54 -0.73 (-1.03, -0.44) 0.4299
10 mg 49 -0.73 (-1.05, -0.41)
15 mg 51 -0.85 (-1.16, -0.55)
≥60
5 mg 245 -0.74 (-0.89, -0.60)
10 mg 257 -0.96 (-1.10, -0.82)
15 mg 271 -1.05 (-1.19, -0.92)
ETHNICITY
HISPANIC OR LATINO
5 mg 142 -0.82 (-1.02, -0.62) 0.4464
10 mg 150 -0.94 (-1.14, -0.75)
15 mg 145 -1.07 (-1.26, -0.87)
NOT HISPANIC OR LATINO
5 mg 155 -0.69 (-0.86, -0.52)
10 mg 154 -0.92 (-1.09, -0.76)
15 mg 173 -0.99 (-1.14, -0.83)
-2.5 -2 -1.5 -1 -0.5 0 0.5 1
⇐ Favors TZP
Favors Insulin Glargine ⇒
LSMean Difference versus Insulin Glargine for Change from Baseline in HbA1c(%)


Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
HbA1c
≤8.5%
5 mg 173 -0.77 (-0.93, -0.61) 0.2072
10 mg 160 -0.84 (-1.00, -0.68)
15 mg 182 -0.95 (-1.10, -0.79)
>8.5%
5 mg 126 -0.73 (-0.95, -0.51)
10 mg 146 -1.03 (-1.24, -0.82)
15 mg 140 -1.13 (-1.33, -0.92)
OAM
Metformin + SU + SGLT2i
5 mg 32 -0.66 (-1.06, -0.26) 0.0584
10 mg 38 -0.99 (-1.37, -0.61)
15 mg 32 -0.77 (-1.17, -0.37)
Metformin + SGLT2i
5 mg 34 -0.53 (-0.91, -0.15)
10 mg 35 -0.91 (-1.29, -0.53)
15 mg 43 -0.97 (-1.32, -0.63)
Metformin + SU
5 mg 120 -0.86 (-1.07, -0.66)
10 mg 126 -1.05 (-1.24, -0.85)
15 mg 120 -1.30 (-1.50, -1.11)
Metformin Alone
5 mg 93 -0.74 (-0.96, -0.52)
10 mg 96 -0.78 (-1.01, -0.56)
15 mg 106 -0.80 (-1.01, -0.59)
Other
5 mg 20 -1.10 (-1.59, -0.60)
10 mg 11 -1.07 (-1.68, -0.47)
15 mg 21 -0.91 (-1.41, -0.41)
-2.5 -2 -1.5 -1 -0.5 0 0.5 1
⇐ Favors TZP
Favors Insulin Glargine ⇒
LSMean Difference versus Insulin Glargine for Change from Baseline in HbA1c(%)





GPGI Study (SURPASS-5): results

Primary endpoint: Mean change from baseline in HbA1c

Tirzepatide 5, 10, and 15 mg demonstrated statistically significant reduction in HbA1c from baseline to 40 weeks compared with placebo. Additionally, compared to placebo, all three doses of tirzepatide had significantly higher proportions of patients who achieved HbA1c target values of <7.0%, ≤6.5%, and <5.7%.

Summary of HbA1c Efficacy Endpoints for Study GPGI, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
HbA1c (%)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	8.30 → 6.21	8.36 → 5.92	8.22 → 5.98	8.38 → 7.45
Change from baseline at Week 40	-2.11[†††]	-2.40[†††]	-2.34[†††]	-0.86[†††]
Difference from placebo (95% CI)	-1.24*** (-1.48, -1.01)	-1.53*** (-1.77, -1.30)	-1.47*** (-1.71, -1.23)	N/A

	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Efficacy Estimand[b]				
Baseline → Week 40	8.29 → 6.09	8.34 → 5.73	8.22 → 5.74	8.39 → 7.39
Change from baseline at Week 40	-2.23†††	-2.59†††	-2.59†††	-0.93†††
Difference from placebo (95% CI)	-1.30*** (-1.52, -1.07)	-1.66*** (-1.88, -1.43)	-1.65*** (-1.88, -1.43)	N/A
HbA1c (mmol/mol)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	67.2 → 44.4	67.9 → 41.2	66.4 → 41.8	68.1 → 57.9
Change from baseline at Week 40	-23.0†††	-26.2†††	-25.5†††	-9.4†††
Difference from placebo (95% CI)	-13.6*** (-16.2, -11.0)	-16.8*** (-19.3, -14.2)	-16.1*** (-18.7, -13.5)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	67.1 → 43.1	67.7 → 39.2	66.4 → 39.2	68.2 → 57.3
Change from baseline at Week 40	-24.4†††	-28.3†††	-28.3†††	-10.2†††
Difference from placebo (95% CI)	-14.2*** (-16.6, -11.7)	-18.1*** (-20.6, -15.7)	-18.1*** (-20.5, -15.6)	N/A
Percentage of patients with HbA1c <7.0% (<53 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	87.3***	89.6***	84.7***	34.5
Efficacy Estimand[d]	93.0***	97.4***	94.0***	33.9
Percentage of patients with HbA1c ≤6.5% (≤48 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	74.3###	85.9###	79.5###	17.3
Efficacy Estimand[d]	80.0###	94.7###	92.3###	17.0
Percentage of patients with HbA1c <5.7% (<39 mmol/mol) at Week 40 (%)				
Treatment-Regimen Estimand[c]	24.4###	41.6***	49.6***	2.7
Efficacy Estimand[d]	26.1###	47.8***	62.4***	2.5

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; HbA1c = glycosylated hemoglobin A1c; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using placebo imputation; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using placebo imputation.

d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

***p-Value <0.001 versus placebo subject to type 1 error rate control.

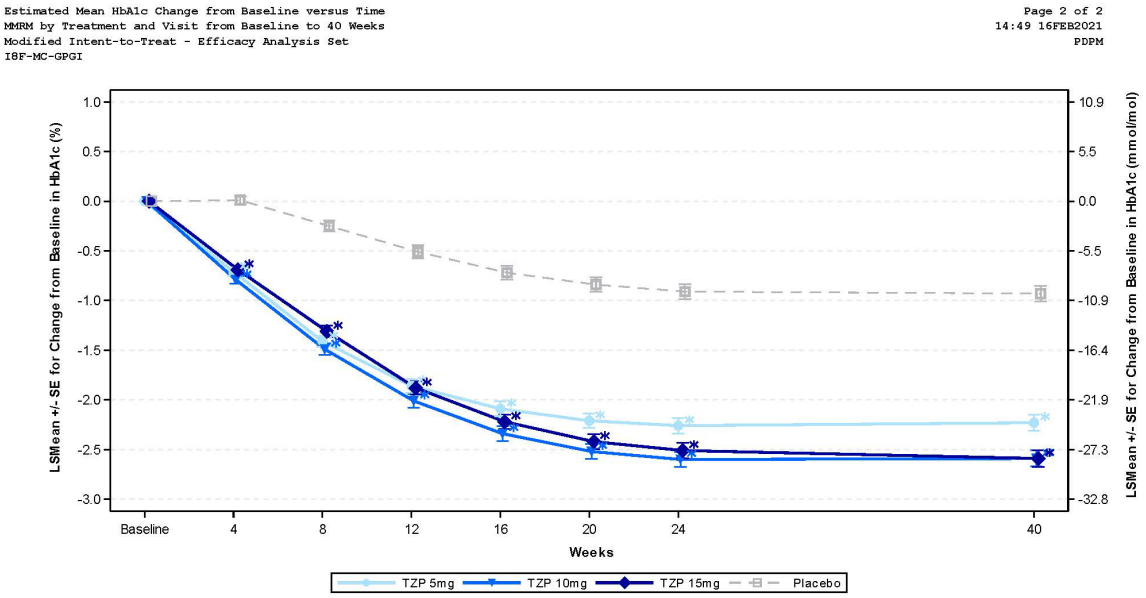
###Nominal p-value <0.001 versus placebo, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Mean change from baseline in HbA1c over time to 40 weeks

All 3 doses of tirzepatide achieved mean reductions from baseline in HbA1c at all time points assessed. Because, per protocol, the insulin glargine dose could not be modified during the first 4 weeks, no meaningful response from the placebo group was expected before this time point. However, at Week 8 and all

subsequent time points, all tirzepatide doses were associated with significantly greater reductions from baseline in HbA1c compared with placebo. Maximal reductions in HbA1c by all tirzepatide doses were reached around 24 weeks and were maintained through 40 weeks.



Abbreviations: ANOVA = analysis of variance; HbA1c= hemoglobin A1c; LSMean = least squares mean; MMRM = mixed model repeated measures; TZP = tirzepatide.

Note 1: MMRM for post-baseline measures: Variable = Baseline + Baseline Metformin Use (Yes, No) + Pooled Country + Treatment + Visit + Treatment*Visit (Type III sum of squares). Variance-Covariance structure = Unstructured.
Note 2: * - P-value for TZP versus Placebo comparison less than 0.05.

Secondary endpoints

All key secondary efficacy objectives were controlled for type 1 error.

Fasting serum glucose

Tirzepatide 5, 10, and 15 mg showed statistically significant mean reductions in FSG from baseline to 40 weeks compared with placebo.

Insulin glargine was titrated throughout the study to achieve an FSG <100 mg/dL (5.6 mmol/L). At Week 40, significantly higher proportions of patients in all tirzepatide dose groups compared to placebo achieved the FSG target of <100 mg/dL (5.6 mmol/L):

- tirzepatide 5 mg: 54.8%
- tirzepatide 10 mg: 61.1%
- tirzepatide 15 mg: 64.1%, and
- placebo: 29.1%.

7-Point SMBG

Tirzepatide 5, 10, and 15 mg significantly reduced SMBG overall daily mean, premeal daily mean, and postmeal daily mean from baseline to 40 weeks compared with placebo.

Additionally, compared to placebo, all 3 doses of tirzepatide significantly reduced mean SMBG levels for all 7 time points. Treatment with all 3 doses of tirzepatide enabled patients to have lower mean blood glucose values throughout the day compared with the patients who received placebo.

Summary of Blood Glucose Efficacy Endpoints for Study GPGI, mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
FSG (mg/dL)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	162.9 → 104.4	162.6 → 98.6	160.4 →100.0	164.4 → 123.4
Change from baseline at Week 40	-58.2†††	-64.0†††	-62.6†††	-39.2†††
Difference from placebo (95% CI)	-19.0*** (-26.6, -11.4)	-24.9*** (-32.3, -17.4)	-23.4*** (-31.0, -15.8)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	162.2 → 101.5	162.9 → 94.9	160.4 → 95.1	164.4 → 123.9
Change from baseline at Week 40	-61.4†††	-67.9†††	-67.7†††	-38.9†††
Difference from placebo (95% CI)	-22.5*** (-29.5, -15.4)	-29.0*** (-36.0, -22.0)	-28.8*** (-35.9, -21.6)	N/A
FSG (mmol/L)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	9.0 → 5.80	9.0 →5.47	8.9 → 5.55	9.1 → 6.85
Change from baseline at Week 40	-3.23†††	-3.56†††	-3.47†††	-2.17†††
Difference from placebo (95% CI)	-1.05*** (-1.48, -0.63)	-1.38*** (-1.79, -0.97)	-1.30*** (-1.72, -0.88)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	9.0 → 5.6	9.0 → 5.3	8.9 → 5.3	9.1 → 6.9
Change from baseline at Week 40	-3.4†††	-3.8†††	-3.8†††	-2.2†††
Difference from placebo (95% CI)	-1.3*** (-1.64, -0.86)	-1.6*** (-2.00, -1.22)	-1.6*** (-1.99, -1.20)	N/A
Daily Mean 7-Point SMBG (mg/mL)				
Efficacy Estimand[a]				
Overall daily mean				
Baseline → Week 40	186.6 → 118.0	188.7 → 113.4	183.0 → 111.4	182.0 → 145.7
Change from baseline at Week 40	-67.1###	-71.7###	-73.7###	-39.4###
Difference from placebo (95% CI)	-27.7### (-33.5, -22.0)	-32.3### (-38.1, -26.6)	-34.3### (-40.1, -28.5)	N/A
Premeal daily mean				
Baseline → Week 40	162.2 → 106.3	167.0 → 103.2	161.0 → 104.1	158.4 → 125.3
Change from baseline at Week 40	-55.8###	-58.9###	-58.1###	-36.8###
Difference from placebo (95% CI)	-19.0### (-24.0, -14.0)	-22.1### (-27.2, -17.1)	-21.2### (-26.3, -16.1)	N/A
2-Hour postmeal daily mean				
Baseline → Week 40	209.2 → 129.6	207.4 → 123.9	203.3 → 118.8	204.9 → 165.7
Change from baseline at Week 40	-76.7###	-82.3###	-87.4###	-40.5###
Difference from placebo (95% CI)	-36.2### (-43.6, -28.7)	-41.8### (-49.2, -34.4)	-46.9### (-54.4, -39.5)	N/A
Daily Mean 7-Point SMBG (mmol/L)				
Efficacy Estimand[b]				

	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Overall daily mean				
Baseline → Week 40	10.36 → 6.55	10.48 → 6.29	10.16 → 6.18	10.10 → 8.09
Change from baseline at Week 40	-3.73###	-3.98###	-4.09###	-2.19###
Difference from placebo (95% CI)	-1.54### (-1.86, -1.22)	-1.79### (-2.11, -1.48)	-1.91### (-2.23, -1.58)	NA
Premeal daily mean				
Baseline → Week 40	9.00 → 5.90	9.27 → 5.73	8.94 → 5.78	8.79 → 6.96
Change from baseline at Week 40	-3.10###	-3.27###	-3.22###	-2.04###
Difference from placebo (95% CI)	-1.06### (-1.33, -0.78)	-1.23### (-1.51, -0.95)	-1.18### (-1.46, -0.89)	N/A
2-Hour postmeal daily mean				
Baseline → Week 40	11.61 → 7.19	11.51 → 6.88	11.28 → 6.59	11.37 → 9.20
Change from baseline at Week 40	-4.26†††	-4.57†††	-4.85†††	-2.25†††
Difference from placebo (95% CI)	-2.01### (-2.42, -1.60)	-2.32### (-2.73, -1.91)	-2.61### (-3.02, -2.19)	N/A

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; FSG = fasting serum glucose; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; SMBG = self-monitored blood glucose; TZP = tirzepatide.

a ANCOVA with multiple imputation of missing data at the primary endpoint visit using placebo imputation; ANOVA used at baseline.

b MMRM analysis assuming MAR; ANOVA used at baseline.

Note: Shown are the least-squares means.

***p-Value <0.001 versus placebo subject to type 1 error rate control.

###Nominal p-value <0.001 versus placebo, not included in graphical testing procedure.

†††p-Value <0.001 versus baseline.

Insulin glargine dose

At baseline, the daily mean insulin glargine dose was similar across the tirzepatide and placebo groups. All three doses of tirzepatide compared with placebo led to a significant percent change from baseline in the daily insulin glargine dose.

Summary of Insulin Glargine Dose for GPGI; mITT Population – Efficacy Analysis Set

Parameter	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Units				
Baseline → Week 40	34.3 → 37.6	32.0 → 35.7	35.0→ 29.4	32.9→ 58.8
Change from baseline at 40 weeks	4.4	2.7	-3.8	25.1
Percent change from baseline at 40 weeks (%)	13.0	8.1	-11.4	75.0†††
Placebo-adjusted percent change at 40 weeks (%) (95% CI)	-35.4### (-46.0, -22.8)†††	-38.2### (-48.3, -26.1)†††	-49.3### (-57.7, -39.4)†††	N/A

IU/kg/day				
Baseline → Week 40	0.37 → 0.43	0.35 → 0.43	0.37 → 0.36	0.36 → 0.62
Change from baseline at 40 weeks	0.08	0.07	0	0.26
Percent change from baseline at 40 weeks (%)	20.9††	19.0††	0	72.3†††
Placebo-adjusted percent change at 40 weeks (%) (95% CI)	-29.8### (-41.1, -16.4)†††	-31.0### (-42.1, -17.7)†††	-42.0### (-51.4, -30.7)†††	N/A

Abbreviations: CI = confidence interval; IU = International Units; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide.

Note: MMRM analysis with log transformation.

Note: Shown are the estimated means.

###Nominal p-values <0.001 versus placebo, not included in graphical testing procedure.

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

Body weight

Tirzepatide 5, 10, and 15 mg demonstrated statistically significant reductions in body weight from baseline to 40 weeks compared with placebo. Conversely, patients in the placebo group showed an increase from baseline in mean body weight. Additionally, compared to placebo, all three doses of tirzepatide had significantly higher proportions of patients who achieved mean weight reductions of ≥5%, ≥10%, and ≥15%.

Summary of Body Weight Measures for Study GPGI,
mITT Population – Full Analysis Set; Efficacy Analysis Set

	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Body Weight (kg)				
Treatment-Regimen Estimand[a]				
Baseline → Week 40	95.8→ 89.7	94.6 → 87.7	96.0→ 86.3	94.2 → 96.8
Change from baseline at Week 40	-5.4†††	-7.5†††	-8.8†††	1.6††
Difference from placebo (95% CI)	-7.1*** (-8.7, -5.4)	-9.1*** (-10.7, -7.5)	-10.5*** (-12.1, -8.8)	N/A
Efficacy Estimand[b]				
Baseline → Week 40	95.5 → 89.6	95.4 → 87.5	96.2 → 84.8	94.1 → 97.4
Change from baseline at Week 40	-6.2†††	-8.2†††	-10.9†††	1.7††
Difference from placebo (95% CI)	-7.8*** (-9.4, -6.3)	-9.9*** (-11.5, -8.3)	-12.6*** (-14.2, -11.0)	N/A
Percentage of patients with Weight Loss ≥5% at Week 40 (%)				
Treatment-Regimen Estimand[c]	47.9###	57.9###	71.6###	6.0
Efficacy Estimand[d]	53.9###	64.6###	84.6###	5.9
Percentage of patients with Weight Loss ≥10% at Week 40 (%)				
Treatment-Regimen Estimand[c]	20.7###	41.6###	40.7###	0.8
Efficacy Estimand[d]	22.6###	46.9###	51.3###	0.9
Percentage of patients with Weight Loss ≥15% at Week 40 (%)				
Treatment-Regimen Estimand[c]	6.9#	23.7##	22.9##	0.0
Efficacy Estimand[d]	7.0#	26.6##	31.6###	0.0

Abbreviations: ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; MAR = missing at random; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients in the efficacy analysis set and full analysis set; N/A = not applicable; TZP = tirzepatide.

a Shown are the least-squares means; ANCOVA with multiple imputation of missing data at the primary endpoint visit using placebo imputation; ANOVA used at baseline.

b Shown are the least-squares means; MMRM analysis assuming MAR; ANOVA used at baseline.

c Logistic regression with multiple imputation of missing data at the primary endpoint visit using placebo imputation.

d Logistic regression with imputation of missing data at the primary endpoint visit using MMRM analysis.

***p-value <0.001 versus placebo subject to type 1 error rate control.

#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus placebo, not included in graphical testing procedure.

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

Mean change from baseline in body weight over time to 40 weeks

All three tirzepatide dose groups had significantly greater mean reductions from baseline in body weight compared with placebo beginning with Week 4. For the tirzepatide groups, the curves for 10 and 15 mg diverged from 5 mg at Week 16, and the 15-mg curve diverged from 10 mg at Week 20, and thereafter. Mean weight reductions continued through 40 weeks and did not appear to plateau.

Estimated Mean Weight (kg) Change from Baseline versus Time
MMRM by Treatment and Visit from Baseline to 40 Weeks
Modified Intent-to-Treat - Efficacy Analysis Set
I8F-MC-GPGI

Page 2 of 2
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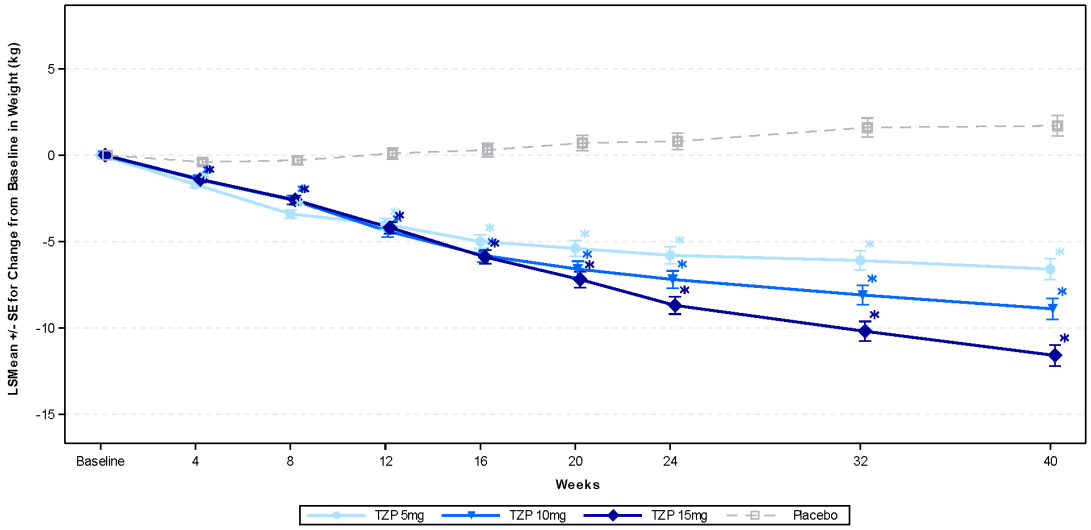


Abbreviations: ANOVA = analysis of variance; HbA1c= hemoglobin A1c; LSMean = least squares mean; MMRM = mixed model repeated measures; TZP = tirzepatide.

Note 1: MMRM model for post-baseline measures: Change in Weight = Baseline Weight + Pooled Country + Baseline HbA1c Group (<= 8.0%, >8.0%) + Baseline Metformin Use (Yes, No) + Treatment + Visit + Treatment*Visit (Type III sum of squares). Variance-Covariance structure = Unstructured.
Note 2: * - P-value for TZP versus Placebo comparison less than 0.05.

Program Location: //lillyce/prd/ly3298176/i8f_mc_gpgi/final/programs/stat/tfl/grvs12.sas
Output Location : //lillyce/prd/ly3298176/i8f_mc_gpgi/final/output/shared/grvs12.rtf
Dataset Location: //lillyce/prd/ly3298176/i8f_mc_gpgi/final/data/analysis/shared

Lipid parameter results

At 40 weeks, all tirzepatide groups significantly reduced triglycerides, total cholesterol, LDL-C, and VLDL-C from baseline. No significant differences were observed for HDL-C for any of the treatment groups compared to baseline.

Additionally, all three doses of tirzepatide significantly reduced triglycerides, total cholesterol, LDL-C, and VLDL-C at 40 weeks compared with placebo. No significant differences were observed for HDL-C in any of the three tirzepatide groups compared with placebo.

Summary of Lipid Parameters for Study GPGI, mITT Population – Efficacy Analysis Set

Parameter		TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Triglycerides					
Baseline → 40 Weeks	(mg/dL)	153.5 → 122.3	144.0 → 116.4	138.3 → 108.3	141.4 →134.5
	(mmol/L)	1.7 → 1.4	1.6 → 1.3	1.6 → 1.2	1.6 → 1.5
Change from baseline at 40 weeks	(mg/dL)	-22.0	-27.9	-35.9	-9.8
	(mmol/L)	-0.2	-0.3	-0.4	-0.1
Percent change from baseline at 40 weeks (%)		-15.2†††	-19.3†††	-24.9†††	-6.8

Parameter		TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Placebo-adjusted percent change from placebo at 40 weeks (%) (95% CI)		-9.07# (-17.23, -0.12)	-13.48## (-21.23, -4.97)	-19.43### (-26.80, -11.33)	N/A
Total cholesterol					
Baseline → 40 Weeks	(mg/dL)	167.1 → 151.6	166.3 → 149.1	163.4 → 144.7	167.7 → 165.6
	(mmol/L)	4.3 → 3.9	4.3 → 3.9	4.2 → 3.7	4.3 → 4.3
Change from baseline at 40 weeks	(mg/dL)	-14.6	-17.1	-21.5	-0.6
	(mmol/L)	-0.4	-0.4	-0.6	0.0
Percent change from baseline at 40 weeks (%)		-8.8†††	-10.3†††	-12.9†††	-0.4
Placebo-adjusted percent change from placebo at 40 weeks (%) (95% CI)		-8.43### (-12.28, -4.42)	-9.93### (-13.71, -5.98)	-12.61### (-16.36, -8.70)	N/A
HDL-C					
Baseline → 40 Weeks	(mg/dL)	44.1 → 45.8	45.2 → 45.7	45.5 → 45.3	44.8 → 45.6
	(mmol/L)	1.1 → 1.2	1.2 → 1.2	1.2 → 1.2	1.2 → 1.2
Change from baseline at 40 weeks	(mg/dL)	0.9	0.8	0.4	0.8
	(mmol/L)	0	0	0	0
Percent change from baseline at 40 weeks (%)		2.1	1.8	0.9	1.7
Placebo-adjusted percent change from placebo at 40 weeks (%) (95% CI)		0.37 (-3.63, 4.54)	0.09 (-3.90, 4.24)	-0.80 (-4.83, 3.41)	N/A
LDL-C					
Baseline → 40 Weeks	(mg/dL)	83.6 → 77.6	85.7 → 74.3	83.9 → 72.0	87.5 → 87.6
	(mmol/L)	2.2 → 2.0	2.2 → 1.9	2.2 → 1.9	2.3 → 2.3
Change from baseline at 40 weeks	(mg/dL)	-7.6	-10.9	-13.2	2.4
	(mmol/L)	-0.2	-0.3	-0.3	0.1
Percent change from baseline at 40 weeks (%)		-8.9†††	-12.8†††	-15.5†††	2.8
Placebo-adjusted percent change from placebo at 40 weeks (%) (95% CI)		-11.44## (-17.63, -4.79)	-15.23### (-21.15, -8.87)	-17.83### (-23.70, -11.50)	N/A
VLDL-C					
Baseline → 40 Weeks	(mg/dL)	30.5 → 24.2	28.6 → 23.2	27.2 → 21.6	27.7 → 26.9
	(mmol/L)	0.8 → 0.6	0.7 → 0.6	0.7 → 0.6	0.7 → 0.7
Change from baseline at 40 weeks	(mg/dL)	-4.3	-5.3	-6.9	-1.6
	(mmol/L)	-0.1	-0.1	-0.2	0.0
Percent change from baseline at 40 weeks (%)		-15.1†††	-18.7†††	-24.1†††	-5.5

Parameter	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Placebo-adjusted percent change from placebo at 40 weeks (%) (95% CI)	-10.15# (-18.11, -1.42)	-13.96## (-21.56, -5.62)	-19.70### (-26.96, -11.72)	N/A

Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; N = number of patients who were randomized and received at least 1 dose of study drug, excluding patients who discontinued study drug due to inadvertent enrollment; N/A = not applicable; TZP = tirzepatide; VLDL-C = very-low-density lipoprotein cholesterol.
Note: ANOVA analysiss on log-transformed data then converted back to original scale.
Note: Data shown are estimated means.
#Nominal p-Value <0.05, ## nominal p-Value <0.01, ### nominal p-Value <0.001 versus placebo, not included in graphical testing procedure.
†††p-Value <0.001 versus baseline.

PRO measures

IW-SP

There were significant differences in the total transformed IW-SP scores for the 10 and 15 mg tirzepatide doses compared with placebo at 40 weeks, indicating better self-perception.

APPADL

The 10 and 15 mg tirzepatide doses significantly improved the APPADL transformed scores from baseline to 40 weeks compared with placebo, indicating better self-reported ability to perform physical activities of daily living.

DTSQs and DTSQc

Each of the 3 tirzepatide groups had a significantly higher total DTSQc score, indicating greater improvement in treatment satisfaction compared with placebo. Each of the 3 tirzepatide groups had a statistically significant lower perceived frequency of hyperglycaemia compared with the placebo group. No significant differences were seen for the perceived frequency of hypoglycaemia scores between each of the 3 tirzepatide groups, indicating similar self-perceived problems with hypoglycaemia compared with the placebo group.

EQ-5D-5L

There was significant difference in the EQ VAS score for the tirzepatide 10 mg group compared with placebo at 40 weeks, indicating better overall health-related quality of life. There were significant differences in the EQ-5D Index scores for the tirzepatide 10 and 15 mg groups compared with placebo at 40 weeks, indicating better overall health-related quality of life.

Summary of PRO Efficacy Endpoints for Study GPGI, mITT Population – Efficacy Analysis Set

	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
IW-SP (Transformed Scores)[a]				
N	106	106	98	111
Baseline	62.9	63.4	64.8	64.7
Change from baseline at 40 weeks (LOCF)	5.2††	12.0†††	14.0†††	1.7
Change difference from placebo (95% CI)	3.5 (-1.5, 8.5)	10.3### (5.3, 15.3)	12.3### (7.2, 17.4)	N/A
APPADL (Transformed Scores)[a]				
N	106	106	98	111

	TZP 5 mg (N=116)	TZP 10 mg (N=118)	TZP 15 mg (N=118)	Placebo (N=119)
Baseline	63.6	68.0	69.1	69.1
Change from baseline at 40 weeks (LOCF)	1.6	5.0†††	6.9†††	-1.3
Change difference from placebo (95% CI)	3.0 (-1.0, 6.9)	6.3$^{\#\#}$ (2.3, 10.3)	8.3$^{\#\#\#}$ (4.2, 12.3)	N/A
DTSQs and DTSQc[a]				
Total[b]				
N	105	105	95	109
DTSQs at baseline	29.1	29.5	29.0	29.2
DTSQc at Week 40	14.1	14.5	13.7	10.7
Change difference from placebo (95% CI)	3.35$^{\#\#\#}$ (1.90, 4.80)	3.72$^{\#\#\#}$ (2.27, 5.17)	2.91$^{\#\#\#}$ (1.42, 4.40)	N/A
Hyperglycaemia[c]				
N	105	105	95	109
DTSQs at baseline	2.8	3.2	2.9	2.8
DTSQc at Week 40	-1.8	-1.4	-1.6	-0.9
Change difference from placebo (95% CI)	-0.98$^{\#\#\#}$ (-1.46, -0.50)	-0.55$^{\#}$ (-1.04, -0.07)*	-0.72$^{\#\#}$ (-1.21, -0.22)	N/A
Hypoglycaemia[d]				
N	105	105	95	108
DTSQs at baseline	1.0 (0.15)	0.8 (0.15)	0.8 (0.15)	0.9 (0.15)
DTSQc at Week 40	-0.5 (0.19)	-0.1 (0.19)	-0.6 (0.20)	-0.4 (0.19)
Change difference from placebo (95% CI)	-0.03 (-0.56, 0.50)	0.37 (-0.16, 0.90)	-0.20 (-0.75, 0.34)	N/A
EQ-5D-5L (UK)[a]				
N	105	105	98	111
Baseline	0.78	0.80	0.82	0.82
Change from baseline at 40 weeks (LOCF)	-0.02	0.04†	0.03	-0.03
Change difference from placebo (95% CI)	0.01 (-0.03,0.05)	0.07$^{\#\#}$ (0.03,0.11)	0.06$^{\#\#}$ (0.02, 0.11)	N/A
EQ VAS[a]				
N	105	106	98	111
Baseline	75.0	73.9	78.2	77.1
Change from baseline at 40 weeks (LOCF)	1.7	5.8†††	2.3	-0.9
Change difference from placebo (95% CI)	2.6 (-1.2, 6.3)	6.7$^{\#\#\#}$ (3.0, 10.5)	3.2 (-0.6, 7.0)	N/A

Abbreviations: ANCOVA = analysis of covariance; APPADL = Ability to Perform Physical Activities of Daily Living; CI = confidence interval; DTSQc = Diabetes Treatment Satisfaction Questionnaire (change); DTSQs = Diabetes Treatment Satisfaction Questionnaire (status); EAS = efficacy analysis set; EQ VAS = EQ visual analog scale; IW-SP = Impact of Weight on Self-Perception; LOCF = last observation carried forward; mITT = modified intent-to-treat; n = number of patients in the mITT EAS with baseline and at least 1 postbaseline values; N = number of patients in EAS; N/A =not applicable; TZP = tirzepatide.

a ANCOVA, LOCF. Only the nonmissing postbaseline observation prior to rescue or study drug discontinuation was carried forward.

b A greater score indicates greater patient satisfaction with treatment.

c Represents the following question on the instrument answered by patients: "How often have you felt that your blood sugars have been unacceptably high recently?" Lower scores indicate blood glucose levels closer to the ideal. Higher scores indicate problems.

d Represents the following question on the instrument answered by patients: "How often have you felt that your blood sugars have been unacceptably low recently?" Lower scores indicate blood glucose levels closer to the ideal. Higher scores indicate problems.

Note: Shown are the least-squares means.

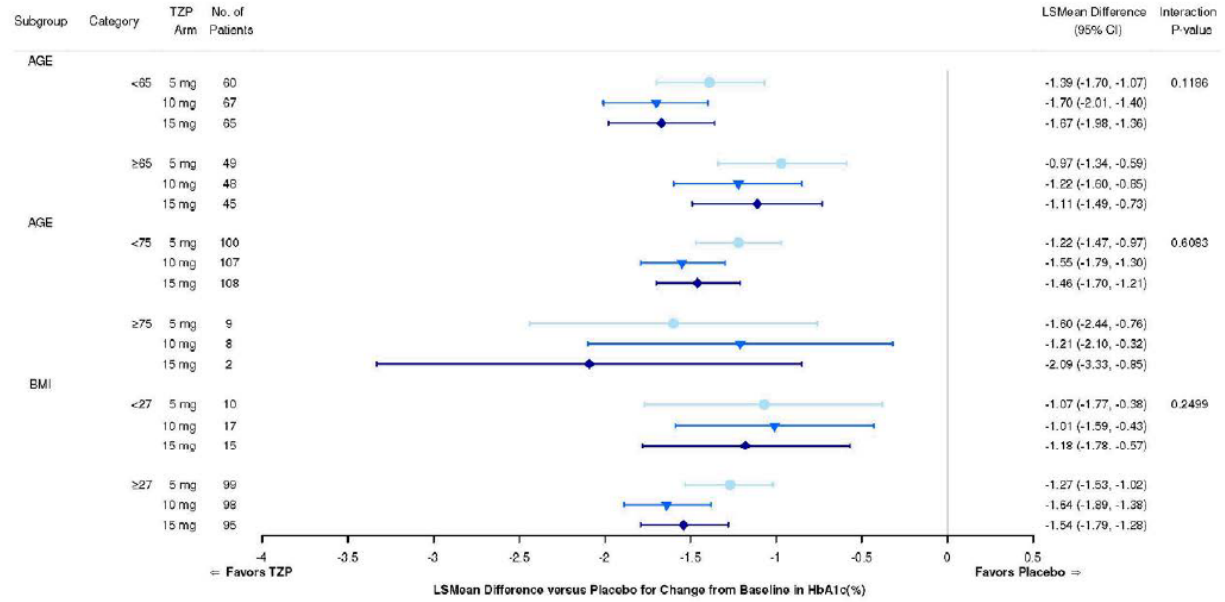
#Nominal p-value <0.05, ##nominal p-value <0.01, ###nominal p-value <0.001 versus insulin glargine, not included in graphical testing procedure.

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

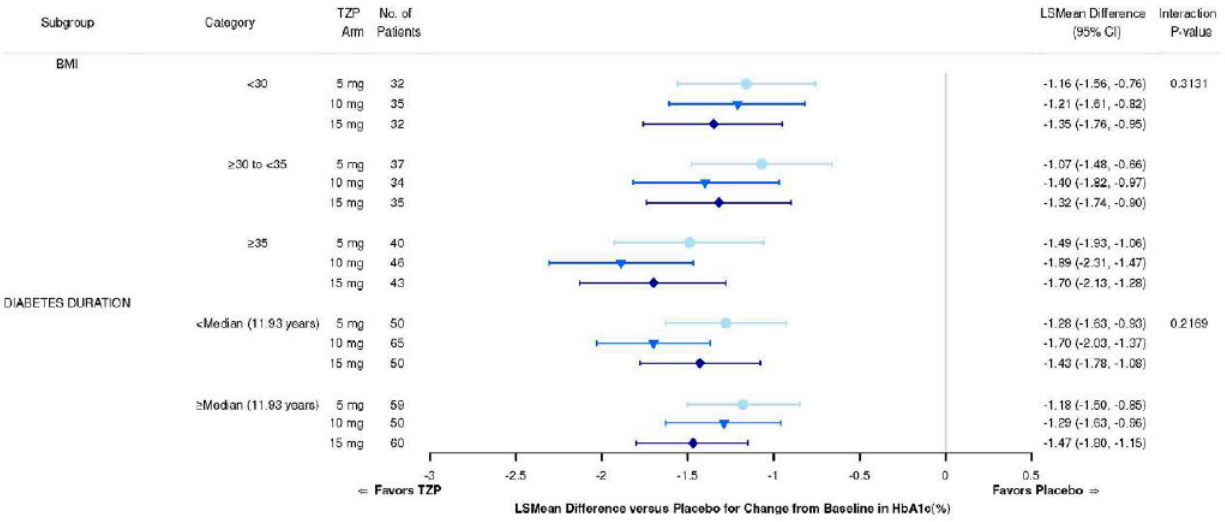
Subgroup analyses of the primary endpoint

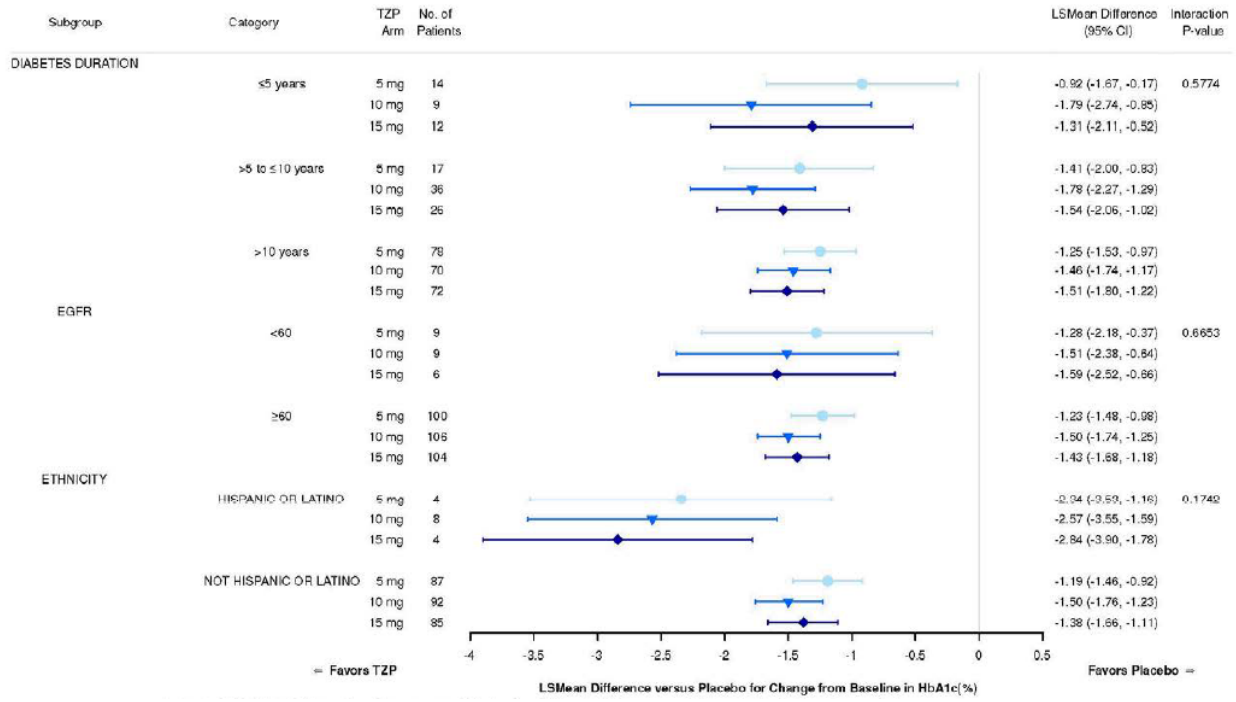
Analyses of change from baseline in the HbA1c at 40 weeks (primary endpoint) across patient characteristic subgroups were consistent with the primary results, with the treatment difference favouring all 3 doses of tirzepatide compared with placebo. Forest plots are given in the following:

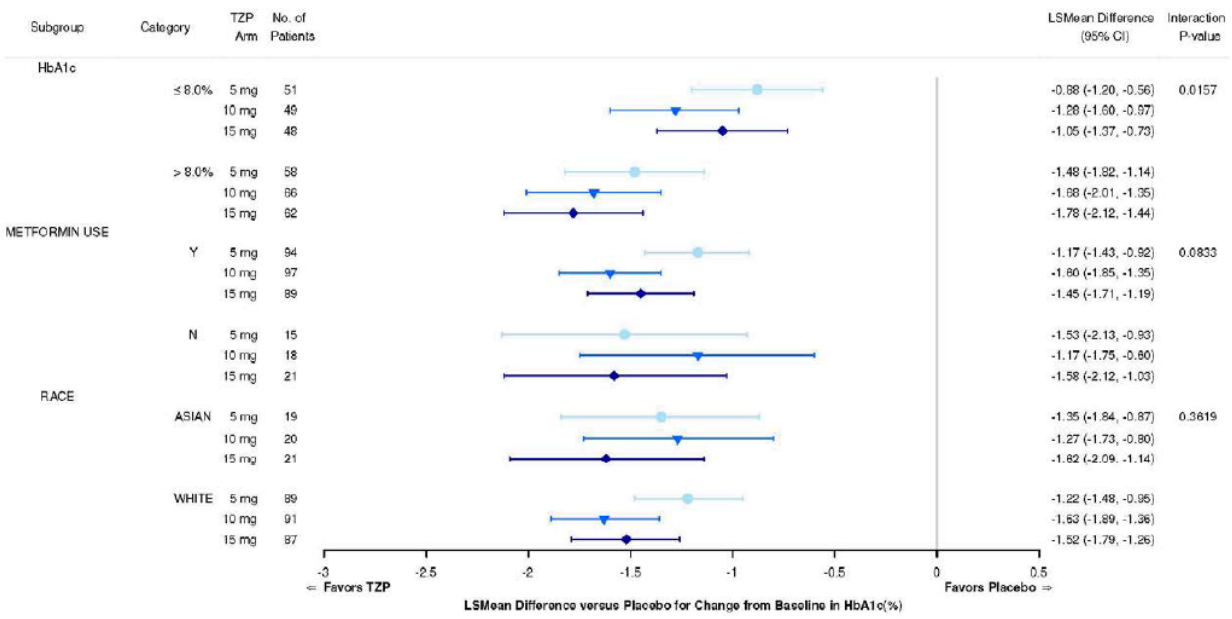
Subgroup Analysis of HbA1c(%) - Change from Baseline at Week 40
Modified Intent-to-Treatment Population - Treatment-Regimen (ANCOVA)
ANCOVA with Imputation Method: Placebo Imputation
I8F-MC-GPGI

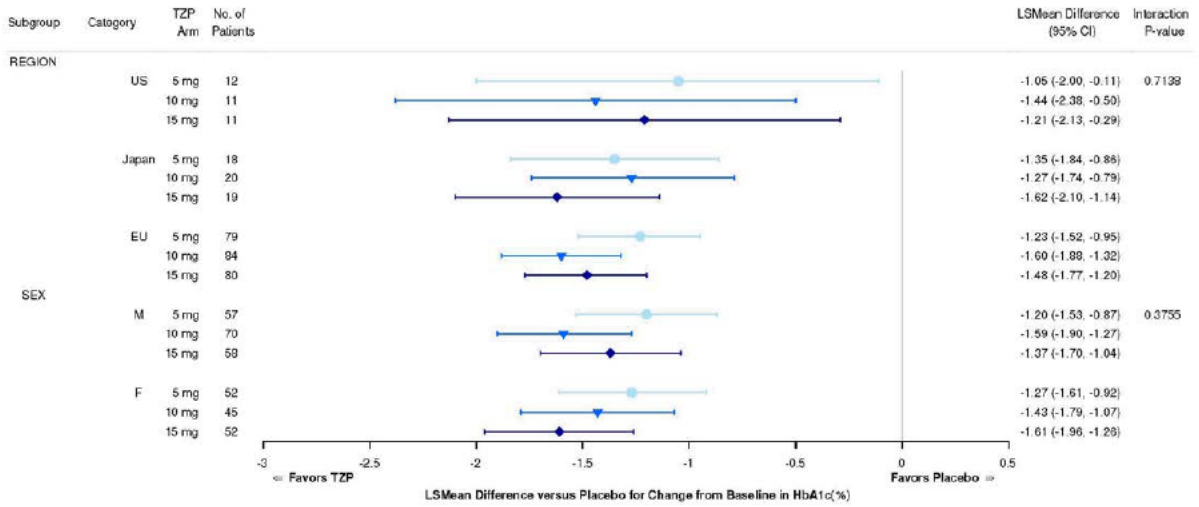


Footnote: ANCOVA model for postbaseline measures. Units for Age, BMI and eGFR are years, kg/m2, and mL/min/1.73m2, respectively.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; LSMean = least squares mean; TZP = tirzepatide.




Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
DIABETES DURATION
≤5 years
5 mg 14 -0.92 (-1.67, -0.17) 0.5774
10 mg 9 -1.79 (-2.74, -0.85)
15 mg 12 -1.31 (-2.11, -0.52)
>5 to ≤10 years
5 mg 17 -1.41 (-2.00, -0.83)
10 mg 36 -1.78 (-2.27, -1.29)
15 mg 26 -1.54 (-2.06, -1.02)
>10 years
5 mg 78 -1.25 (-1.53, -0.97)
10 mg 70 -1.46 (-1.74, -1.17)
15 mg 72 -1.51 (-1.80, -1.22)
EGFR
<60
5 mg 9 -1.28 (-2.18, -0.37) 0.6653
10 mg 9 -1.51 (-2.38, -0.64)
15 mg 6 -1.59 (-2.52, -0.66)
≥60
5 mg 100 -1.23 (-1.48, -0.98)
10 mg 105 -1.50 (-1.74, -1.25)
15 mg 104 -1.43 (-1.68, -1.18)
ETHNICITY
HISPANIC OR LATINO
5 mg 4 -2.04 (-3.59, -1.16) 0.1742
10 mg 8 -2.57 (-3.55, -1.59)
15 mg 4 -2.84 (-3.90, -1.78)
NOT HISPANIC OR LATINO
5 mg 87 -1.19 (-1.46, -0.92)
10 mg 92 -1.50 (-1.76, -1.23)
15 mg 85 -1.38 (-1.66, -1.11)
-4 -3.5 -3 -2.5 -2 -1.5 -1 -0.5 0 0.5
⇐ Favors TZP
Favors Placebo ⇒
LSMean Difference versus Placebo for Change from Baseline in HbA1c(%)


Subgroup
Category
TZP Arm
No. of Patients
LSMean Difference (95% CI)
Interaction P-value
HbA1c
≤ 8.0%
5 mg 51 -0.88 (-1.20, -0.56) 0.0157
10 mg 49 -1.28 (-1.60, -0.97)
15 mg 48 -1.05 (-1.37, -0.73)
> 8.0%
5 mg 58 -1.48 (-1.82, -1.14)
10 mg 66 -1.88 (-2.01, -1.35)
15 mg 62 -1.78 (-2.12, -1.44)
METFORMIN USE
Y
5 mg 94 -1.17 (-1.43, -0.92) 0.0833
10 mg 97 -1.80 (-1.85, -1.35)
15 mg 89 -1.45 (-1.71, -1.19)
N
5 mg 15 -1.53 (-2.13, -0.93)
10 mg 18 -1.17 (-1.75, -0.60)
15 mg 21 -1.58 (-2.12, -1.03)
RACE
ASIAN
5 mg 19 -1.35 (-1.84, -0.87) 0.3619
10 mg 20 -1.27 (-1.73, -0.80)
15 mg 21 -1.82 (-2.09, -1.14)
WHITE
5 mg 89 -1.22 (-1.48, -0.95)
10 mg 91 -1.63 (-1.89, -1.36)
15 mg 87 -1.52 (-1.79, -1.26)
-3 -2.5 -2 -1.5 -1 -0.5 0 0.5
⇐ Favors TZP
Favors Placebo ⇒
LSMean Difference versus Placebo for Change from Baseline in HbA1c(%)



- **Summary of main efficacy results**

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

SURPASS 1: Results at Week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)		121	121	120	113
HbA_{1c} (%)	Baseline (mean)	7.97	7.88	7.88	8.08
	Change from baseline	-1.87##	-1.89##	-2.07##	+0.04
	Difference from placebo [95 % CI]	-1.91** [-2.18, -1.63]	-1.93** [-2.21, -1.65]	-2.11** [-2.39, -1.83]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	63.6	62.6	62.6	64.8
	Change from baseline	-20.4##	-20.7##	-22.7##	0.4
	Difference from placebo [95 % CI]	-20.8** [-23.9, -17.8]	-21.1** [-24.1, -18.0]	-23.1** [-26.2, -20.0]	-
Patients (%) achieving HbA_{1c}	< 7 %	86.8**	91.5**	87.9**	19.6
	≤ 6.5 %	81.8††	81.4††	86.2††	9.8
	< 5.7 %	33.9**	30.5**	51.7**	0.9
FSG (mmol/L)	Baseline (mean)	8.5	8.5	8.6	8.6
	Change from baseline	-2.4##	-2.6##	-2.7##	+0.7#
	Difference from placebo [95 % CI]	-3.13** [-3.71, -2.56]	-3.26** [-3.84, -2.69]	-3.45** [-4.04, -2.86]	-
FSG (mg/dL)	Baseline (mean)	153.7	152.6	154.6	155.2
	Change from baseline	-43.6##	-45.9##	-49.3##	+12.9#
	Difference from placebo [95 % CI]	-56.5** [-66.8, -46.1]	-58.8** [-69.2, -48.4]	-62.1** [-72.7, -51.5]	-
Body weight (kg)	Baseline (mean)	87.0	85.7	85.9	84.4
	Change from baseline	-7.0##	-7.8##	-9.5##	-0.7
	Difference from placebo [95 % CI]	-6.3** [-7.8, -4.7]	-7.1** [-8.6, -5.5]	-8.8** [-10.3, -7.2]	-
Patients (%) achieving weight loss	≥ 5 %	66.9††	78.0††	76.7††	14.3
	≥ 10 %	30.6††	39.8††	47.4††	0.9
	≥ 15 %	13.2†	17.0†	26.7†	0.0

* $p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

† $p < 0.05$, †† $p < 0.001$ compared to placebo, not adjusted for multiplicity.

# $p < 0.05$, ## $p < 0.001$ compared to baseline.

SURPASS 2: Results at Week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1 mg
mITT population (n)		470	469	469	468
HbA_{1c} (%)	Baseline (mean)	8.33	8.31	8.25	8.24
	Change from baseline	-2.09##	-2.37##	-2.46##	-1.86##
	Difference from semaglutide [95 % CI]	-0.23** [-0.36, -0.10]	-0.51** [-0.64, -0.38]	-0.60** [-0.73, -0.47]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	67.5	67.3	66.7	66.6
	Change from baseline	-22.8##	-25.9##	-26.9##	-20.3
	Difference from semaglutide [95 % CI]	-2.5** [-3.9, -1.1]	-5.6** [-7, -4.1]	-6.6** [-8, -5.1]	N/A
Patients (%) achieving HbA_{1c}	< 7 %	85.5*	88.9**	92.2**	81.1
	≤ 6.5 %	74.0†	82.1††	87.1††	66.2
	< 5.7 %	29.3††	44.7**	50.9**	19.7
FSG (mmol/L)	Baseline (mean)	9.67	9.69	9.56	9.49
	Change from baseline	-3.11##	-3.42##	-3.52##	-2.70##
	Difference from semaglutide [95 % CI]	-0.41† [-0.65, -0.16]	-0.72†† [-0.97, -0.48]	-0.82†† [-1.06, -0.57]	-
FSG (mg/dL)	Baseline (mean)	174.2	174.6	172.3	170.9
	Change from baseline	-56.0##	-61.6##	-63.4##	-48.6##
	Difference from semaglutide [95 % CI]	-7.3† [-11.7, -3.0]	-13.0†† [-17.4, -8.6]	-14.7†† [-19.1, -10.3]	-
Body weight (kg)	Baseline (mean)	92.6	94.9	93.9	93.8
	Change from baseline	-7.8##	-10.3##	-12.4##	-6.2##
	Difference from semaglutide [95 % CI]	-1.7** [-2.6, -0.7]	-4.1** [-5.0, -3.2]	-6.2** [-7.1, -5.3]	-
Patients (%) achieving weight loss	≥ 5 %	68.6†	82.4††	86.2††	58.4
	≥ 10 %	35.8††	52.9††	64.9††	25.3
	≥ 15 %	15.2†	27.7††	39.9††	8.7

* $p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.
† $p < 0.05$, †† $p < 0.001$ compared to semaglutide 1 mg, not adjusted for multiplicity.
# $p < 0.05$, ## $p < 0.001$ compared to baseline.

SURPASS 3: Results at Week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin degludec[a]
mITT population (n)		358	360	358	359
HbA_{1c} (%)	Baseline (mean)	8.17	8.19	8.21	8.13
	Change from baseline	-1.93##	-2.20##	-2.37##	-1.34##
	Difference from insulin degludec [95 % CI]	-0.59** [-0.73, -0.45]	-0.86** [-1.00, -0.72]	-1.04** [-1.17, -0.90]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	65.8	66.0	66.3	65.4
	Change from baseline	-21.1##	-24.0##	-26.0##	-14.6##
	Difference from insulin degludec [95 % CI]	-6.4** [-7.9, -4.9]	-9.4** [-10.9, -7.9]	-11.3** [-12.8, -9.8]	-
Patients (%) achieving HbA_{1c}	< 7 %	82.4**	89.7**	92.6**	61.3
	≤ 6.5 %	71.4††	80.3††	85.3††	44.4
	< 5.7 %	25.8††	38.6††	48.4††	5.4
FSG (mmol/L)	Baseline (mean)	9.54	9.48	9.35	9.24
	Change from baseline	-2.68##	-3.04##	-3.29##	-3.09##
	Difference from insulin degludec [95 % CI]	0.41† [0.14, 0.69]	0.05 [-0.24, 0.33]	-0.20 [-0.48, 0.08]	-
FSG (mg/dL)	Baseline (mean)	171.8	170.7	168.4	166.4
	Change from baseline	-48.2##	-54.8##	-59.2##	-55.7
	Difference from insulin degludec [95 % CI]	7.5† [2.4, 12.5]	0.8 [-4.3, 5.9]	-3.6 [-8.7, 1.5]	-
Body weight (kg)	Baseline (mean)	94.5	94.3	94.9	94.2
	Change from baseline	-7.5##	-10.7##	-12.9##	+2.3##
	Difference from insulin degludec [95 % CI]	-9.8** [-10.8, -8.8]	-13.0** [-14.0, -11.9]	-15.2** [-16.2, -14.2]	-
Patients (%) achieving weight loss	≥ 5 %	66.0††	83.7††	87.8††	6.3
	≥ 10 %	37.4††	55.7††	69.4††	2.9
	≥ 15 %	12.5††	28.3††	42.5††	0.0

[a] The mean dose of insulin degludec at week 52 was 49 units/day.

* $p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.
† $p < 0.05$, †† $p < 0.001$ compared to insulin degludec, not adjusted for multiplicity.
# $p < 0.05$, ## $p < 0.001$ compared to baseline.

SURPASS 4: Results at Week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin glargine[a]
mITT population (n)		328	326	337	998
52 weeks					
HbA_{1c} (%)	Baseline (mean)	8.52	8.60	8.52	8.51
	Change from baseline	-2.24##	-2.43##	-2.58##	-1.44##
	Difference from insulin glargine [95 % CI]	-0.80** [-0.92, -0.68]	-0.99** [-1.11, -0.87]	-1.14** [-1.26, -1.02]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	69.6	70.5	69.6	69.5
	Change from baseline	-24.5##	-26.6##	-28.2##	-15.7##
	Difference from insulin glargine [95 % CI]	-8.8** [-10.1, -7.4]	-10.9** [-12.3, -9.6]	-12.5** [-13.8, -11.2]	-
Patients (%) achieving HbA_{1c}	< 7 %	81.0**	88.2**	90.7**	50.7
	≤ 6.5 %	66.0††	76.0††	81.1††	31.7
	< 5.7 %	23.0††	32.7††	43.1††	3.4
FSG (mmol/L)	Baseline (mean)	9.57	9.75	9.67	9.37
	Change from baseline	-2.8##	-3.06##	-3.29##	-2.84##
	Difference from insulin glargine [95 % CI]	0.04 [-0.22, 0.30]	-0.21 [-0.48, 0.05]	-0.44†† [-0.71, -0.18]	-
FSG (mg/dL)	Baseline (mean)	172.3	175.7	174.2	168.7
	Change from baseline	-50.4##	-54.9##	-59.3##	-51.4##
	Difference from insulin glargine [95 % CI]	1.0 [-3.7, 5.7]	-3.6 [-8.2, 1.1]	-8.0†† [-12.6, -3.4]	-
Body weight (kg)	Baseline (mean)	90.3	90.7	90.0	90.3
	Change from baseline	-7.1##	-9.5##	-11.7##	+1.9##
	Difference from insulin glargine [95 % CI]	-9.0** [-9.8, -8.3]	-11.4** [-12.1, -10.6]	-13.5** [-14.3, -12.8]	-
Patients (%) achieving weight loss	≥ 5 %	62.9††	77.6††	85.3††	8.0
	≥ 10 %	35.9††	53.0††	65.6††	1.5
	≥ 15 %	13.8††	24.0††	36.5††	0.5

[a] The mean dose of insulin glargine at week 52 was 44 units/day.

* $p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

† $p < 0.05$, †† $p < 0.001$ compared to insulin glargine, not adjusted for multiplicity.

# $p < 0.05$, ## $p < 0.001$ compared to baseline.

SURPASS 5: Results at Week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo[a]
mITT population (n)		116	118	118	119
HbA_{1c} (%)	Baseline (mean)	8.29	8.34	8.22	8.39
	Change from baseline	-2.23$^{\#\#}$	-2.59$^{\#\#}$	-2.59$^{\#\#}$	-0.93$^{\#\#}$
	Difference from placebo [95 % CI]	-1.30** [-1.52, -1.07]	-1.66** [-1.88, -1.43]	-1.65** [-1.88, -1.43]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	67.1	67.7	66.4	68.2
	Change from baseline	-24.4$^{\#\#}$	-28.3$^{\#\#}$	-28.3$^{\#\#}$	-10.2$^{\#\#}$
	Difference from placebo [95 % CI]	-14.2** [-16.6, -11.7]	-18.1** [-20.6, -15.7]	-18.1** [-20.5, -15.6]	-
Patients (%) achieving HbA_{1c}	< 7 %	93.0**	97.4**	94.0**	33.9
	≤ 6.5 %	80.0††	94.7††	92.3††	17.0
	< 5.7 %	26.1††	47.8††	62.4††	2.5
FSG (mmol/L)	Baseline (mean)	9.00	9.04	8.91	9.13
	Change from baseline	-3.41$^{\#\#}$	-3.77$^{\#\#}$	-3.76$^{\#\#}$	-2.16$^{\#\#}$
	Difference from placebo [95 % CI]	-1.25** [-1.64, -0.86]	-1.61** [-2.00, -1.22]	-1.60** [-1.99, -1.20]	-
FSG (mg/dL)	Baseline (mean)	162.2	162.9	160.4	164.4
	Change from baseline	-61.4$^{\#\#}$	-67.9$^{\#\#}$	-67.7$^{\#\#}$	-38.9$^{\#\#}$
	Difference from placebo [95 % CI]	-22.5** [-29.5, -15.4]	-29.0** [-36.0, -22.0]	-28.8** [-35.9, -21.6]	-
Body weight (kg)	Baseline (mean)	95.5	95.4	96.2	94.1
	Change from baseline	-6.2$^{\#\#}$	-8.2$^{\#\#}$	-10.9$^{\#\#}$	+1.7$^{\#}$
	Difference from placebo [95 % CI]	-7.8** [-9.4, -6.3]	-9.9** [-11.5, -8.3]	-12.6** [-14.2, -11.0]	-
Patients (%) achieving weight loss	≥ 5 %	53.9††	64.6††	84.6††	5.9
	≥ 10 %	22.6††	46.9††	51.3††	0.9
	≥ 15 %	7.0†	26.6†	31.6††	0.0

[a] The overall median dose of insulin glargine at baseline was 34 units/day. The median dose of insulin glargine at week 40 was 38, 36, 29 and 59 units/day for tirzepatide 5 mg, 10 mg, 15 mg and placebo respectively.

* $p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

† $p < 0.05$, †† $p < 0.001$ compared to placebo, not adjusted for multiplicity.

# $p < 0.05$, ## $p < 0.001$ compared to baseline.

2.6.5.3. Clinical studies in special populations

Renal impairment

In most phase 3 studies patients with mild to moderate renal impairment were included (lower limit of eGFR 30 ml/min/1.73 m2), except for study GPGM which had no exclusion criterion based on eGFR. It is stated in section 4.2 of the SmPC that "no dose adjustment is needed based on… renal impairment including ESRD". With the Response it had been clarified that very few (n=16) patients with eGFR <30 mL/minute/1.73 m2 were treated with tirzepatide. By-participant data showed that efficacy seemed not to be lower in this subset compared to the overall study population, both with regard to HbA1c and weight. No unexpected safety issues occurred in these patients and no deterioration in renal function (eGFR) was noted. Hence, the available data do not justify a dose adjustment in patients with stage 4 or 5 CKD in section 4.2 of the SmPC. Instead, a revised wording indicating limited experience in patients with severe renal impairment and ESRD in section 4.2 of the SmPC has been added to section 4.2.

Hepatic impairment

Patients with hepatic impairment were excluded from the phase 3 studies. A clinical pharmacology study (Study GPGQ) was conducted in patients with hepatic impairment. No clinically relevant effects of hepatic impairment were observed on the PK of tirzepatide in this study. The applicant concluded that patients with hepatic impairment do not require different dosing regimens (and inserted a respective wording in section 4.2 of the SmPC). This was further justified in the Response by hinting at study results which suggest improvement of liver-related clinical markers (e. g. liver fat content). The lack of data on patients has been reflected with the addition of a sentence in section 4.2 of the SmPC.

Paediatric population

Tirzepatide has not been studied in children below the age of 18 years. A PIP for tirzepatide (EMEA-C1-002360-PIP01-18) reached a decision (P/0311/2019) on 10 Sep 2019 for the treatment of T2D in paediatrics from 10 to less than 18 years of age and a clinical study in T2DM paediatrics from 10 to less than 18 years of age is currently being initiated by the applicant.

Elderly

At baseline,

- 2082 patients (33.2%) were aged ≥65 years, with 1314 of those patients treated with tirzepatide
- 317 patients (5.1%) were aged ≥75 years, with 179 of those patients treated with tirzepatide, and
- 13 patients (0.2%)were aged ≥85 years with 6 of those patients treated with tirzepatide

Proportions of Patients Aged 65 Years and above in the Global Phase 3 Studies mITT Population

	n (%)				
	Study GPGK (SURPASS-1) (N=478)	Study GPGL (SURPASS-2) (N=1878)	Study GPGH (SURPASS-3) (N=1437)	Study GPGM (SURPASS-4) (N=1995)	Study GPGI (SURPASS-5) (N=475)
Age Group 1					
<65 years	373 (78.0)	1420 (75.6)	1058 (73.6)	1047 (52.5)	283 (59.6)
≥65 years	105 (22.0)	458 (24.4)	379 (26.4)	948 (47.5)	192 (40.4)
Age Group 2					
<75 years	468 (97.9)	1835 (97.7)	1395 (97.1)	1797 (90.1)	451 (94.9)
≥75 years	10 (2.1)	43 (2.3)	42 (2.9)	198 (9.9)	24 (5.1)
Age Group 3					
<85 years	477 (99.8)	1876 (99.9)	1437 (100.0)	1985 (99.5)	475 (100.0)
≥85 years	1 (0.2)	2 (0.1)	0 (0)	10 (0.5)	0 (0)

Abbreviations: mITT = modified intent-to-treat; n = number of patients in the specified category; N = number of patients who were randomly assigned and received at least 1 dose of study drug. Exposure of subjects ≥75 years is limited, taken into account that treatment for T2D is usually not discontinued on the basis of age. However, the concerns relate primarily to safety, not efficacy.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

In this section results are summarised across the five phase 3 studies. For brevity, only results for the treatment regimen estimand are provided within the text (efficacy estimand results are provided in some of the figures).

HbA1c change from baseline to primary endpoint

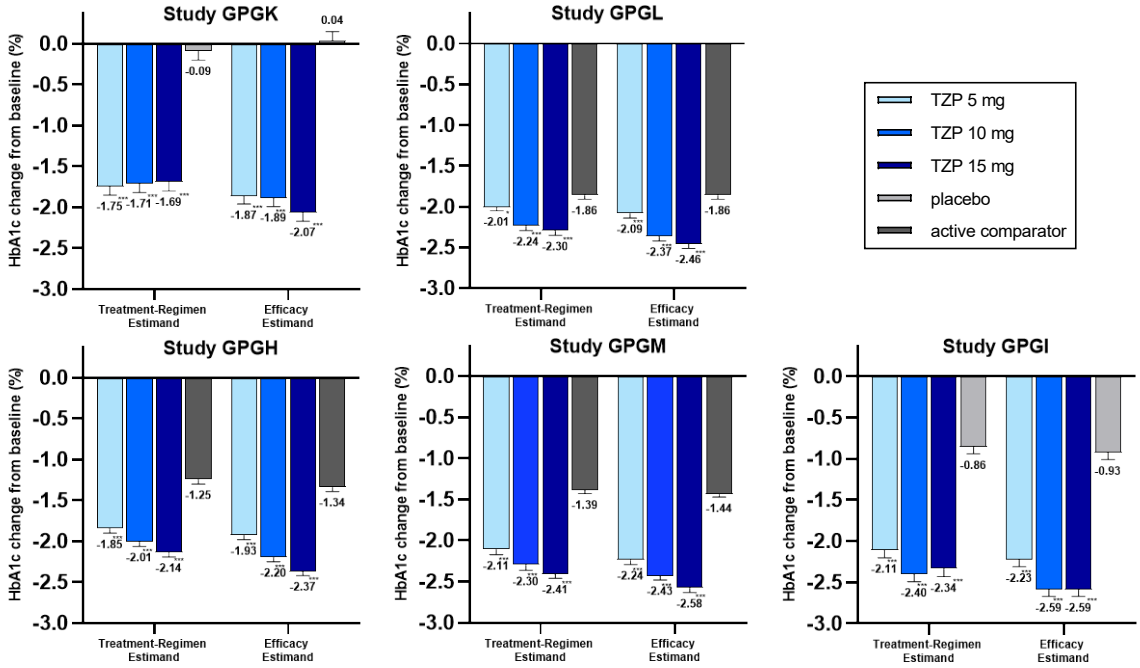
At the primary endpoint of each study, all doses of tirzepatide significantly reduced HbA1c compared to placebo and all active comparators studied. For the treatment-regimen estimand, the mean changes in HbA1c from baseline to primary endpoint ranged from

tirzepatide 5 mg: -1.75% [Study GPGK, 40 weeks] to -2.11% [Study GPGI, 40 weeks],

tirzepatide 10 mg: -1.71% [Study GPGK, 40 weeks] to -2.40% [Study GPGI, 40 weeks], and

tirzepatide 15 mg: -1.69% [Study GPGK, 40 weeks] to -2.41% [Study GPGM, 52 weeks].

Mean change from baseline in HbA1c (%) at primary endpoint for the treatment-regimen estimand (left) and efficacy estimand (right): mITT population – full analysis set (left), efficacy analysis set (right)

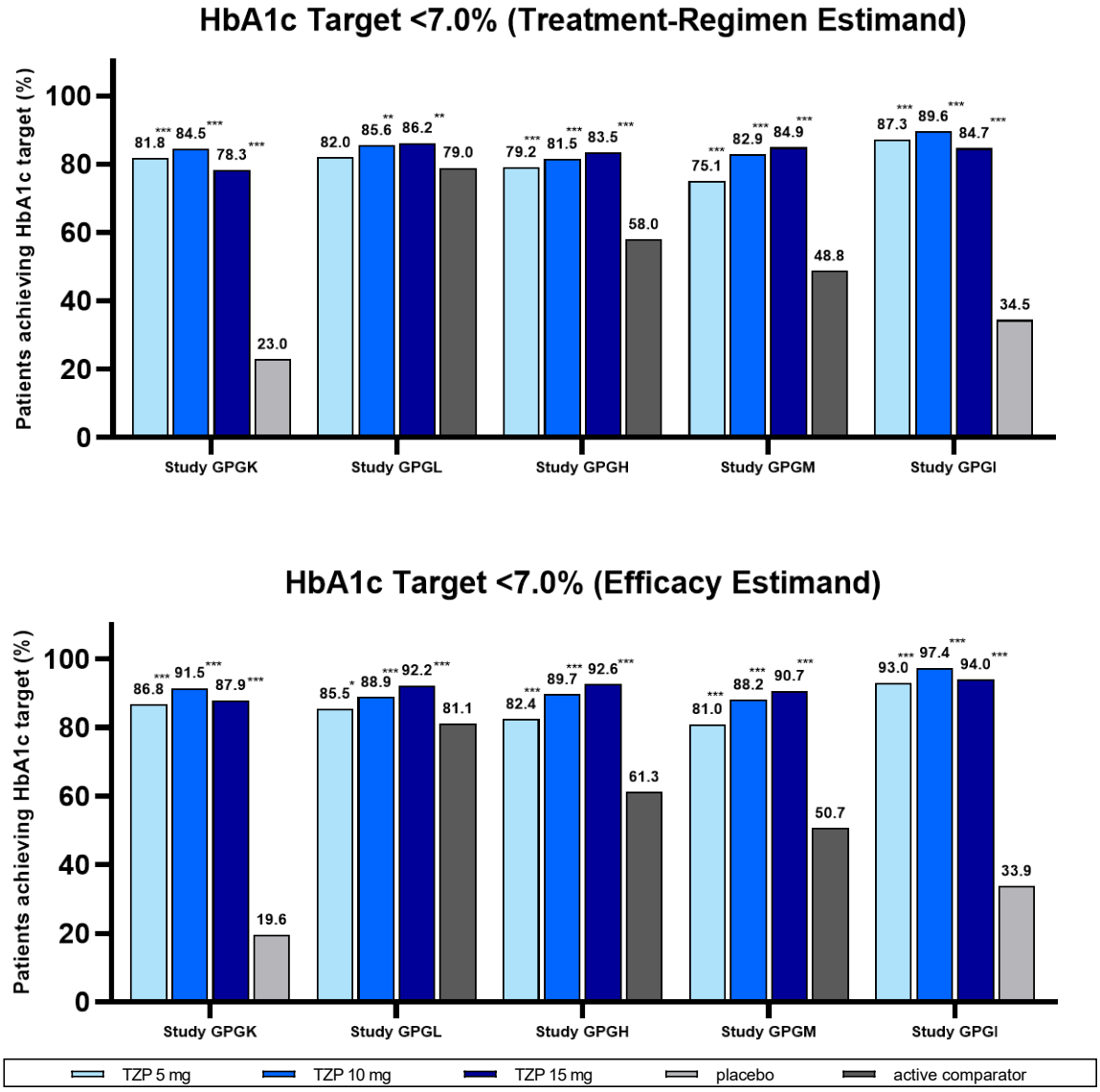


Abbreviations: ANCOVA = analysis of covariance; HbA1c = glycosylated hemoglobin A1c; LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; TZP = tirzepatide.
Note: Primary endpoint is 40 weeks for Studies GPGK, GPGL, and GPGI and 52 weeks for Studies GPGH and GPGM.
Note: Treatment-regimen estimand: ANCOVA analysis, mITT population (full analysis set). Efficacy Estimand: MMRM analysis, mITT population (efficacy analysis set). Data presented are LS means ± standard errors.
*p-Value <0.05, ***p-value <0.001 versus placebo (Studies GPGK and GPGI) or active comparator (semaglutide 1 mg for Study GPGL, insulin degludec for Study GPGH, and insulin glargine for Study GPGM).

Proportion of patients achieving HbA1c targets

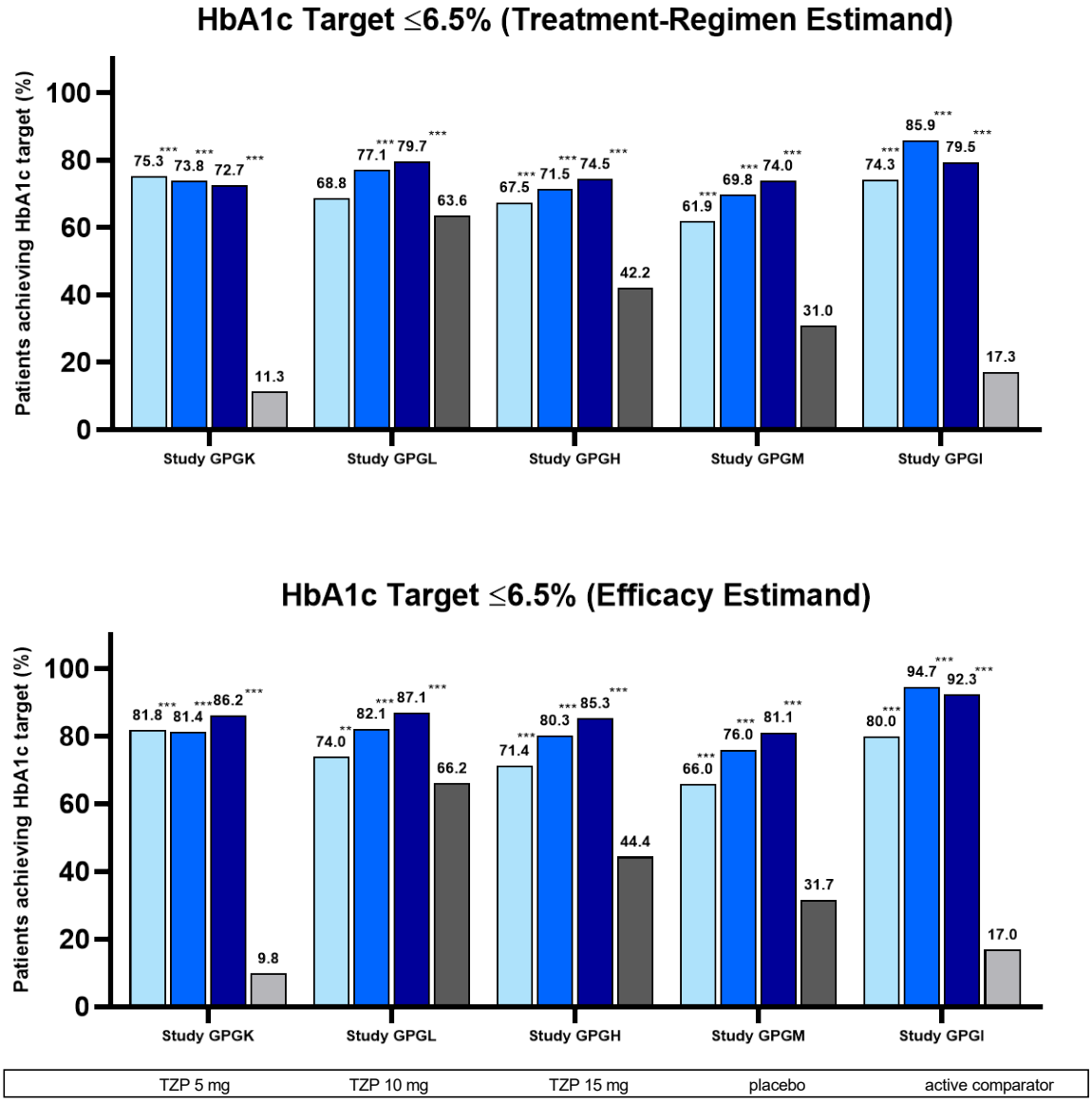
At the primary endpoint of Studies GPGK, GPGL, GPGH, GPGM, and GPGI all three doses of tirzepatide had significantly greater proportions of patients achieving HbA1c targets of <7.0%, ≤6.5%, and <5.7% compared to placebo and all active comparators studied.

Overview of patients achieving HbA1c target value of <7.0% for the treatment-regimen estimand (top) and efficacy estimand (bottom): mITT population – full analysis set (top) and efficacy analysis set (bottom)



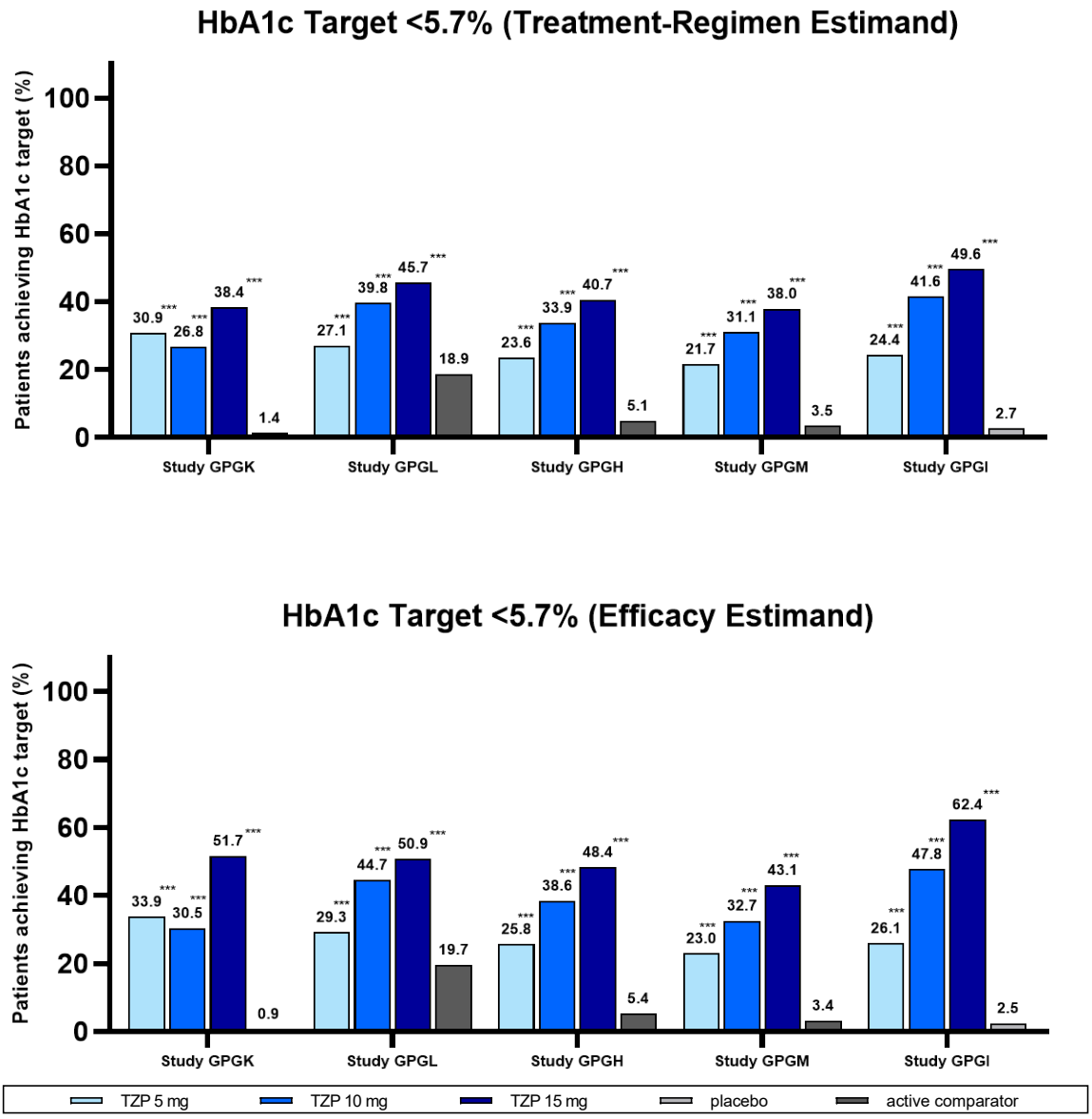
Abbreviations: HbA1c = glycosylated hemoglobin A1c; mITT = modified intent-to-treat; TZP = tirzepatide.
*p-Value <0.05, **p-value <0.01, ***p-value <0.001 versus placebo (Studies GPGK and GPGI) or active comparator (semaglutide 1 mg for Study GPGL, insulin degludec for Study GPGH, and insulin glargine for Study GPGM).

Overview of patients achieving HbA1c target value of ≤6.5% (<48 mmol/mol) for the treatment-regimen estimand (top) and efficacy estimand (bottom): mITT population – full analysis set (top) and efficacy analysis set (bottom)



Abbreviations: HbA1c = glycosylated hemoglobin A1c; TZP = tirzepatide.
*p-Value <0.05, **p-value <0.01, ***p-value <0.001 versus placebo (Studies GPGK and GPGI) or active comparator (semaglutide 1 mg for Study GPGL, insulin degludec for Study GPGH, and insulin glargine for Study GPGM).

Overview of patients achieving HbA1c target value of <5.7% (<39 mmol/mol)for the treatment-regimen estimand (top) and efficacy estimand (bottom): mITT population – full analysis set (top) and efficacy analysis set (bottom)



Abbreviations: HbA1c = glycosylated hemoglobin A1c; mITT = modified intent-to-treat; TZP = tirzepatide.
***p-Value <0.001 versus placebo (GPGK and GPGI) or active comparator (semaglutide 1 mg for GPGL, insulin degludec for GPGH, and insulin glargine for GPGM).

Patients achieving HbA1c <5.7% (<39 mmol/mol) corresponding to normoglycemia

Between 21.7% and 49.6% of patients taking tirzepatide achieved HbA1c <5.7%. A post hoc analysis investigated the proportion of patients achieving HbA1c <5.7% at primary endpoint without clinically significant (<54 mg/dL) or severe hypoglycaemia, for each of the five phase 3 studies

Summary of Patients Achieving HbA1c <5.7% at Primary Endpoint without Clinically Significant Documented Symptomatic (<54 mg/dL) or Severe Hypoglycaemia; Modified Intent-to-Treat Population – Safety Analysis Set

Study		TZP 5 mg	TZP 10 mg	TZP 15 mg
Study GPGK	N	114	112	104
	Achieved HbA1c <5.7%, n (%)	37 (32.46)	32 (28.57)	45 (43.27)
	Achieved HbA1c <5.7% without clinically significant (<54 mg/dL) or severe hypoglycaemia, n (%)	37 (32.46)	32 (28.57)	45 (43.27)
Study GPGL	N	451	445	447
	Achieved HbA1c <5.7%, n (%)	127 (28.16)	183 (41.12)	212 (47.43)
	Achieved HbA1c <5.7% without clinically significant (<54 mg/dL) or severe hypoglycaemia, n (%)	127 (28.16)	182 (40.90)	210 (46.98)
Study GPGH	N	335	324	340
	Achieved HbA1c <5.7%, n (%)	83 (24.78)	119 (36.73)	145 (42.65)
	Achieved HbA1c <5.7% without clinically significant (<54 mg/dL) or severe hypoglycaemia, n (%)	83 (24.78)	119 (36.73)	143 (42.06)
Study GPGM	N	300	308	323
	Achieved HbA1c <5.7%, n (%)	69 (23.00)	99 (32.14)	127 (39.32)
	Achieved HbA1c <5.7% without clinically significant (<54 mg/dL) or severe hypoglycaemia, n (%)	64 (21.33)	92 (29.87)	120 (37.15)
Study GPGI	N	109	115	110
	Achieved HbA1c <5.7%, n (%)	28 (25.69)	49 (42.61)	58 (52.73)
	Achieved HbA1c <5.7% without clinically significant (<54 mg/dL) or severe hypoglycaemia, n (%)	23 (21.10)	41 (35.65)	52 (47.27)

Abbreviations: HbA1c = glycosylated hemoglobin A1c; n = number of patients in the category; N = number of patients in the safety analysis set; TZP = tirzepatide.

Change from baseline in FSG

In Studies GPGK and GPGI, all three doses of tirzepatide reduced FSG significantly more than placebo. Similarly, in Study GPGL, all three doses of tirzepatide reduced FSG significantly more than semaglutide. In Study GPGH, insulin degludec was titrated to an FBG <90 mg/dL. In Study GPGH, there were no significant differences observed in reductions in FSG between insulin degludec and tirzepatide 10- and 15 mg groups, while there was a significantly larger reduction in insulin degludec compared with tirzepatide 5 mg. In Study GPGM, insulin glargine was titrated to an FBG <100 mg/dL. In Study GPGM, tirzepatide 5 and 10 mg showed similar reductions in FSG compared with insulin glargine, while tirzepatide 15 mg had a significantly larger reduction compared with insulin glargine.

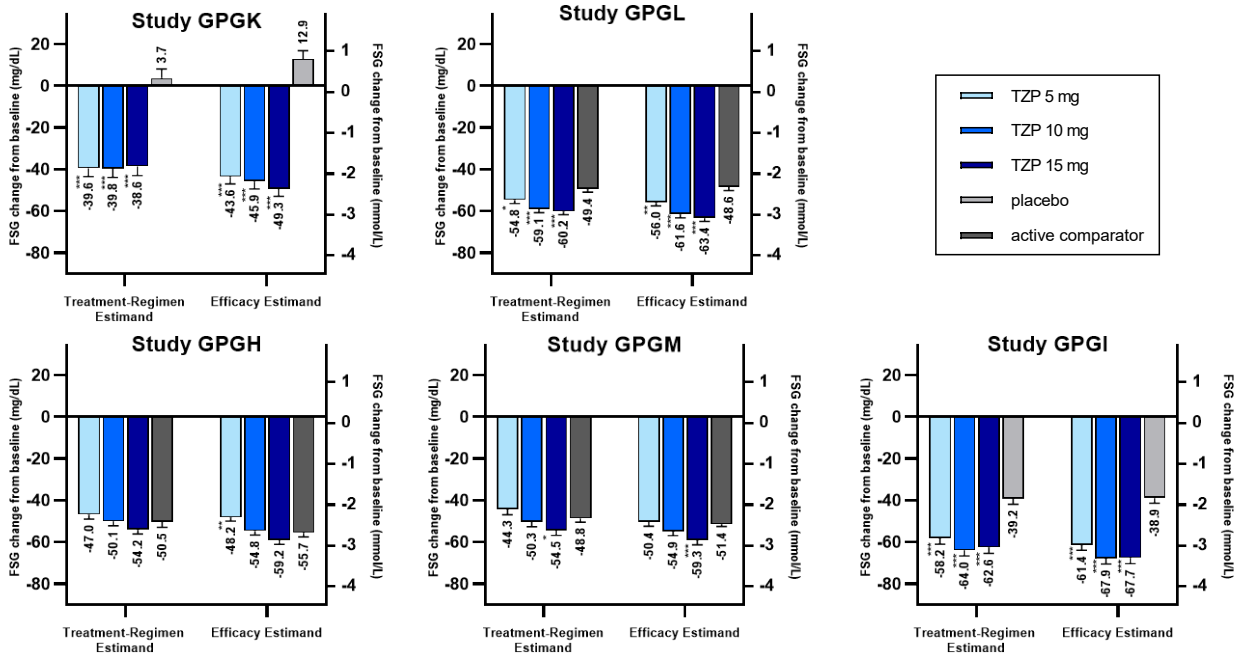
For the treatment-regimen estimand, the mean changes in FSG from baseline to primary endpoint ranged from

-tirzepatide 5 mg: -39.6 mg/dL (-2.2 mmol/L) [Study GPGK, 40 weeks] to -58.2 mg/dL (-3.2 mmol/L) [Study GPGI, 52 weeks],

-tirzepatide 10 mg: -39.8 mg/dL (-2.2 mmol/L) [Study GPGK, 40 weeks] to -64.0 mg/dL (-3.6 mmol/L) [Study GPGI, 40 weeks], and

-tirzepatide 15 mg: -38.6 mg/dL (-2.1 mmol/L) [Study GPGK, 40 weeks] to -62.6 mg/dL (-3.5 mmol/L) [Study GPGI, 40 weeks].

Mean change from baseline in FSG (mg/dL and mmol/L) at primary endpoint for the treatment-regimen estimand (left) and efficacy estimand (right): mITT population – full analysis set (left), efficacy analysis set (right).



Abbreviations: FSG = fasting serum glucose; LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; TZP = tirzepatide.

Note: The numbers provided in the graph are in mg/dL.

Note: Primary endpoint is 40 weeks for Studies GPGK, GPGL, and GPGI and 52 weeks for Studies GPGH and GPGM.

Note: Treatment-regimen estimand: ANCOVA analysis, mITT population (full analysis set). Efficacy Estimand: MMRM analysis, mITT population (efficacy analysis set). Data presented are LS means ± standard errors.

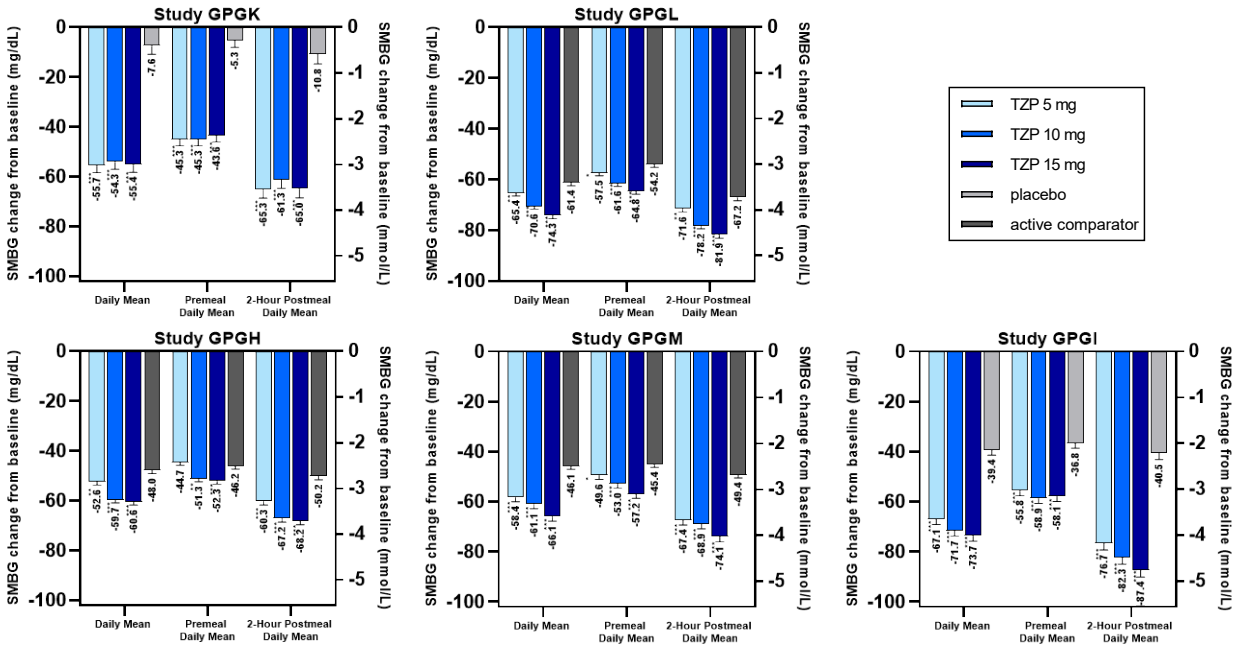
* p-Value <0.05, **p-value <0.01, ***p-value <0.001 versus placebo (Studies GPGK and GPGI) or active comparator (semaglutide 1 mg for Study GPGL, insulin degludec for Study GPGH, and insulin glargine for Study GPGM).

7-point SMBG

In all phase 3 studies, treatment with all three doses of tirzepatide demonstrated significant reductions from baseline in SMBG overall daily mean, premeal daily mean, and 2-hour postmeal daily mean at the primary endpoint. At the primary endpoint for all global Phase 3 studies, all daily mean SMBG values were <140 mg/dL (7.8 mmol/L) across all 3 tirzepatide groups.

Additional details regarding 7-point SMBG, including change in SMBG levels from baseline at 52 weeks for all 7 time points and daily 2-hour postmeal SMBG excursions, are not described in this Overview.

Mean change from baseline in 7-point SMBG (mg/dL and mmol/L) at primary endpoint, daily means for the efficacy estimand: mITT population – efficacy analysis set.



Abbreviations: LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; SMBG = self-monitored blood glucose; TZP = tirzepatide.

Note: The numbers provided in the graph are in mg/dL.

Note: Primary endpoint is 40 weeks for Studies GPGK, GPGL, and GPGI and 52 weeks for Studies GPGH and GPGM.

Note: Efficacy Estimand: MMRM analysis, mITT population (efficacy analysis set). Data presented are LS means ± standard errors.

*p-Value <0.05, **p-value <0.01, ***p-value <0.001 versus placebo (Studies GPGK and GPGI) or active comparator (semaglutide 1 mg for Study GPGL, insulin degludec for Study GPGH, and insulin glargine for Study GPGM).

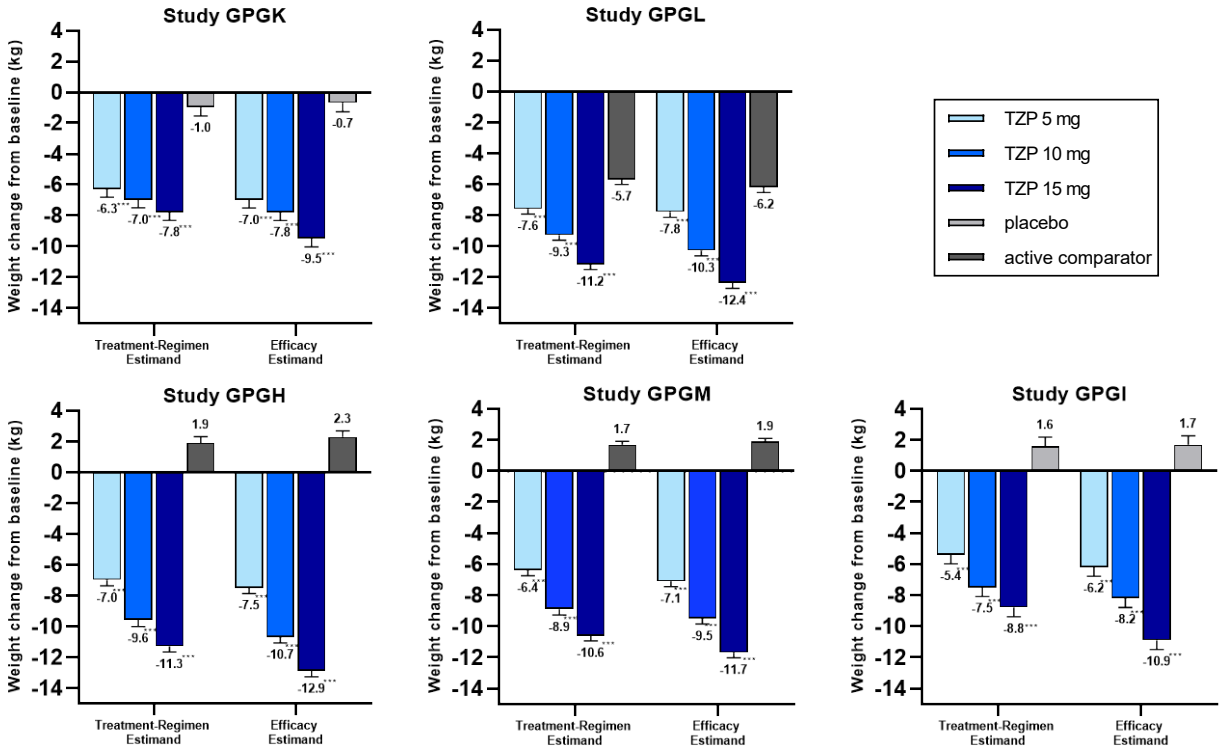
Body Weight

At the primary endpoint of each phase 3 study, tirzepatide significantly reduced body weight compared to placebo and all active comparators studied. For the treatment-regimen estimand, the mean changes in body weight from baseline to primary endpoint ranged from

-tirzepatide 5 mg: -5.4 kg (Study GPGI, 40 weeks) to -7.6 kg (Study GPGL, 40 weeks)
-tirzepatide 10 mg: -7.0 kg (Study GPGK, 40 weeks) to -9.6 kg (Study GPGH, 52 weeks), and
-tirzepatide 15 mg: -7.8 kg (Study GPGK, 40 weeks) to -11.3 kg (Study GPGH, 52 weeks).

Steady decreases in weight were seen at the first time point assessed, continued through the end of the study, and *did not appear to plateau by the end of the treatment period*, for both the 40- and 52-week studies.

Mean change from baseline in body weight (kg) at primary endpoint for the treatment-regimen estimand (left) and efficacy estimand (right): mITT population – full analysis set (left), efficacy analysis set (right)



Abbreviations: ANCOVA = analysis of covariance; LS = least-squares; mITT = modified intent-to-treat; MMRM = mixed model repeated measures; TZP = tirzepatide.

Note: Primary endpoint is 40 weeks for Studies GPGK, GPGL, and GPGI and 52 weeks for Studies GPGH and GPGM.

Note: Efficacy Estimand: MMRM analysis, mITT population (efficacy analysis set). Treatment-regimen estimand: ANCOVA analysis, mITT population (full analysis set). Data presented are LS means ± standard errors.

***p-Value <0.001 versus placebo (Studies GPGK and GPGI) or active comparator (semaglutide 1 mg for Study GPGL, insulin degludec for Study GPGH, and insulin glargine for Study GPGM).

Lipid Parameters

For brevity, results for VLDL-C and total cholesterol are not provided in this section; these are given in the description of the individual studies.

Triglycerides: in all 5 global phase 3 studies, at the primary endpoint, all doses of tirzepatide demonstrated significantly larger decreases in triglycerides compared to placebo (Studies GPGK and GPGI), semaglutide 1 mg (Study GPGL), and insulin glargine (Study GPGM). Tirzepatide 10 and 15 mg demonstrated significantly larger decreases in triglycerides compared to insulin degludec (Study GPGI).

For the efficacy estimand, the mean percent changes in triglycerides from baseline to primary endpoint ranged from

-tirzepatide 5 mg: -15.2% (-22.0 mg/dL; -0.2 mmol/L) [Study GPGI, 40 weeks] to -19.0% (-31.4 mg/dL; -0.35 mmol/L) [Study GPGL, 40 weeks]
-tirzepatide 10 mg: -18.2% (-27.6 mg/dL; -0.31 mmol/L) [Study GPGK, 40 weeks] to
-26.7% (-43.6 mg/dL; -0.49 mmol/L) [Study GPGH, 52 weeks], and

-tirzepatide 15 mg: -21.0% (-31.8 mg/dL; -0.36 mmol/L) [Study GPGK, 40 weeks] to
-25.2% (-41.2 mg/dL; -0.46 mmol/L) [Study GPGH, 52 weeks].

Total cholesterol: greater reductions from baseline in total cholesterol levels were observed for all 3 doses of tirzepatide compared with placebo and insulin glargine. The magnitudes of the reductions were not statistically different when the tirzepatide doses were compared with semaglutide or insulin degludec. The percent changes from baseline at the primary endpoint were:

-Study GPGK: tirzepatide, -5.5% to -8.4%; placebo, -0.8%
-Study GPGL: tirzepatide, -5.5% to -6.3%; semaglutide, -4.8%
-Study GPGH: tirzepatide, -4.3% to -5.8%; insulin degludec, -2.9%
-Study GPGM: tirzepatide, -5.0% to -5.6%; insulin glargine, 0%
-Study GPGI: tirzepatide, -8.8% to -12.9%; placebo, -0.4%

LDL-C: greater reductions from baseline in LDL-C levels were observed for tirzepatide 15 mg compared with placebo in Study GPGK, whereas all 3 doses of tirzepatide significantly reduced LDL-C compared with placebo in Study GPGI. In Study GPGM, all 3 doses of tirzepatide significantly reduced LDL-C compared with insulin glargine. The magnitudes of the reductions were not statistically significant when the tirzepatide doses were compared with semaglutide or insulin degludec. The percent changes from baseline at the primary endpoint were:

-Study GPGK: tirzepatide, -6.7% to -12.4%; placebo, -1.6%
-Study GPGL: tirzepatide, -5.2% to -7.7%; semaglutide, -6.4%
-Study GPGH: tirzepatide, -5.7% to -6.6%; insulin degludec, -2.7%
-Study GPGM: tirzepatide, -6.7% to -8.4%; insulin glargine, 1.3%
-Study GPGI: tirzepatide, -8.9% to -15.5%; placebo, 2.8%

HDL-C: greater increases from baseline in HDL-C levels were observed for all 3 doses of tirzepatide compared with placebo (Study GPGK), semaglutide, insulin degludec, and insulin glargine. In Study GPGI, no statistically significant differences were observed between the tirzepatide and placebo groups in this population of patients on a background of insulin glargine. The percent changes from baseline at the primary endpoint were:

-Study GPGK: tirzepatide, 3.2% to 7.5%; placebo, -3.8%
-Study GPGL: tirzepatide, 6.8% to 7.9%; semaglutide, 4.4%
-Study GPGH: tirzepatide, 5.5% to 10.2%; insulin degludec, 1.0%
-Study GPGM: tirzepatide, 6.8% to 10.9%; insulin glargine, 2.9%
-Study GPGI: tirzepatide, 0.9% to 2.1%; placebo, 1.7%.

Patient-Reported Outcomes

Please see description of individual studies.

2.6.5.6. Supportive study(ies)

Two phase three studies in Japanese patients (GPGO and GPGP) were conducted to support the license application in Japan and other Asian countries.

Overview of Japanese Phase 3 Studies

Study	Design	Rationale for Exclusion	Link to CSR
Study I8F-JE-GPGP (GPGP)	Open-label study with no comparator designed to assess the safety and tolerability of tirzepatide add-on to different classes of anti-hyperglycaemic medications in Japanese patients	Designed primarily as a safety study	GPGP CSR
Study I8F-JE-GPGO (GPGO)	Monotherapy study in a Japanese population comparing tirzepatide with dulaglutide.	Tirzepatide monotherapy was evaluated in the global Phase 3 Study GPGK, which included Japanese patients. Comparison of tirzepatide to dulaglutide was assessed in Phase 2 Study GPGB	GPGO CSR

The two Japanese phase 3 studies (GPGO and GPGP) were 52-week, multicenter studies to meet local registration requirements. Study GPGO was a double-blind study designed to assess the safety and efficacy of tirzepatide compared with dulaglutide 0.75 mg in patients with T2DM who discontinued OAM monotherapy or were OAM-naïve. Dulaglutide 0.75 mg is the only dulaglutide dose currently registered in Japan and was the active comparator chosen since it is marketed in Japan as monotherapy in patients with T2DM. Study GPGP was an open-label study without comparator, designed to assess safety and efficacy of tirzepatide in combination with monotherapy of OAMs. These two regional studies used the tirzepatide 5, 10, and 15 mg maintenance doses and the same tirzepatide dose-escalation scheme as was used in the phase 3 studies.

Methodology and key results of study GPGO are summarised in the following table (for brevity, results of the uncontrolled safety and tolerability study GPGP are not provided; efficacy endpoints in this study showed no unexpected findings).

Objectives, endpoints, Statistical Methods, and Results:
This table lists the primary and secondary (controlled for Type 1 error) objectives, endpoints, statistical methods, and results described in this report.

<table>
<tr><th>Objectives</th><th>Endpoints</th><th>Statistical Methods</th><th>Results</th></tr>
<tr><td colspan="4">Primary</td></tr>
<tr><td>To demonstrate that once-weekly tirzepatide 5 mg, and/or 10 mg, and/or 15 mg were superior to dulaglutide 0.75 mg in HbA1c change from baseline to 52 weeks in patients with T2DM who had discontinued OAM monotherapy or were OAM-naive</td><td>Mean change in HbA1c from baseline at Week 52</td><td>Efficacy estimand: MMRM Treatment-regimen estimand: ANCOVA with multiple imputation for missing HbA1c</td><td>Tirzepatide 5 mg, 10 mg, and 15 mg were superior to dulaglutide 0.75 mg on mean change from baseline in HbA1c at 52 weeks using both estimands (***p<0.001).
<table>
<tr><th>Parameter
HbA1c (%)</th><th>TZP 5 mg
(N=159)</th><th>TZP 10 mg
(N=158)</th><th>TZP
15 mg
(N=160)</th><th>Dulaglutide
0.75 mg
(N=159)</th></tr>
<tr><td colspan="5">Efficacy Estimand—Efficacy Analysis Set</td></tr>
<tr><td>Baseline</td><td>8.17</td><td>8.20</td><td>8.20</td><td>8.15</td></tr>
<tr><td>Change from baseline at 52 weeks</td><td>-2.37†††</td><td>-2.55†††</td><td>-2.82†††</td><td>-1.29†††</td></tr>
<tr><td>Change difference from dulaglutide (95% CI) at 52 weeks</td><td>-1.09***
(-1.27, -0.90)</td><td>-1.27***
(-1.45, -1.08)</td><td>-1.53***
(-1.71, -1.35)</td><td>N/A</td></tr>
<tr><td colspan="5">Treatment-Regimen Estimand—Full Analysis Set</td></tr>
<tr><td>Baseline</td><td>8.18</td><td>8.19</td><td>8.19</td><td>8.15</td></tr>
<tr><td>Change from baseline at 52 weeks</td><td>-2.24†††</td><td>-2.36†††</td><td>-2.57†††</td><td>-1.27†††</td></tr>
<tr><td>Change difference from dulaglutide (95% CI) at 52 weeks</td><td>-0.97***
(-1.16, -0.78)</td><td>-1.10***
(-1.29, -0.90)</td><td>-1.30***
(-1.49, -1.11)</td><td>N/A</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Objectives</th><th>Endpoints</th><th>Statistical Methods</th><th>Results</th></tr>
<tr><td colspan="4">Secondary Efficacy Endpoints (Controlled for Type 1 error)</td></tr>
<tr><td>To compare the efficacy of once-weekly tirzepatide versus dulaglutide 0.75 mg at 52 weeks</td><td>Mean change in body weight</td><td>Efficacy estimand: MMRM Treatment-regimen estimand: ANCOVA with multiple imputation</td><td>Tirzepatide 5 mg, 10 mg, and 15 mg were superior to dulaglutide 0.75 mg on mean change in body weight from baseline to 52 weeks using both estimands (***p<0.001).
<table>
<tr><th rowspan="2">Parameter
Weight</th><th colspan="4">kg</th></tr>
<tr><th>TZP 5 mg
(N=159)</th><th>TZP 10 mg
(N=158)</th><th>TZP 15 mg
(N=160)</th><th>Dulaglutide
0.75 mg
(N=159)</th></tr>
<tr><td colspan="5">Efficacy Estimand—Efficacy Analysis Set</td></tr>
<tr><td>Baseline</td><td>78.6</td><td>79.1</td><td>78.9</td><td>76.5</td></tr>
<tr><td>Change from baseline at 52 weeks</td><td>-5.8†††</td><td>-8.5†††</td><td>-10.7†††</td><td>-0.5</td></tr>
<tr><td>Change difference from dulaglutide (95% CI) at 52 weeks</td><td>-5.2***
(-6.4, -4.1)</td><td>-7.9***
(-9.1, -6.8)</td><td>-10.1***
(-11.3, -9.0)</td><td>N/A</td></tr>
<tr><td colspan="5">Treatment-Regimen Estimand—Full Analysis Set</td></tr>
<tr><td>Baseline</td><td>78.5</td><td>78.9</td><td>78.9</td><td>76.5</td></tr>
<tr><td>Change from baseline at 52 weeks</td><td>-5.4†††</td><td>-7.2†††</td><td>-9.4†††</td><td>-0.4</td></tr>
<tr><td>Change difference from dulaglutide (95% CI) at 52 weeks</td><td>-4.9***
(-6.1, -3.8)</td><td>-6.8***
(-8.0, -5.6)</td><td>-8.9***
(-10.1, -7.8)</td><td>N/A</td></tr>
</table></td></tr>
</table>

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; HbA1c = glycosylated hemoglobin A1c; MMRM = mixed-model repeated measures; N/A = not applicable; OAM = oral antihyperglycemic medication; T2DM = type 2 diabetes mellitus; TZP = tirzepatide.

Note: Data presented are least-squares means.

††† p<0.001 versus baseline.

*** p<0.001 versus dulaglutide 0.75 mg.

Human Factors Engineering Study (**RPT-392683 Tirzepatide Autoinjector Human Factors Engineering Report; 19-Aug-2021**)

The results of the human factors validation testing indicated that the tirzepatide autoinjector is safe and effective for use by the intended user population in the intended use environments.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of tirzepatide for the treatment of adults with T2DM is supported by two phase 2 studies (GPGB and GPGF), five global phase 3 studies (GPGK, GPGL, GPGH, GPGM, and GPGI) and two phase 3 studies conducted in Japan (GPGO and GPGP); the latter are considered as supportive in the EU context.

The two phase 2 studies (GPGB and GPGF) were double-blind studies investigating efficacy and safety of tirzepatide at doses between 1 and 15 mg to enable dose selection and optimization of the dose-escalation scheme. Patients had T2DM and inadequate glycaemic control on diet and exercise with or without a stable dose of metformin. Study GPGB was a 26-week study that explored the dose response relationship of tirzepatide (1, 5, 10, and 15 mg) compared to placebo and dulaglutide 1.5 mg (meanwhile higher dulaglutide doses of 3 and 4.5 mg are licensed; results have to be viewed in the light of the rather low dose of dulaglutide). Study GPGF was a 12-week study which evaluated three different dose-escalation schemes; the schemes differed with regard to starting dose, duration of escalation steps and magnitude of dose increase compared with placebo. Study GPGF provided key data for determining which dose-escalation scheme allowed patients to reach the highest tirzepatide dose with the lowest incidence of GI AEs.

The five phase 3 studies were designed to assess the efficacy and safety of tirzepatide 5, 10, and 15 mg once-weekly. Within Study GPGH, two substudies were performed, to investigate the 24-hour glucose profile captured with continuous glucose monitoring (CGM, n=234) and to characterize potential changes in hepatic fat content through magnetic resonance imaging. The clinical studies utilized double-blinded (GPGK, GPGI) or open-label designs; open-label performance was unavoidable in studies GPGL, GPGH, GPGM due to differences in devices and application schemes for tirzepatide and its active comparators semaglutide, insulin degludec and insulin glargine.

Doses and dose-escalation scheme and possibility to de-escalate

Treatment durations of 40 weeks (Studies GPGK, GPGL, and GPGI), 52 weeks (Study GPGH), or 52 to 104 weeks (Study GPGM) allowed for tirzepatide dose initiation at a dose of 2.5 mg and escalation in steps of 2.5 mg every 4 weeks, followed by at least 16 weeks at steady state for all treatment groups, including tirzepatide 15 mg, which had the longest dose-escalation period. The duration of treatment at steady state is considered appropriate to assess the glycaemic efficacy of tirzepatide. In the open-label studies GPGH amd GPGM patients had the possibility to de-escalate the dose during the first 24 weeks; in the other studies no dose-de-escalation was allowed.

Background therapies and active comparators

Background therapies ranged from diet and exercise alone (study GPGK), metformin (GPGL), 1 to 3 OAMs (GPGH, GPGM) and basal insulin with or without metformin (GPGI).

The active comparators chosen for studies GPGL (semaglutide at a dose of 1 mg) and GPGH (insulin degludec) and GPGM (insulin glargine) are acceptable. Semaglutide had shown superior improvement in glycaemic control relative to other GLP-1 agonists (e.g. Ahmann et al, 2018; comparison with exenatide). Semaglutide 1 mg is the highest currently marketed dose; 2 mg semaglutide for treatment of T2DM is currently subject to a line extension procedure. However, the comparably low 1 mg dose may have contributed to differences in glycaemic potency (especially no on par comparison between semaglutide 1 mg and tirzepatide 15 mg).

Endpoints

The primary endpoint for assessment of efficacy in the phase 2 and phase 3 studies was change from baseline in HbA1c. Change from baseline in body weight was a key secondary endpoint (controlled for type 1 error) in all studies. Additional clinical endpoints included, but were not limited to, proportions of patients

reaching glycaemic and body weight loss targets, change from baseline in FSG, 7-point SMBG, waist circumference, change from baseline in lipid profile, and patient-reported outcomes. The GPGH substudies provided data on continuous glucose monitoring (CGM), change from baseline in liver fat content, volume of visceral adipose tissue, and volume of abdominal subcutaneous adipose tissue; the CGM substudy aimed to evaluate the 24-hour glucose profile captured with CGM for tirzepatide versus insulin degludec; both were compared as regards the percentage of time in the hyper- and hypoglycaemic range. Further, glucose variability was assessed. In general, CGM results are considered valuable to contextualise results on patient reported outcomes.

These endpoints are in line with recommendations in the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev.2; 9 January 2018). An additional stricter responder criterion (proportion of patients who reached HbA1c<5.7%=normoglycemia) than those given in the Guideline was used supplemented by an analysis on how many patients achieved this target without hypoglycaemia, which is endorsed.

Population studied

A total of 6263 patients were randomly assigned and treated with at least on dose of study drug. The patients included in the studies were representative of the T2DM target population. Inadequate glycaemic control was defined in most of the studies as an HbA1c level of ≥7.0 and ≤10.5%, which is appropriate; in the placebo-controlled monotherapie study GPGK a lower upper limit was chosen (≤9.5%).

The majority of the patients in the phase 3 studies had BMI in the obesity or overweight range. The lower limit of the BMI inclusion criterium was BMI ≥25 kg/m2 at screening in studies GPGL, GPGH and GPGM. Studies GPGK and GPGI with a lower limit of BMI ≥23 kg/m2 included a proportion of normal weight patients.

In most phase 3 studies patients with mild to moderate renal impairment were included (lower limit of eGFR 30 ml/min/1.73 m2), except for study GPGM which had no exclusion criterion based on eGFR. It is stated in section 4.2 of the SmPC that "no dose adjustment is needed based on… renal impairment including ESRD". With the Response it had been clarified that very few (n=16) patients with eGFR <30 mL/minute/1.73 m2 were treated with tirzepatide. By-participant data showed that efficacy seemed not to be lower in this subset compared to the overall study population, both with regard to HbA1c and weight. No unexpected safety issues occurred in these patients and no deterioration in renal function (eGFR) was noted. Hence, the available data do not justify a dose adjustment in patients with stage 4 or 5 CKD in section 4.2 of the SmPC. Instead, a revised wording indicating limited experience in patients with severe renal impairment and ESRD in section 4.2 of the SmPC has been added to section 4.2.

Patients with hepatic impairment were excluded from the phase 3 studies. A clinical pharmacology study (Study GPGQ) was conducted in patients with hepatic impairment. No clinically relevant effects of hepatic impairment were observed on the PK of tirzepatide in this study. The applicant concluded that patients with hepatic impairment do not require different dosing regimens (and inserted a respective wording in section 4.2 of the SmPC). This was further justified in the Response by hinting at study results which suggest improvement of liver-related clinical markers (e. g. liver fat content). The lack of data on patients has been reflected with the addition of a sentence in section 4.2 of the SmPC.

Study GPGM also included patients with increased cardiovascular risk, defined by coronary heart disease, peripheral arterial disease, cerebrovascular disease, age 50 years or older with a history of CKD and eGFR <60ml/min/1.73 m2, or 50 years or older with congestive heart failure. Therefore, this study contributed data to support cardiovascular safety (see safety part of this AR).

Study protocols had no upper age limit; 317 patients who were ≥75 years, and 13 subjects who were ≥85 years of age were included. Hence, more than 100 geriatric patients were included in the phase 3 program and, as such, the requirement as outlined in EMA/ CHMP/ ICH/604661/2009 (ICH topic E7 Studies in Support of special populations: Geriatrics Q and A) was met.

Overall, the patients included in the phase 3 studies were representative of the T2DM target population.

Statistical methods

Two estimands were specified for evaluating primary and key secondary objectives (subjected to type I error control). The "treatment-regimen" estimand was based on a treatment policy strategy targeting the effect regardless of premature treatment discontinuation or initiation of rescue antihyperglycaemic medication. Analyses aligned to the "treatment-regimen" estimand were conducted using all available data obtained up to the primary endpoint visit, regardless of adherence to study drug or initiation of rescue antihyperglycaemic medication. The "efficacy" estimand was based on a hypothetical strategy targeting the effect if all patients had not prematurely discontinued study treatment and rescue antihyperglycaemic medication had not been introduced. Analyses aligned to the "efficacy" estimand were conducted using data obtained up to the primary endpoint visit excluding data after initiation of rescue antihyperglycaemic medication or permanent discontinuation of study drug (last dose date + 7 days).

As per the EMA Draft Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2), the actual adherence to study treatment (e.g. treatment discontinuation due to intolerance, lack of efficacy) should be reflected in the target of estimation and the evaluation of the effect of test product should not be confounded by rescue medication. Therefore, the **estimand of primary interest for the EU** would be the one targeting the effect regardless of adherence to study treatment (treatment policy strategy) and had rescue medication not been introduced (hypothetical strategy). For this estimand, data obtained after treatment discontinuation are of interest (patients are not expected to benefit once treatment is discontinued), but data obtained after initiation of rescue medication are not (they reflect the effect of the rescue medication itself). An analysis had been requested for this estimand (using a treatment policy strategy for discontinuations and a hypothetical strategy for rescue medication). As expected, given that the frequency of initiation of rescue medication in all treatment groups in all studies (except for the placebo group in Study GPGK) was low, results for the estimands as specified for evaluating primary and key secondary objectives turned out to be much in line with the newly submitted results obtained for the estimand per guideline.

Conduct of the studies

Studies were generally well conducted. Patient retention was high (between 89.5% and 94.9% completed the study), which is considered reassuring. Of note, patient retention seemed not to depend of the possibility to de-escalate the dose. In addition, the frequency of add-on rescue antihyperglycaemic therapies to tirzepatide or control was low (tirzepatide 0% to 1.7%; comparator 0.5% to 4.2%). The COVID-19 pandemic did not impact evaluation of the efficacy or safety of tirzepatide in any of the phase 3 studies.

Efficacy data and additional analyses

Results of the phase 2 studies

The results of study GPGB showed dose-depended effects on glycaemic control and body weight reduction over the dose range of 1 mg to 15 mg tirzepatide. Picking the 5mg, 10mg and 15mg tirzepatide dose strengths for further evaluation in the phase 3 program is considered acceptable in the light of the incremental effect size and the considerably greater proportions of patients achieving HbA1c targets in the 5

mg, 10 mg and 15 mg tirzepatide groups compared to the 1 mg group. In addition, the effect on body weight seemed to be more robust at the higher doses.

Study GPGF supported a dosing algorithm starting at a dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks. This scheme was expected to minimize gastrointestinal adverse drug reactions and was selected for the phase 3 studies; it is also proposed as the recommended dose-escalation scheme in section 4.2 of the SPC, which is considered acceptable.

Results of the phase 3 studies (all figures refer to the treatment regimen estimand)

Study results supported the use of once-weekly tirzepatide for glycaemic control in T2DM. All doses of tirzepatide were superior to placebo and the active comparators evaluated (semaglutide 1 mg, insulin degludec, and insulin glargine) for the mean HbA1c change from baseline (absolute effect sizes ranged for tirzepatide 5 mg from -1.75% to -2.11%, for tirzepatide 10 mg from -1.71% to -2.40% and for tirzepatide 15 mg from -1.69% to -2.41%). Sustainability of glycaemic efficacy through 76 weeks was shown in study GPGM. Incremental improvements across the tirzepatide dose range were small; they were absent in study GPGK in which patients in an early stage of the disease were included.

Between 75.1% and 89.6% of patients taking tirzepatide achieved HbA1c <7.0% at the primary endpoint; between 21.7% and 49.6% of patients taking tirzepatide achieved HbA1c <5.7%, considered a normal HbA1c value. An analysis was performed of patients achieving <5.7% HbA1c at primary endpoint without clinically significant documented symptomatic (<54 mg/dL) or severe hypoglycaemia. Reassuringly, the vast majority of patients reached HbA1c targets below 5.7% safely: 93.6% to 100% of patients not on a background of insulin glargine and 85.9% of patients on a background of insulin glargine. Mainly, cases of clinically significant or severe hypoglycaemia were recorded in studies GPGM and GPGI, in which tirzepatide was administered add-on SUs (study GPGM) and insulin (study GPGI). There was no discernible dose-dependency for development of hypoglycaemia. The risk of hypoglycaemia may have been overestimated in the phase 3 studies as it has to be taken into account that patients in the phase 3 studies underwent forced up-titration. In clinical practice up-titration is expected to be performed according to the individual patients' needs (and some patients will reach their glycaemic goal at the 5 mg dose).

Significant changes from baseline in FSG at the primary endpoint were observed for all tirzepatide groups compared to placebo/active comparator. Notably, FSG improved to the near-normal range, and 7-point SMBG showed normalization of mean postprandial glucose (<140 mg/dl) at the primary endpoint. Glycaemic control seemed to be improved throughout the day, including post-prandial glycaemic excursions. Only a weak dose-response relationship was seen for lowering of FSG.

The GPGH CGM addendum demonstrated that tirzepatide led to significantly more time spent in the euglycaemic range (71-140mg/dL) at 52 weeks; this was not achieved at the expense of increased hypoglycaemia. The overall time spent in hypoglycaemic range ≤70 mg/dL (≤3.9 mmol/L) was significantly reduced to less than 1% of time in a 24 hour period, for all 3 doses of tirzepatide compared to insulin degludec (2%) at 52 weeks; this was likewise shown for clinically significant hypoglycaemia, <54mg/dL. The incidence of nocturnal hypoglycaemia was relatively low, however only tirzepatide 5 mg had significantly fewer events compared to insulin degludec. Glycaemic control was further established by improved glycaemic variability for patients with tirzepatide compared to insulin degludec.

Overall, the weak dose-response on glycaemic endpoints is not considered of concern; individual patients are expected to attain their glycaemic goals only after up-titration to the highest 15 mg dose. Generally, up-titration is an effective means to prevent overtreatment.

All doses of tirzepatide were superior to placebo and the active comparators (semaglutide 1 mg, insulin degludec, and insulin glargine) for the mean body weight change from baseline at the primary endpoint. Reductions in body weight were observed regardless of concomitant therapy with SU or insulin which are known to promote weight gain. The mean changes in body weight from baseline to primary endpoint ranged from -5.4 kg to -7.6 kg (tirzepatide 5mg), -7.0 kg to -9.6 kg (tirzepatide 10mg) and -7.8 kg to -11.3 kg (tirzepatide 15mg). Steady decreases in weight were seen continuing through the end of the study; they did not appear to plateau by the end of the treatment period, for both the 40- and 52-week studies. In contrast to glycaemic benefit, the dose-response relationship for weight loss was pronounced.

Results from the GPGH MRI sub-study showed significantly greater reductions from baseline in liver fat content, volume of visceral adipose tissue, and volume of abdominal subcutaneous adipose tissue compared with insulin degludec. Reduction of visceral adipose tissue is considered beneficial as it is thought to improve cardiovascular health (e. g. Ferrara et al., 2019).

Albeit weight loss is surely beneficial in the majority of study participants, there is some concern that weight loss may be an undesired effect in patients without overweight. In light of ongoing weight loss exceeding the observational period in the phase 3 studies, some patients may struggle to keep their weight during chronic therapy. To further elucidate the benefit/risk of tirzepatide in the subgroup of patients with BMI between 23 and 24.9 kg/m2 (from studies GPGK and GPGI) an analysis has been provided with the Response. It has been further detailed how many patients had BMI below 18.5 kg/m2 at week 40 or week 52.

The requested subgroup analysis showed maintained efficacy and no significant safety concerns in patients with BMI ≥23 and <25 kg/m2 at baseline. A total of nine patients from studies GPGK (n=478), GPGI (n=475), and GPGO (n=636), which included seven patients with BMI ≥23 and <25 kg/m2 at baseline, had a BMI ≤18.5 kg/m2 at the end of the study (Week 40 and Week 52, respectively), which is considered a low number.

In clinical practice, the risk of underweight may even be lower, as the treating physician will not have to adhere to an assigned dose and will adjust the dose of tirzepatide according to the therapeutic needs and the tolerability of each patient.

On the other hand, patients with lower initial BMI than 23 kg/m2 may be treated with tirzepatide, as use of tirzepatide is not restricted per BMI. Therefore, it can be expected that some patients may experience weight loss as an undesired effect.

Therefore, while it is agreed that a general and somewhat arbitrary BMI cut-off for the use of tirzepatide in the SmPC or a warning is not warranted (in line with other GLP-1 receptor agonists); "weight decreased" is listed as adverse event in section 4.8 of the SmPC.

At the primary endpoint, all tirzepatide groups showed significant decreases from baseline in triglycerides, total cholesterol, LDL-C, and VLDL-C. Significant increases from baseline were also observed for HDL-C in studies GPGK, GPGL, GPGH, and GPGM. At the primary endpoint, all 3 doses of tirzepatide had significant reductions in triglycerides and VLDL-C and significant increases in HDL-C compared to semaglutide in Study GPGL. Tirzepatide seemed to improve (diabetic) dyslipidemia which supports the beneficial effects on glycaemic control and body weight. Diastolic and systolic blood pressure were reduced.

Across all QoL measures results for tirzepatide showed improvement from baseline for the vast majority of measurement scores (for all but 1 out of 108 PRO scores). Tirzepatide led to greater improvement in scores compared to placebo/active comparator indicating an increase in the patients` satisfaction with treatment and weight-loss related and overall QoL. These results suggest that the achieved weight-loss and the

improved glycaemic control throughout 24 hours as demonstrated in the CGM substudy seemed to translate into better well-being from the patients` perspective. Results from the open-label studies were considered less reliable than the double-blind studies GPGK and GPGI, as score ratings may have been influenced by the awareness of treatment group assignment. However, no distinct pattern for score changes could be identified between open-label and double-blind studies.

2.6.7. Conclusions on the clinical efficacy

Across the five pivotal phase 3 studies, tirzepatide 5, 10, and 15 mg consistently demonstrated statistically superior and clinically meaningful glycaemic control and weight loss compared with placebo and current standard-of-care diabetes regimens among individuals at different stages of T2DM. Clinically meaningful effects on glycaemic control were achieved with a very small increase in hypoglycaemic events, despite forced up-titration even to the high 15 mg dose. In clinical practice, where patients are up-titrated in accordance with their glycaemic needs and tolerability, the risk of hypoglycaemia is considered low.

Glycaemic and weight loss benefit was supported by other parameters reflecting cardiometabolic health, like favourable effects on the lipid profile, on blood pressure, and on liver and abdominal fat content. The patient perspective was taken into account. PRO results reflected an improved QoL.

Uncertainty with respect to the representation and the B/R in certain subpopulations (patients with stage 4 and 5 renal impairment, hepatic impairment, and normal weight patients) is removed by amendments to the label.

Initially, a MO had been raised as regards the wording of the indication. The reference to weight was found unacceptable. Consecutively, the Applicant consented to delete the reference to "weight" from section 4.1. This was considered necessary since the last sentence pointing to 5.1 should be restricted to micro- and macrovascular complications of type 2 diabetes mellitus. The benefits shown for the respective entities (e.g. "cardiovascular benefit", once confirmed by a CV outcome trial) should be applicable for the entire target population (in the SURPASS studies patients with type 2 diabetes mellitus have been investigated). Weight reduction was investigated as a secondary endpoint in the SURPASS studies; a small proportion of the studied population was not overweight (lower cut-off for BMI in studies GPGK and GPGI 23 kg/m2). As the SmPC does not restrict use of tirzepatide with respect to BMI and patients with even lower BMI than 23 kg/m2 (BMI cut-off in the phase 3 studies) might be treated in clinical practise, a proportion of patients may experience weight loss as an unwanted effect.

Furthermore, it was consented by CHMP to add "insufficiently controlled" to the indication wording in line with the wording of other GLP1 agonists. Generally, the CHMP agreed on an indication wording ("treatment of adults with insufficiently controlled type 2 diabetes") omitting "to improve glycaemic control" even if a benefit with respect to cardiovascular outcome has not yet been shown. Results of the performed CV safety meta-analysis exclude an excessive cardiovascular risk but do not demonstrate a benefit (see 2.6.8.2 under Cardiovascular Safety). Tirzepatide, in addition to the improvements in glycaemic control measures, was also associated with significant improvements on other health outcomes relevant in the treatment of T2DM patients. It is considered undesired to have a long list of separate outcomes and the treatment of T2DM should be consider in a more holistic way hence a more simple reference to 5.1 to support this. All relevant information is included section 5.1 and study results on effects on glycaemic control are cross-referenced and reflected in section 5.1 of the SmPC.

Overall, the following wording in 4.1 was found acceptable:

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 weight, and cardiovascular events,~~ and the populations studied, see sections 4.4, 4.5 and 5.1.

2.6.8. Clinical safety

The safety population comprises patients who took ≥1 dose of study drug. The safety assessments were based on all available data through treatment period and subsequent 4-week safety follow-up. The applicant presents 5 analysis sets (AS1 – AS5; see **Table 1**). Due to their common phase 3-specific dose escalation scheme, the phase 3 studies were analysed separately from the phase 2 studies. Analysis of the pooled comparator group was presented for both the CV meta-analysis (dataset AS5) and for the safety analysis set AS2. Additional safety data, including those from the biopharmaceutic and clinical pharmacology program (phase 1), are part of an Integrated Summary of Safety (ISS).

Table 1: Safety analysis sets presented by the applicant

Analysis Set	Studies	Time period	Treatment comparison	Analyses
AS 1 (Phase 3 placebo-controlled) N= 953	GPGK, GPGI	First dose of treatment to end of safety follow-up visit or date of study withdrawal	TZP 5 mg, 10 mg, 15 mg, TZP_ALL *vs.* placebo	Full set of safety analyses*
AS 2 (Phase 3 dose - effect) N = 5119	GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, GPGP		10 mg vs. 5 mg 15 mg vs. 5 mg 15 mg vs. 10 mg TZP 5 mg, 10 mg, 15 mg, TZP_ALL *vs.* comparator	
AS 3 (Phase 2/3) N = 5415	All nine phase 2/3 studies		Summary only, no comparison	Exposure, demographics, TEAEs, SAEs, DCAEs, AESIs, labs, vital signs, ECG shift to high/low
AS 4 (Phase 2/3 placebo-controlled) N = 1274	GPGB, GPGF, GPGK, GPGI	On treatment First dose of treatment to earliest date of: • Last dose date plus 14 days • Withdrawal date from study • Initiation of new antihyperglycaemic drug after randomization	TZP_ALL *vs.* placebo	Demographics, TEAEs, SAEs, DCAEs, labs, vital signs, ECG shift to high/low
AS 5 (CV Meta-Analysis) N = 7215	GPGB, GPGK, GPGL, GPGH, GPGM, GPGI, GPGO	First dose of treatment to end of safety follow-up visit or date of study withdrawal	TZP_ALL vs. Pooled comparators	CV events

*includes exposure, demographics, medical history, concomitant medications, disposition, TEAEs, SAEs, DCAEs, AESIs, labs, immunogenicity, vital signs, ECGs.

2.6.8.1. Patient exposure

7769 patients received study treatment (TZP or comparator) in 9 completed Phase 2 and 3 studies.
5415 patients received TZP for 4833.1 patient-years.
2375 patients received TZP for ≥52 weeks in phase 2/3
535 patients received treatment for ≥78 weeks.

The population exposed to TZP and the duration of exposure is considered sufficiently large to detect adverse events (AEs) of reasonable frequency (0.5 - 5%) and to elucidate, whether frequently occurring AEs increase or decrease over time. A sufficiently large number of patients was exposed long-term (≥52 weeks). In summary, exposure meets the recommendations in the "Note for Guidance on Population Exposure" (CPMP/ICH/375/95) and is considered acceptable.

2.6.8.2. Adverse events

Overview
In AS2 (comparison across TZP dosing groups, phase 3; **Table 2**, upper part), the number of TEAEs and discontinuations of study drug increased incrementally across TZP doses. The percentage of patients with SAEs or discontinuations from study due to an AE was similar across TZP dose groups. In AS4 (TZP *vs.* placebo, phase 2/3; **Table 2**, lower part), more TEAEs, SAEs, discontinuations from study and from study treatment occurred with TZP than with placebo.

Table 2: Overview of AEs, safety population, phase 3 dose-effect analysis set (AS2; from SCS Table 2.7.4.13) and Phase 2/3 placebo-controlled analysis set (AS4; from Table ISS.4.34)

AS2				
Category[a]	**TZP 5 mg (N=1701) n (%)**	**TZP 10 mg (N=1702) n (%)**	**TZP 15 mg (N=1716) n (%)**	**TZP_ALL (N=5119) n (%)**
Deaths[b]	20 (1.18)	8 (0.47)	13 (0.76)	41 (0.80)
SAEs	134 (7.88)	135 (7.93)	122 (7.11)	391 (7.64)
Discontinuation from study due to AE	37 (2.18)	32 (1.88)	33 (1.92)	102 (1.99)
Discontinuation from study drug due to AE	121 (7.11)	145 (8.52)	169 (9.85)	435 (8.50)
TEAEs	1158 (68.08)	1202 (70.62)	1276 (74.36)	3636 (71.03)

AS4		
Adverse event[a]	**TZP_ALL (N=962) n (%)**	**Placebo (N=312) n (%)**
Deaths[b]	0	1 (0.3)
Serious Adverse Events (SAEs)	37 (3.8)	13 (4.2)
Discontinuations from Study due to AE	12 (1.2)	2 (0.6)
Discontinuation from study drug due to AE	68 (7.1)	8 (2.6)
TEAEs	680 (70.7)	190 (60.9)

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

AEs according to MedDRA Terms

Most common TEAEs (≥5% of either treatment group) in safety analysis sets AS2 and AS4:

In analogy to the safety profile of GLP1 receptor agonists, the most common TEAEs (≥5% of either treatment group) were gastrointestinal AEs. In the placebo-controlled dataset AS4, nausea, vomiting, diarrhoea, dyspepsia, constipation and decreased appetite occurred more often with TZP than with placebo, while hyperglycaemia was reduced by TZP.

Table 3 illustrates that in the phase 3 dataset AS2, the percentage of nausea, diarrhoea, decreased appetite, and vomiting incrementally increased with higher TZP doses. All AEs except for nasopharyngitis occurred more often with TZP than with comparator. Moreover, "lipase increased" was higher with TZP than with comparator, pointing to a pancreatic effect, which is also known from GLP1 agonists.

Table 3: TEAEs with an incidence of **≥5%** in either treatment group in the analysis set **AS2** (from SCS Table 2.7.4.15)

Preferred term	TZP 5 mg (N=1701) n (%)	TZP 10 mg (N=1702) n (%)	TZP 15 mg (N=1716) n (%)	TZP_ALL (N=5119) n (%)	Pooled controls* (N=2223) n(%)
Nausea	224 (13.17)	312 (18.33)	381 (22.20)	917 (17.91)	135 (6.07)
Diarrhoea	224 (13.17)	268 (15.75)	272 (15.85)	764 (14.92)	144 (6.48)
Decreased appetite	132 (7.76)	166 (9.75)	200 (11.66)	498 (9.73)	42 (1.89)
Vomiting	93 (5.47)	132 (7.76)	167 (9.73)	392 (7.66)	66 (2.97)
Dyspepsia	101 (5.94)	125 (7.34)	115 (6.70)	341 (6.66)	52 (2.34)
Constipation	110 (6.47)	110 (6.46)	112 (6.53)	332 (6.49)	56 (2.52)
Nasopharyngitis	109 (6.41)	101 (5.93)	113 (6.59)	323 (6.31)	154 (6.93)
Lipase increased	64 (3.76)	60 (3.53)	90 (5.24)	214 (4.18)	46 (2.07)

Abbreviation: N = number of patients in treatment group; n = number of patients with at least 1 treatment-emergent adverse event; TZP = tirzepatide.
*****study GPGP did not have a control group

Less frequent AEs (incidence ≥1% and <5%) in safety analysis set AS2:

The following less frequent AEs were ***increased*** by TZP:

- About half of the less frequent AEs were in the gastrointestinal disorders SOC
- Pancreatic AEs like "pancreatic enzymes increased" or "amylase increased"
- Unspecific AEs like *dizziness, asthenia, fatigue, vertigo, illness and malaise*, some of which were less prominent with pure GLP-1 receptor agonist controls (semaglutide in study GPGL, and dulaglutide in study GPGO)
- The PTs "weight decreased", "injection site reaction" and "hypotension" were more frequently reported with TZP than with comparator.
- The PT *renal cyst* was more frequently reported with TZP as compared to comparator (TZP 5 mg: 6 [0.35%]; 10 mg: 10 [0.59%]; 15 mg: 20 [1.17%] and comparator: 8 [0.36%]).

The following less frequent AEs were ***decreased*** by TZP:

- PTs describing infectious diseases like urinary tract infection, influenza, COVID-19 pneumonia, sinusitis, pneumonia and cystitis
- Hypertension, Oedema peripheral
- Hyperglycamia, Hypertriglyceridaemia, anaemia

AEs of special interest (AESIs)

For discussion of the AESI *"Immunogenicity"* please refer to section 2.6.8.7 ("**Immunological events**").

Gastrointestinal Adverse Events

The most commonly occurring severe/serious GI TEAEs were nausea, diarrhoea and vomiting. In AS1, mild and moderate GI TEAEs occurred more often in TZP- than placebo-treated patients. Mild GI TEAEs incrementally increased with TZP dose, but no such trend was seen for severe GI TEAEs. The frequency of severe TEAEs did also not differ between TZP_ALL and placebo (**Table 4**). Similar safety data were obtained with analysis set AS2. There was also no imbalance between TZP dosing groups in AS1 and AS2 for pooled severe and serious GI TEAEs.

Table 4: Summary of TEAEs by maximum severity in the GI SOC in the safety population of AS1 (from CSS, Table 2.7.4.25)

Maximum Severity	n (%)				
	TZP 5 mg (N=237)	**TZP 10 mg (N=240)**	**TZP 15 mg (N=241)**	**TZP_ALL (N=718)**	**Placebo (N=235)**
Patients with ≥1 GI TEAE	88[a] (37.1)	95 (39.6)	105 (43.6)	288 (40.1)	48 (20.4)
Mild	61 (25.7)	72 (30.0)	80 (33.2)	213 (29.7)	32 (13.6)
Moderate	23 (9.7)	22 (9.2)	22 (9.1)	67 (9.3)	14 (6.0)
Severe	3 (1.3)	1 (0.4)	3 (1.2)	7 (1.0)	2 (0.9)
Abbreviations: GI = gastrointestinal; N = number of patients who were randomized and received ≥1 dose of study drug; n = number of patients with events meeting the specified criteria; Plc = Placebo, SOC = system organ class; TEAE = treatment-emergent adverse event; TZP = tirzepatide. [a]Total includes one patient with a missing severity					

In contrast to phase 2, GI AEs like nausea, vomiting and diarrhoea were considerably mitigated in phase 3 by introduction of a dose escalation period (week 0-24). For example, in the phase 2 study GPGB, nausea occurred in 20.0 – 41.5% of TZP-treated patients (placebo: 5.9%), while this proportion was reduced to 12.2 – 18.3% in phase 3 analysis set AS1 (placebo: 4.3%).

Comparison with GLP1 receptor agonists (Studies GPGL and GPGO)

Phase 3 study GPGL compared TZP (5, 10 and 15 mg) with semaglutide (Sema) 1 mg. The proportion of patients with ≥1 GI TEAE was similar with TZP 5 mg and Sema 1 mg. However, the 10 mg and 15 mg TZP groups show a numerically higher percentage of affected patients than Sema 1 mg, specifically in case of nausea and vomiting (**Table 5**). Similarly, in the regional (Japan) phase 3 study GPGO, comparing TZP with dulaglutide (Dula) 0.75 mg, all TZP dosing groups showed numerically higher percentages of patients affected by GI TEAEs than the dulaglutide control group (**Table 5**). This suggests that TZP was not compared *on par* with semaglutide or dulaglutide, and the GLP1 receptor agonists were rather underdosed relatve to TZP.

Table 5 (CSS Tables 2.7.4.30 and 2.7.4.31): Summary of GI TEAEs (PTs) in ≥5% of patients in study GPGL (TZP *vs.* sema) and GPGO (TZP *vs.* dula)

Study GPGL				
Event Category or Term	**n (%)**			
	TZP 5 mg (N=470)	**TZP 10 mg (N=469)**	**TZP 15 mg (N=470)**	**Sema 1 mg (N=469)**
Patients with ≥1 GI TEAE	188 (40.0)	216 (46.1)	211 (44.9)	193 (41.2)
Nausea	82 (17.4)	90 (19.2)	104 (22.1)	84 (17.9)

Diarrhoea	62 (13.2)	77 (16.4)	65 (13.8)	54 (11.5)
Vomiting	27 (5.7)	40 (8.5)	46 (9.8)	39 (8.3)
Study GPGO				
Event Category or Term	**n (%)**			
	TZP 5 mg (N=159)	**TZP 10 mg (N=158)**	**TZP 15 mg (N=160)**	**Dula 0.75 mg (N=159)**
Patients with ≥1 GI TEAE	81 (50.9)	76 (48.1)	86 (53.8)	50 (31.4)
Nausea	19 (11.9)	31 (19.6)	32 (20.0)	12 (7.5)
Diarrhoea	27 (17.0)	14 (8.9)	18 (11.3)	11 (6.9)
Vomiting	13 (8.2)	8 (5.1)	19 (11.9)	2 (1.3)

Nausea, vomiting, and diarrhoea over time in AS2
Combined and individual **incidence** of nausea, vomiting, and diarrhoea depended on TZP dose and were higher during dose-escalation than in steady state.

The graphical representation of the gastrointestinal AEs throughout the entire phase 3 study program (AS2 dataset) suggests that, in the 15 mg TZP group, the prevalence of vomiting remains elevated throughout the study as compared to the first 4 weeks. According to the Applicant, the seemingly prolonged prevalence of vomiting is mainly driven by study GPGM, which had a longer duration than all other studies in AS2. In addition, the prevalence of vomiting may have additionally been prolonged by the study centres keeping an AE open in case of intermittent episodes of vomiting. However, as the product can be discontinued in clinical practice in case of inacceptable GI adverse events and since the GI AEs are most likely reversible, this issue is not further pursued.

In addition, it is noted that the prevalence of vomiting remained incrementally increased with TZP dose at safety follow-up (e.g., in AS2: vomiting: TZP 5 mg: 0.12%; 10 mg: 0.36% and 15 mg: 0.60%). This is most likely due to the long half-life of TZP, which may have prolonged the AE e.g., after study discontinuation due to GI AEs.

Renal Safety

In AS1, a numerically higher percentage of patients reported ≥1 renal TEAE for TZP_ALL (1.1%) than for placebo (0.4%) (no dose dependency was observed). Similar results were obtained for AS2. However, in AS2, seven (0.14%) of the 65 patients with ≥1 renal TEAE in AS2 had severe or serious AEs (TZP 5 mg: 0.12%; 10 mg: 0.18%; 15 mg: 0.12%).

A search for MedDRA PTs revealed that the PT *"renal cyst"* incrementally increased with TZP in safety analysis set AS2 and was higher with TZP 10 mg and 15 mg than with pooled comparator (TZP 5 mg: 6 [0.35%]; TZP 10 mg: 10 [0.59%]; TZP 15 mg: 20 [1.17%] and pooled comparator: 8 [0.36%]). However, it is noted that out of the 36 TZP-treated patients with renal cysts in AS2, 15 patients had a pre-existing condition of kidney-related disease. Moreover, renal cysts were only reported as incidental findings in several patients, and in general, there is an increased incidence of renal cysts in T2DM patients. Thus, it is difficult to firmly establish a connection with TZP treatment. No difference in the incidence of renal cysts as compared to placebo was observed in the placebo-controlled datasets AS1 and AS4.

At 40 weeks and safety follow-up, the mean **eGFR** (estimated glomerular filtration rate) reductions from baseline did not show clinically meaningful differences between TZP doses or between TZP_ALL and comparator (AS2). Accordingly, the percentage of patients shifting to higher/lower eGFR categories was comparable across treatment groups.

In AS1, mean UACR (urine albumin/creatinine ratio) decreased with TZP, while it increased with placebo. Fewer patients shifted to higher UACR categories with TZP (9.6%) than with placebo (18.8%), and more patients shifted to lower UACR categories with TZP (13.5%) than with placebo (9.0%). Similar trends occurred in AS2. In the subpopulation of patients with renal impairment (eGFR<60, Study GPGM), the renal safety profile was similar to that of the total study population.

Exocrine Pancreas Safety

Pancreatitis

In AS2, no relevant differences between TZP dosing groups were observed for any category of pancreatic event. Only 11 of 58 CEC-assessed pancreatitis events were adjudicated as acute pancreatitis (**Table 6**). In AS3, 13 (0.24%) TZP-treated patients and 4 (0.17%) comparator-treated patients had treatment-emergent, positively adjudicated pancreatitis.

Table 6: Summary of adjudicated pancreatic in AS2 (CSS Table 2.7.4.63)

Events	n (%); events			
	TZP 5 mg (N=1701)	**TZP 10 mg (N=1702)**	**TZP 15 mg (N=1716)**	**TZP_ALL (N=5119)**
Investigator-reported events	16 (0.94); 16[a]	20 (1.18); 20[b]	20 (1.17); 22[c]	56 (1.09); 58
Non-investigator reported evens	1 (0.06); 1	1 (0.06); 1	0	2 (0.04); 2
CEC-assessed pancreatitis	17 (1.00); 17[d]	21 (1.23); 21[e]	20 (1.17); 22[f]	58 (1.13); 60
Adjudicated as acute pancreatitis*	3 (0.18); 3	4 (0.24); 4	4 (0.23); 4	11 (0.21); 11

Abbreviations: CEC = clinical endpoint committee; N = total number of patients in specified treatment group; n = number of patients with ≥ pancreatic event

Duplicate events (=multiple events reported that should have been reported as a single event. None of these events were adjudicated as pancreatitis): [a]3 patients with 1 duplicate event; [b]2 patients with duplicate event. [c]1 patient with 1 duplicate event; [d]1 patient with duplicate event; [e]2 patients with 3 duplicate events; [f]2 patients with 2 duplicate events.

*no chronic pancreatitis was identified by the CEC

Pancreatic enzymes

The data strongly suggest a causal relationship between TZP therapy and elevation of pancreatic enzymes, which is a known effect of GLP1 receptor agonists.

AS1 (Similar tendencies in AS2):

p-amylase shifted from normal levels (≤1×ULN) at baseline to higher categories more frequently with TZP than with placebo (plc):

- shift to >1 x ULN: TZP 5 mg: 14.4%; 10 mg: 16.7%; 15 mg: 18.6%, plc.: 5.1%
- shift to >1 x ULN to ≤3 x ULN: TZP_ALL: 15.9%; plc.: 5.1%
- shift to >3 to ≤5 x ULN: TZP_ALL: 0.7%; plc.: 0

Serum lipase shifted from normal levels (≤1×ULN) at baseline to higher categories more frequently with TZP than with placebo (plc):

- shift to >1 x ULN: TZP 5 mg: 29.1%; 10 mg: 35.4%; 15 mg: 34%; plc.: 15.8%
- shift to >3 x ULN to ≤5×ULN: TZP_ALL: 2.8%; plc.: 0.9%
- shift to >5 x ULN to ≤10×ULN: TZP_ALL: 0.6%; plc.: 0
- shift to >10×ULN: TZP_ALL: 0.3%; plc.: 0

Both enzymes plateaued at ~24 weeks and decreased after 40 weeks. At safety follow-up, the values were still higher than baseline.

Thyroid Safety

Calcitonin plasma levels were determined in all phase 3 studies. The results indicate that TZP treatment increases plasma calcitonin.

A search across the phase 3 study CSRs for the PT *"blood calcitonin increased"* revealed a TZP-dose-dependent increase, and a higher frequency with TZP than with comparator (TZP 5 mg: 9 [0.53%]; TZP 10 mg: 11 [0.65%]; TZP 15 mg: 16 [0.93%] *vs.* pooled comparators: 5 [0.22%]). From the 36 events of "*blood calcitonin increased*" reported in the TZP-treated groups, 27 were mild in severity, and the remainder was moderate. No case occured in the pooled placebo groups.

In study GPGO, post-baseline blood calcitonin was also elevated by TZP, while dulaglutide 0.75 mg had no effect (TZP 5 mg: 33 [20.75%]; TZP 10 mg: 36 [22.78%]; TZP 15 mg: 42 [26.25%] and dulaglutide 0.75 mg: 16 [10.06%]. The time course of blood calcitonin in study GPGO is shown in **Figure 1**.

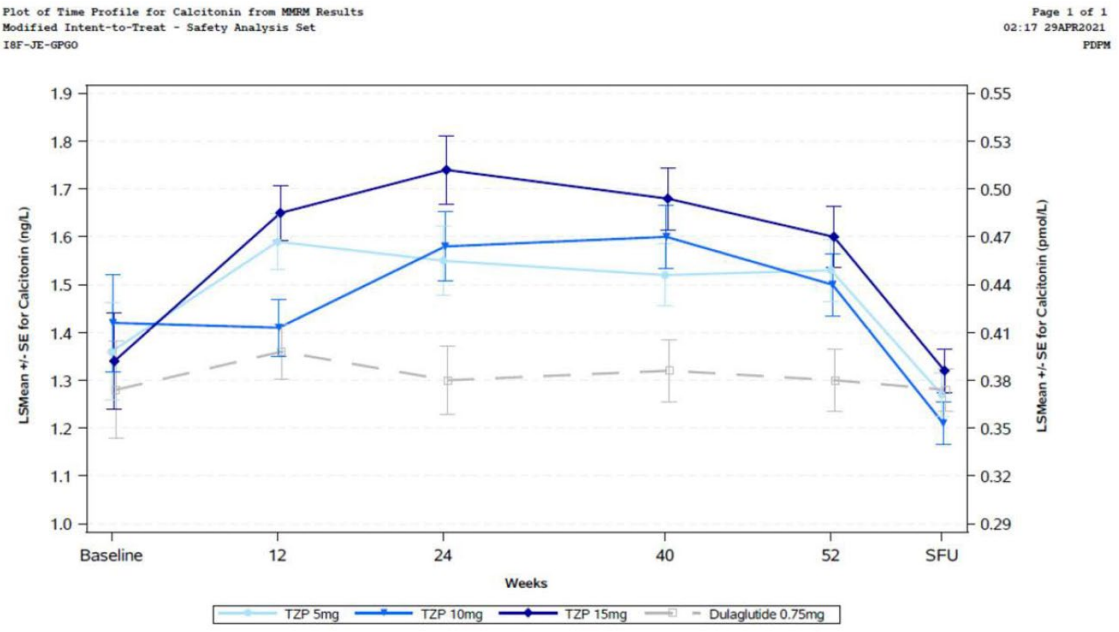


Figure 1: Blood calcitonin levels over time during study GPGO (Fig. GPGO 8.9, CSR of study GPGO)

The TZP-dependent elevation of blood calcitonin in study GPGO is also confirmed by the data from the other phase 3 studies. The calcitonin levels stayed elevated until the last week of the treatment phase and returned to or below baseline levels at safety follow-up (see **Table 7**, showing change from baseline). It is noted that no calcitonin elevation was observed in the semaglutide 1 mg and dulaglutide 0.75 mg comparator groups of study GPGL and GPGO, respectively (**Table 7**, highlighted in red; for GPGO, see additionally **Figure 1**). Apparently, TZP seems to act differently on the thyroid gland than the established GLP1 receptor agonists.

Table 7: Change from baseline in calcitonin levels at week 12 (upper part of table), after last week on treatment (middle part of table) and at safety follow-up (lower part of table) in the phase 3 global and regional studies (data extracted from individual study reports)

Study (week)	Change from baseline (pmol/L)* at week 12			
	TZP 5 mg	**TZP 10 mg**	**TZP 15 mg**	**comparator**
GPGH (week 12)	+0.09	+0.13	+0.24	-0.02 (degludec)
GPGI (week 12)	+0.11	+0.21	+0.22	+0.00 (placebo)
GPGK (week 12)	+0.10	+0.14	+0.05	-0.05 (placebo)
GPGL (week 12)	+0.12	+0.12	+0.14	-0.02 (sema 1 mg)
GPGM (week 12)	+0.11	+0.18	+0.17	-0.03 (glargine)
GPGO* (week 12)	+0.24	+0.05	+0.30	+0.02 (dula 0.75 mg)
GPGP* (week 12)	+0.34	+0.20	+0.49	---
	Change from baseline (pmol/L)*, last value on treatment			
GPGH (week 52)	+0.21	+0.17	+0.24	+0.05 (degludec)
GPGI (week 40)	+0.15;	+0.20	+0.28	+0.01 (placebo)
GPGK (week 40)	+0.01	+0.13	-0.06	-0.02 (placebo)
GPGL (week 40)	+0.09	+0.12	+0.10	-0.04 (sema 1 mg)
GPGM (week 104)	+0.22	+0.34	+0.17	+0.02 (glargine)
GPGO* (week 52)	+0.18	+0.13	+0.26	-0.04 (dula 0.75 mg)
GPGP* (week 52)	+0.32	+0.29	+0.41	---
	Change from baseline (pmol/L)* at safety follow-up (SFU)			
GPGH (SFU)	+0.03	+0.01	+0.02	+0.04 (degludec)
GPGI (SFU)	+0.05	-0.02	+0.20	+0.00 (placebo)
GPGK (SFU)	-0.05	-0.12	-0.11	-0.05 (placebo)
GPGL (SFU)	-0.05	-0.04	-0.04	-0.07 (sema 1 mg)
GPGM (SFU)	+0.08	+0.03	+0.04	+0.10 (glargine)
GPGO* (SFU)	-0.09	-0.15	-0.03	-0.07 (dula 0.75 mg)
GPGP* (SFU)	-0.05	-0.12	0	---
*Regional studies GPGO and GPGP: calcitonin levels reported using "conventional units" (ng/L)				

Hypoglycaemia

The events of severe hypoglycaemia occurring in the phase 3 studies are summarised in the table below. Overall, there were few events with TZP, most often in the high-dose (15 mg) TZP groups.

Table 8: Summary of severe hypoglycaemia post-baseline through the safety follow-up, excluding hypoglycaemic episodes occurring after initiation of a new anti-hyperglycaemic therapy (from CSS, Table 2.7.4.74)

Background Therapy	Study (Comparator)	TZP 5 mg N n(%); episodes	TZP 10 mg N n(%); episodes	TZP 15 mg N n(%); episodes	Comparator N n(%); episodes
None	**GPGK** (Placebo)	121 0	119 0	120 0	115 0
Metformin	**GPGL** (Sema 1 mg)	470 1 (0.21); 1	469 0	470 1 (0.21); 1	469 0
Metformin ±	**GPGH**	356	360	359	358

SGLT-2i	(Insulin degludec)	0	0	1 (0.28); 1	0
Metformin + SGLT-2i	*GPGH subset*	*112* *0*	*118* *0*	*112* *0*	*116* *0*
Metformin	*GPGH subset*	*244* *0*	*242* *0*	*247* *1 (0.40); 1*	*242* *0*
Metformin ± SGLT-2i ± SU	**GPGM** (Insulin glargine)	329 1 (0.30); 1	328 0	338 3 (0.89); 5	1000 11 (1.10); 15
on SU	*GPGM subset*	*189* *1 (0.53); 1*	*181* *0*	*179* *1 (0.56); 1*	*537* *6 (1.12); 10*
not on SU	*GPGM subset*	*140* *0*	*147* *0*	*159* *2 (1.26); 4*	*463* *5 (1.08); 5*
Insulin glargine ± metformin	**GPGI** (Placebo)	116 0	119 2 (1.68); 2	120 1 (0.83); 1	120 0

N = number of patients in the population with baseline and post-baseline value at the specified time point; n = number of patients with hypoglycaemia; SGLT-2i = sodium-glucose co-transporter 2 inhibitor; Sema = semaglutide; SU = sulfonylurea; TZP = tirzepatide.

The risk of "*BG **<54 mg/dL** or severe hypoglycaemia*" was higher with TZP than with placebo in study GPGI, where insulin glargine was part of the background therapy (TZP 5 mg: 15.52%; TZP 10 mg: 19.33%; TZP 15 mg: 14.17% vs. placebo: 12.5%).

Not only with insulin as background therapy but also as add-on to metformin, TZP showed a numerically higher frequency of "*BG **<54 mg/dL** or severe hypoglycaemia*" than the comparator semaglutide (TZP 5 mg: 0.85%; TZP 10 mg: 0.21%; TZP 15 mg: 1.70% *vs.* semaglutide 1 mg: 0.43%; Study GPGL). Similarly, more hypoglycaemias of this category occurred with TZP as compared to dulaglutide 0.75 mg in the regional study GPGO. This finding could be related to the relative under-dosing of semaglutide and dulaglutide in these studies as already discussed (e.g., semaglutide, in contrast to TZP, was not given in its maximally weight-reducing dose).

Cardiovascular Safety

TZP consistently led to small decreases in systolic and diastolic **blood pressure** (TZP *vs.* plc in AS1: in mean by around 6 mmHg for systolic and by 2 mmHg for diastolic blood pressure).

Heart rate was increased vs. plc across studies by around 4 bpm. Accordingly, the number of patients reporting HR increase by more than 20 bpm vs. baseline was higher in the TZP than in the plc groups (TZP 5mg, 9.7%, TZP 10 mg, 12.2%, TZP 15 mg, 15.0%; placebo: 6.4%, AS1).

In ECG, the **PR interval** was prolonged by 2.7 – 4.5 msec with TZP vs. placebo; no clear dependency on the TZP dose was observed. Due to the small magnitude, the finding is not considered clinically relevant.

Major adverse cardiovascular events (CV safety meta-analysis)
In accordance with the requirements of the Reflection paper EMA/CHMP/50549/2015, 25 February 2016), a CV safety meta-analysis based on data from all phase 2 and phase 3 clinical studies was performed to assess the effect of TZP on CV risk. The events were prospectively adjudicated by an independent CEC.

A vast majority of the MACE came from Study GPGM. The primary endpoint of the CV meta-analysis was the time to first occurrence of MACE-4, a composite endpoint of death from CV or undetermined causes, MI, stroke, and hospitalisation for unstable angina pectoris (HUA). For the meta-analysis, the pooled TZP group combined patients randomized to 1 mg, 5 mg, 10 mg, and 15 mg maintenance doses. MACE-3 was investigated as an additional endpoint.

Statistical method

The CV meta-analysis was planned to be conducted after approximately 133 patients reach MACE-4 endpoint.

An interim CV meta-analysis was conducted after all the following conditions were met:

1. At least 100 patients have reached primary MACE-4 endpoint confirmed by the CEC across all the studies included in the CV meta-analysis.
2. Global Phase 3 Studies GPGK, GPGI, GPGH, and GPGL have achieved their database lock.
3. All patients in Study GPGM who have not discontinued the study before 12 months have completed the 12-month primary endpoint (change in HbA1c) assessment.
4. At least 300 patients in Study GPGM have reached 18 months or longer of exposure to tirzepatide.

Alpha level for the interim analysis was determined based on Hwang, Shih, DeCani (Hwang et al. 1990) with Gamma=-6.6 and the information fraction based on the total of 133 MACE-4 endpoints.

Since 116 of the 133 planned CEC-confirmed MACE-4 endpoints were available at the interim analysis, that is, 116/133 fraction of MACE-4 endpoints, a significance level of 0.0215 was utilized at the interim analysis. Accordingly, 97.85% CI for the HR (pooled tirzepatide versus pooled comparator) guided the decision to discharge excess CV risk with tirzepatide.

Since the pre-marketing safety requirement was met at the interim CV meta-analysis with 116 MACE-4 endpoints, the complete analysis with 142 MACE-4 endpoints was presented as an additional supportive analysis. Therefore, no alpha level adjustment was warranted, and all analyses with 142 MACE-4 endpoints were conducted using a 2-sided alpha level of 0.05.

All analyses were assessed using the mITT population which consisted of all randomized patients receiving at least 1 treatment dose according to the treatment to which they were randomly assigned. In all summaries and analyses, mITT population patients randomly assigned to any dose of tirzepatide were included in the pooled tirzepatide group, and mITT population patients randomly assigned to placebo or an active comparator were included in the pooled control group. Unless otherwise specified, only CV events that occurred during the treatment period and the 4-week follow-up period that were positively adjudicated by the CEC, were included in the CV meta-analysis.

Since the CV risk of different studies varied based on patient population and other considerations such as duration of follow-up, a stratification factor by study-level CV risk was set as follows:

- Stratum 1: Study GPGM - High CV risk patient population with longer follow-up
- Stratum 2: All other trials enrolling lower CV risk patient population (Studies GPGB, GPGH, GPGI, GPGK, GPGL, and GPGO)

Under the proportional hazards assumption, a Cox proportional hazards model with treatment (pooled tirzepatide arm, pooled control arm) as a fixed effect and stratified by study-level CV risk (Stratum 1 and Stratum 2) was used to derive the HR (pooled tirzepatide versus pooled control) and the associated CI.

Counts and proportions of patients who experienced a primary endpoint event were provided. Person-years of follow-up for the primary endpoint and the incidence rate were calculated. The incidence rate was calculated by dividing the number of patients who developed the event during the study period by the event-specific

person-years of follow-up. Adjusted Kaplan-Meier (KM) estimates of the survival curve for pooled tirzepatide arm and pooled control arm were generated.

Results of the CV safety meta-analysis

For the complete analysis, a total of 142 patients (72 TZP, 70 pooled comparator) were reported with an adjudicated primary endpoint. The results for MACE-4 and its components are tabulated below **(Table 9)**. All point estimates of the hazard ratios (HR) were below 1, except for investigator-reported CV death. HR for CEC-confirmed CV death was below 1.

Table 9: Time-to-Event Analysis of Composite MACE-4 and Individual Components, mITT Population, CV Meta-analysis Set **AS5** (Studies GPGB, GPGH, GPGI, GPGK, GPGL, GPGO and GPGM) – Complete Analysis

	TZP_ALL (N=4887)			**Pooled Comparator (N=2328)**			
	n	Person-yrs of Follow-Up*	n/100 person-yrs**	n	Person-Years of Follow-Up*	n/100 person-yrs**	HR (95% CI)***
Reported by Investigator							
Composite MACE-4	67	5065.20	1.32 [1.26]	58	2720.51	2.13 [1.35]	0.88 (0.61,1.26)
Death Due to CV Cause****	21	5099.16	0.41 [0.39]	15	2756.39	0.54 [0.31]	1.11 (0.56,2.18)
Myocardial Infarction	29	5083.25	0.57 [0.54]	27	2737.19	0.99 [0.65]	0.81 (0.47,1.38)
Stroke	15	5089.17	0.29 [0.27]	15	2747.98	0.55 [0.35]	0.80 (0.39,1.67)
Hospitalization for Unstable Angina	12	5090.46	0.24 [0.23]	11	2745.87	0.40 [0.24]	0.82 (0.36,1.91)
Confirmed by Clinical Endpoint Committee							
Composite MACE-4	72	5064.45	1.42 [1.35]	70	2717.35	2.58 [1.61]	0.80 (0.57,1.11)
Death Due to CV Cause*d	25	5099.16	0.49 [0.46]	22	2756.39	0.80 [0.43]	0.90 (0.50,1.61)
Myocardial Infarction	30	5081.70	0.59 [0.56]	30	2730.91	1.10 [0.71]	0.76 (0.45,1.28)
Stroke	15	5087.03	0.29 [0.27]	15	2747.20	0.55 [0.35]	0.81 (0.39,1.68)
Hospitalization for Unstable Angina	5	5094.05	0.10 [0.09]	9	2749.71	0.33 [0.20]	0.46 (0.15,1.41)

* Person-years of follow-up: time-to-event (=number of days between the date of first dose and the onset date of the event/censoring date plus 1 day) divided by 365.25.
** "[ ]" = adjusted estimate (considers different randomization ratios and differences in patient populations among strata (study-level CV risk: GPGM and all other studies are two distinct strata).
*** Derived from Cox proportional-hazards model with treatment (pooled TZP vs. pooled comparator) as fixed effect, stratified by study-level CV risk (GPGM and all other studies are two distinct strata). P-value is from Wald test. When the total number of outcomes is < 10, survival analysis is not performed.
**** Death due to CV cause (= death due to CV or undetermined cause).

Regarding the outcome of further CV and mortality endpoints, MACE-3, hospitalisation for heart failure and all-cause death, there is numerically decreasing frequency of these endpoints with increasing TZP dose. Accordingly, event rate in the TZP-all group is numerically lower than in the combined comparator group.

Data on CV safety and potential CV benefits of TZP will be provided from the currently ongoing CV outcome study (Study I8F MC GPGN, SURPASS-CVOT), with dulaglutide as an active comparator. This event-driven study is expected to enroll 12,500 patients with a history of CV disease, and will have an average treatment follow up of approximately 4 years.

Hypersensitivity Reactions

No anaphylactic reactions were observed. Hypersensitivity Reactions were more frequently reported in the combined TZP than in the plc group of AS1. In detail:

Immediate: TZP: 4 (0.6%; eczema, injection site hypersensitivity, swelling of eyelid and urticaria); placebo: 1 (0.4%); no event reported by >1 patient.

Non-immediate: TZP: 19 (2.6%); placebo: 3 (1.3%). Events in ≥2 patients of any treatment group: rhinitis allergic (TZP: 5 [0.7%]; placebo: 0); rash (TZP: 3 [0.4%]; placebo: 1 [0.4%]); urticaria (TZP: 3 [0.4%]: placebo, 0); injection site hypersensitivity (TZP: 2 [0.3%]; placebo: 0); mostly mild, no discontinuations.

Since in AS2 no comparator group was included, no meaningful conclusions can be drawn from this dataset. However, one patient in the TZP 5 mg group displayed marked signs of hypersensitivity: the patient experienced 16 events of throat tightness, all occurring on days with TZP administration. Each event resolved within ≤1 day. "Hypersensitivity" was excluded, and the patient completed the study on study drug without additional reports of throat tightness.

Severe/Serious Hypersensitivity Reactions

4 (0.08%) TZP-treated patients reported 4 potential severe or serious non-immediate hypersensitivity reactions. The events were skin necrosis (5 mg TZP, 9 days after last dose, not related to study drug), urticaria (5 mg TZP, 7 events starting on day 19, mostly mild or moderate, one severe; all resolved), allergic rhinitis (5 mg TZP, severe, during safety follow-up, recovering), eczema (TZP 15 mg, severe, led to study drug discontinuation).

Hypersensitive and injection site reactions in Japan studies

In the studies GPGO and GPGP, conducted in Japanese patients, the incidence of potential hypersensitivity reactions was rather high. E.g., potential nonimmediate hypersensitivity occurred in 7.5% of subjects in the 15 mg TZP group of Study GPGO whereas in the non-Japanese phase 3 studies the incidence ranged from 0 to 4.2%. However, incidence of potential hypersensitivity events was also higher in the control (dulaglutide) group of GPGO compared to the control groups of the non-Japanese studies; GPGP had no control group. Thus, the increased incidence of potential hypersensitivity reaction in Japanese subjects is not considered a safety concern of TZP.

Injection Site Reactions

In AS1, the percentage of patients with injection site reactions was higher with TZP than with placebo (3.2% *vs.* 0.4%). Likewise, in AS2, the most frequently reported PT was "injection site reaction" (incremental increase with TZP dose). All events in AS1 and AS2 were mild or moderate in severity.

Diabetic Retinopathy Complications

In the TZP phase 3 program, patients with an increased risk for diabetic retinopathy complications (history of proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy requiring acute treatment) were excluded due to prior findings with semaglutide. In the phase 3 studies, 18 (0.35%) TZP-treated patients reported *worsening of fundoscopic examination results* (retinopathy eCRF). Future results from the ongoing dedicated addendum study to SURPASS-CVOT (investigating the impact of TZP on diabetic

retinopathy progression) should be awaited to allow a more reliable estimation of the TZP-associated retinopathy risk.

Hepatobiliary Disorders

Hepatobiliary events

Hepatobiliary events reported in the different phase 3 studies are tabulated below. In most studies, event rate was higher with TZP than with placebo.

Table 10: Summary of hepatobiliary TEAEs in phase 3 studies

Treatment Arm	Patients with ≥1 TEAE						
	GPGK	**GPGL**	**GPGH**	**GPGI**	**GPGM**	**GPGO**	**GPGP**
TZP_ALL, n/N (%)	4/363 (1.1)	41/1409 (2.9)	29/1077 (2.7)	8/355 (2.3)	42/995 (4.2)	10/447 (2.2)	12/443 (2.7)
Comparator[a], n/N (%)	2/115 (1.7)	10/469 (2.1)	7/360 (1.9)	1/120 (0.8)	39/1000 (3.9)	2/159 (1.3)	- -

Abbreviations: N = total number of patients in treatment group, n = total number of patients reporting ≥1 TEAE; TEAE = treatment-emergent adverse event; TZP = tirzepatide.
[a]Refer to Table 1 of this safety assessment for information on comparator arm used in each study.

Hepatic analytes (ALT, AST, ALP, bilirubin)

Notably, mean values of AST, ALT and ALP dose-dependently decreased from baseline in the TZP groups. However, in AS2, for both post-baseline ALT and AST, a higher percentage of patients in the TZP 15 mg group as compared to the lower TZP doses was reported in the categories ≥3 x ULN and ≥5 x ULN (**Table 11**). Post-baseline ALP was ≥ 2 x ULN in 16 (0.32%) TZP-treated patients (TZP_ALL).

Table 11: Maximum baseline to maximum post-baseline laboratory values for ALT and AST in safety analysis set AS2 (from CSS Table 2.7.4.113)

Maximum post-baseline	*Alanine aminotransferase (ALT)*			*Aspartate aminotransferase (AST)*		
	TZP 5 mg (N=1679)*	TZP 10 mg (N=1682)*	TZP 15 mg (N=1698)*	TZP 5 mg (N=1679)*	TZP 10 mg (N=1682)*	TZP 15 mg (N=1698)*
≥ 3 x ULN	14 (0.83)	12 (0.71)	20 (1.18)	9 (0.54)	8 (0.48)	12 (0.71)
≥ 5 x ULN	3 (0.18)	3 (0.18)	9 (0.53)	1 (0.06)	2 (0.12)	5 (0.29)
≥ 10 x ULN	0	1 (0.06)	1 (0.06)	0	0	1 (0.06)

*all patients ≥1 post-baseline measurement (≤1 x ULN and >1 x ULN) *plus* patients with missing baseline (no patient with missing baseline had elevated post-baseline levels)
n = number of patients with at least 1 observation in both the baseline and post-baseline category; TZP = tirzepatide; ULN = upper level of normal

It is noted that some of the aforementioned patients with elevated ALT/AST levels started already with increased enzyme levels at baseline and/or may have had a history of confounding hepatic diseases like steatosis, NAFLD, hepatitis E or hepatomegaly. Moreover, in some of the patients with ALT/AST elevations ≥3 x ULN, the high enzyme levels were only detected once and returned to the normal range for the duration of the study. Thus, no clear conclusion on a potential causative role of TZP can be drawn.

However, hepatotoxicity of TZP is considered unlikely, as the applicant provided a *drug-induced serious hepatotoxicity (eDISH)* plot, revealing that none of the patients met the criteria for Hy's law. Moreover, as

mentioned above, ALT, AST and ALP were more prominently reduced from baseline to week 52 at higher TZP doses as compared to lower doses in AS2.

Gallbladder-related disorders

AS1: Of 12 TZP-treated patients with ≥1 TEAE of hepatobiliary disorders, 4 (0.6%) had gallbladder disease; all were in the TZP 5 mg group (no serious/severe event; no study drug discontinuation).

AS2: Of 146 TZP-treated patients with ≥1 TEAE of hepatobiliary disorders, 51 (1.00%) had gallbladder disease (independently of TZP dose; mostly cholelithiasis and cholecystitis). A numerically higher percentage of patients reported ≥1 TEAE of gallbladder disease in the pooled TZP group (TZP_ALL) as compared to the comparator group across the phase 3 studies (**Table 12**).

Table 12: Summary of gallbladder-related TEAEs in phase 3 studies

Treatment Arm	Patients with ≥1 TEAE						
	GPGK	GPGL	GPGH	GPGI	GPGM	GPGO	GPGP
TZP_ALL, n/N (%)	2/363 (0.6)	15/1409 (1.1)	10/1077 (0.9)	2/355 (0.6)	14/995 (1.4)	4/447 (0.9)	4/443 (0.9)
Comparator, n/N (%)	0/115 (0)	3/469 (0.6)	1/360 (0.3)	0/120 (0)	13/1000 (1.3)	0/159 (0)	- -

Abbreviations: N = total number of patients in treatment group, n = total number of patients reporting at least 1 TEAE; TEAE = treatment-emergent adverse event; TZP = tirzepatide.

In AS2, 16 TZP-treated patients reported serious/severe gallbladder-related events, mostly cholelithiasis (TZP_ALL: n=7/0.14%) and cholecystitis (TZP_ALL: n=6/0.12%). 14 of these patients had cholecystectomy during the studies. An increase in gallbladder complications, specifically cholelithiasis, is known from other established GLP1 receptor agonists and would also be expected with TZP.

Moreover, a rapporteur's search for imbalances in MedDRA PTs in the phase 3 study reports revealed an increased occurrence of "gallbladder polyp" with TZP 15 mg as compared to lower TZP doses or control groups in AS2 (TZP 5 mg: 3 [0.2%]; TZP 10 mg: 0 [0.0%]; TZP 15 mg: 11 [0.6%] vs. comparator: 1 [0.1%]). It is noted that 6 of the 11 patients affected in the 15 mg group were still in the dose escalation phase. Moreover, in 8 of the patients the Gallbladder polyps were only an incidental finding. Finally, 8 of the 11 cases of gallbladder polyp in the 15-mg group occurred in the Japan studies, and the literature suggests that the prevalence of gallbladder polyps in adults may be higher in East Asian populations. No relevant difference between TZP and placebo groups was visible with regard to this AE in datasets AS1 (0.3% and 0.4%, respectively) and AS4 (0.2% and 0%, respectively).

Major Depressive Disorder/Suicidal Ideation or Behaviour

Eating may be a compensatory behavior in some patients, producing positive emotions and satisfaction and helping to cope with difficult life situations. TZP-associated AEs like loss of appetite, nausea and vomiting could precipitate or worsen depressive episodes in predisposed patients.

In this regard, it is noted that in AS2, more cases of depression (excl. suicide and self-injury) were reported for the TZP 15 mg group as compared to the other dosing groups (TZP 5 mg: 11 [0.65]; 10 mg: 4 [0.24] and 15 mg: 20 [1.17]). This was mainly driven by the PT "depression" (TZP 5 mg: 6 [0.35]; 10 mg: 3 [0.18] and 15 mg: 16 [0.93]).

Four patients (0.08%; none considered related to study drug) experienced ≥1 SAE of major depressive disorder or suicide/self-injury:

TZP 5 mg: 1 (0.06%); intentional overdose
TZP 15 mg: 3 (0.17%); death (depression suicidal); suicide attempt; major depression

It is noted that depression may potentially be associated with rather unspecific symptoms ("masked depression"). An analysis of the PTs asthenia, malaise or fatigue shows that these symptoms dose-dependently increased across the TZP dose-groups and occurred more frequently with TZP as compared to placebo.

In AS1, at least 1 TEAE of major depressive disorder or suicidal ideation occurred in 5 (0.5%) patients (TZP 5 mg: 1 [0.4%]; 10 mg: 1 [0.4%]; 15 mg: 2 [0.8%] and placebo: 1 [0.4%]). No serious or severe major depressive disorder or suicidal ideation events were reported.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

No deaths were reported in the biopharmaceutic/clinical pharmacology studies. In AS2, death occurred in 20 (1.18%), 8 (0.47%) and 13 (0.76%) cases with TZP 5 mg, 10 mg and 15 mg, respectively (TZP_ALL: 41 [0.8%]). With comparator, 39 deaths (1.7%) occurred in AS2 **(Table 13)**. The most frequently reported cause of death was "*sudden cardiac death*", followed by "*undetermined*" and "*infection*". There was no major imbalance between treatment groups (**Table 13**). The adjusted estimates (considering different randomization ratios and differences in patient populations among strata), yielded 1.0% (TZP_ALL) and 1.2% (comparator) deaths.

Table 13: Cause of death as adjudicated by CEC (AS2)

Cause of death as adjudicated by CEC	n (%)							
	TZP 5 mg (N=1756)	**TZP 10 mg (N=1753)**	**TZP 15 mg (N=1825)**	**Insulin degludec (N=360)**	**Insulin glargine (N=1000)**	**Sema 1 mg (N=469)**	**Dula 0.75 mg 1.5 mg (N=213)**	**Placebo (N=312)**
Total	20	8	13	1	35	1	0	2
Sudden cardiac death	4	3	5	0	7	0	0	1
Undetermined	7	2	3	0	12	0	0	0
Infection	6	2	2	1	8	0	0	1
Malignancy	2	1	0	0	2	0	0	0
Pulmonary	0	0	2	0	2	1	0	0
Suicide	0	0	1	0	0	0	0	0
Other: Massive pulmonary embolism	1	0	0	0	0	0	0	0
Acute myocardial infarction	0	0	0	0	1	0	0	0
Cardiovascular procedure	0	0	0	0	1	0	0	0
Non-cardiovasc. procedure or surgery	0	0	0	0	1	0	0	0
Trauma	0	0	0	0	1	0	0	0

Abbreviations: CEC = clinical endpoint committee; Dula = dulaglutide; N = number of patients in treatment group; n = number of patients; Sema = semaglutide; TZP = tirzepatide.

Note: The adjusted estimates (considering different randomization ratios and differences in patient populations among strata), yielded 1.0% (TZP_ALL) and 1.2% (comparator) deaths.;

Note: The randomization ratio for Study GPGM was 1:1:1:3 (TZP 5 mg: TZP 10 mg: TZP 15 mg: insulin glargine), while other Phase 3 studies with a comparator arm were 1:1:1:1 (TZP 5 mg: TZP 10 mg: TZP 15 mg: comparator).

Other SAEs

In AS1, the number of patients with ≥1 SAE was similar across TZP groups, and between pooled TZP groups and placebo (TZP 5 mg: 14 [5.9%]; 10 mg: 15 [6.3%]; 15 mg: 10 [4.1%] and placebo: 13 [5.5%]). The most common SAEs (≥0.5% in TZP_ALL) were in the following SOCs:

Cardiac disorders:	TZP_ALL: 9 (1.3%) *vs.* placebo: 4 (1.7%)
Infections and infestations	TZP_ALL: 8 (1.1%) *vs.* placebo: 1 (0.4%)
Respiratory, thoracic and mediastinal disorders	TZP_ALL: 5 (0.7%) *vs.* placebo: 1 (0.4%)
Neoplasms benign, malignant and unspecified	TZP_ALL: 4 (0.6%) *vs.* placebo: 2 (0.9%)
Nervous system disorders	TZP_ALL: 4 (0.6%) *vs.* placebo: 1 (0.4%)

SAEs in the SOC "infections and infestations" occurred more than twice as frequently with TZP than with placebo in analysis set AS1.

In AS2, the number of patients with ≥1 SAE was similar across TZP groups (TZP 5 mg: 134 [7.88%]; 10 mg: 135 [7.93%]; 15 mg: 122 [7.11%]). The most common SAEs (≥0.5% in TZP_ALL) were in the following SOCs:

Infections and infestations	TZP_ALL: 93 (1.82%)
Cardiac disorders:	TZP_ALL: 87 (1.70%)
Neoplasms benign, malignant and unspecified	TZP_ALL: 47 (0.92%)
Nervous system disorders	TZP_ALL: 36 (0.70%)

In the SOC "*Cardiac disorders*", the number of events tended to decrease with increasing TZP dose. Most frequently, acute myocardial infarction, COVID-19 pneumonia and coronary artery disease were reported.

Analysis of SAEs on individual phase 3 study level revealed the lowest percentage of affected patients in study GPGK (no background treatment; TZP_ALL: 2.2%; comparator: 2.6%). Highest percentages were reported for studies GPGI (background: insulin glargine; TZP_ALL: 8.7%; comparator: 8.3%) and GPGM (background: 1-3 OADs; TZP_ALL: 9.8%; comparator: 13.0%). In GPGL, SAEs occurred more than twice as frequently with TZP_ALL (6.0%) as compared to the control group (2.8%).

2.6.8.4. Laboratory findings

Laboratory findings regarding renal safety (UACR, eGFR), exocrine pancreas safety (p-amylase and lipase), thyroid safety (calcitonin), immunogenicity and hepatobiliary safety (ALT, AST, bilirubin, ALP) are discussed in the corresponding subsections above ("AEs of special interest").

Hemoglobin/Anemia

In AS1, a slight decrease from baseline in haemoglobin (Hb) was observed in all groups including plc. This effect was somewhat more pronounced in the TZP groups and, accordingly, more subjects shifted from normal to low Hb in the combined TZP than in the plc group (16.3% vs. 9.2%). Anaemia was reported infrequently in TZP-treated patients in AS1 (TZP_ALL: 1.1% *vs.* placebo: 0%).

In AS2, the percentage of patients with anemia ranged from 0.2% to 2.5% with TZP and from 0% to 3.5% with comparator, with no consistent pattern between studies. In Study GPGM (largest study, longest treatment duration, about 1:1 randomization to TZP_ALL or comparator insulin glargine), the percentage of patients with ≥1 TEAE of anaemia was similar in TZP- and insulin glargine-treated patients (2.5% and 3.5%, respectively) **(Table 14)**.

Table 14: Summary of Treatment-Emergent Anaemia in Phase 3 Studies Safety Population

Treatment Arm	Patients with ≥1 TEAE of Anemia						
	GPGK	**GPGL**	**GPGH**	**GPGI**	**GPGM**	**GPGO**	**GPGP**
TZP_ALL, n/N(%)	3/363 (0.8)	23/1409 (1.6)	17/1077 (1.6)	5/355 (1.4)	25/995 (2.5)	1/477 (0.2)	3/443 (0.7)
Comparator[a] , n/N (%)	0/115 (0)	4/469 (0.9)	3/360 (0.8)	0/120 (0)	35/1000 (3.5)	1/159 (0.6)	-- --
N = total number of patients in treatment group; n = total number of patients reporting ≥1 treatment-emergent adverse event (TEAE) [a]Refer to Table 1 for information on comparator arms.							

Anaemia is common in patients with T2DM and kidney disease, and the observation that haemoglobin decreased over time in all treatment groups (including placebo) probably reflects the development of the underlying disease. Overall, the data do not suggest that low hemoglobin or anaemia are safety concerns with TZP treatment.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Age

The applicant presents an overview of AE categories by age group for safety analysis set AS3 (phase 2/3 program). Increases in the percentage of patients with increased age were shown for SAEs, AEs leading to study drug discontinuation, accidents and injuries, cardiac and vascular disorders (**Table 15a**).

Table 15a: Overview of adverse events by age category, TZP_ALL group of safety population phase 2/3 analysis set (AS3)

Event Category	Age: < 65 (N=3815)	Age: 65-74 (N=1387)	Age: 75-84 (N=206)	Age: >=85 (N=7)
	n (%)	n (%)	n (%)	n (%)
Total TEAEs	2696 (70.67)	998 (71.95)	155 (75.24)	4 (57.14)
SAEs	237 (6.21)	131 (9.44)	31 (15.05)	1 (14.29)
Fatal	24 (0.63)	12 (0.87)	4 (1.94)	1 (14.29)
Hospitalization	213 (5.58)	117 (8.44)	31 (15.05)	0
Life-Threatening	35 (0.92)	16 (1.15)	2 (0.97)	0
Disability	15 (0.39)	2 (0.14)	1 (0.49)	0
Other	37 (0.97)	26 (1.87)	2 (0.97)	0
AEs leading to study drug discontinuation	247 (6.47)	165 (11.90)	46 (22.33)	2 (28.57)
Accidents and injuries (SMQ)	196 (5.14)	89 (6.42)	18 (8.74)	1 (14.29)
Cardiac disorders (SOC)	167 (4.38)	81 (5.84)	27 (13.11)	1 (14.29)
Infections and infestations (SOC)	987 (25.87)	348 (25.09)	54 (26.21)	2 (28.57)
Nervous system disorders (SOC)	443 (11.61)	136 (9.81)	18 (8.74)	0
Psychiatric disorders (SOC)	96 (2.52)	34 (2.45)	5 (2.43)	0
Vascular disorders (SOC)	172 (4.51)	87 (6.27)	16 (7.77)	1 (14.29)

CNS vascular disorders (SMQ)	28 (0.73)	13 (0.94)	2 (0.97)	0
Quality of life decreased (PT)	0	0	0	0
Fractures *a	37 (0.97)	21 (1.51)	3 (1.46)	0
Hypotension, falls, fractures (LCQ) *b	96 (2.52)	58 (4.18)	13 (6.31)	1 (14.29)
*a HLTs: a) Fractures and dislocations NEC, b) Limb fractures and dislocations, c) Pelvic fractures and dislocations, d) Skull fractures, facial bone fractures and dislocations, e) Spinal fractures and dislocations, f) Thoracic cage fractures and dislocation *b 6 HLTs for fracture (see above), HLGT: Decreased and nonspecific blood pressure disorder and shock, PT of Fall				

Moreover, the applicant presented an overview of AE categories by age group for safety analysis set AS2 (phase 3 program). Tables 15b and 15c show the age-dependent frequencies of AEs for the pooled TZP-treated patients (TZP_ALL) and the pooled comparator groups, respectively.

Table 15b: Overview of adverse events by age category, **TZP_ALL** group of safety population phase 3 analysis set **AS2** (GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, GPGP):

Event Category	< 65 (N=3580)	65-74 (N=1327)	75-84 (N=205)	>=85 (N=7)
	n (%)	n (%)	n (%)	n (%)
Total TEAEs	2516 (70.28)	962 (72.49)	154 (75.12)	4 (57.14)
SAEs	231 (6.45)	128 (9.65)	31 (15.12)	1 (14.29)
Fatal	24 (0.67)	12 (0.90)	4 (1.95)	1 (14.29)
Hospitalization	207 (5.78)	114 (8.59)	31 (15.12)	0
Life-Threatening	34 (0.95)	15 (1.13)	2 (0.98)	0
Disability	15 (0.42)	2 (0.15)	1 (0.49)	0
Other	37 (1.03)	26 (1.96)	2 (0.98)	0
AEs leading to study drug discontinuation	226 (6.31)	162 (12.21)	45 (21.95)	2 (28.57)
Accidents and injuries (SMQ)	181 (5.06)	85 (6.41)	18 (8.78)	1 (14.29)
Cardiac disorders (SOC)	160 (4.47)	78 (5.88)	27 (13.17)	1 (14.29)
Infections and infestations (SOC)	931 (26.01)	335 (25.24)	54 (26.34)	2 (28.57)
Nervous system disorders (SOC)	399 (11.15)	130 (9.80)	18 (8.78)	0
Psychiatric disorders (SOC)	89 (2.49)	33 (2.49)	5 (2.44)	0
Vascular disorders (SOC)	167 (4.66)	83 (6.25)	16 (7.80)	1 (14.29)
CNS vascular disorders (SMQ)	28 (0.78)	12 (0.90)	2 (0.98)	0
Quality of life decreased (PT)	0	0	0	0
Fractures *a	33 (0.92)	21 (1.58)	3 (1.46)	0
Hypotension, falls, fractures (LCQ) *b	92 (2.57)	56 (4.22)	13 (6.34)	1 (14.29)

Table 15c: Overview of adverse events by age category, **pooled comparator** group of safety population phase 3 analysis set **AS2** (GPGK, GPGL, GPGH, GPGM, GPGI, GPGO, GPGP):

Event Category	< 65 (N=1407)	65-74 (N=673)	75-84 (N=136)	>=85 (N=7)
	n (%)	n (%)	n (%)	n (%)
Total TEAEs	897 (63.75)	460 (68.35)	90 (66.18)	6 (85.71)
SAEs	122 (8.67)	102 (15.16)	31 (22.79)	0
Fatal	11 (0.78)	17 (2.53)	10 (7.35)	0
Hospitalization	112 (7.96)	92 (13.67)	28 (20.59)	0
Life-Threatening	20 (1.42)	24 (3.57)	7 (5.15)	0
Disability	5 (0.36)	3 (0.45)	2 (1.47)	0
Other	23 (1.63)	19 (2.82)	6 (4.41)	0
AEs leading to study drug discontinuation	44 (3.13)	35 (5.20)	14 (10.29)	0
Accidents and injuries (SMQ)	89 (6.33)	48 (7.13)	17 (12.50)	1 (14.29)
Cardiac disorders (SOC)	79 (5.61)	63 (9.36)	20 (14.71)	1 (14.29)
Infections and infestations (SOC)	423 (30.06)	194 (28.83)	42 (30.88)	3 (42.86)
Nervous system disorders (SOC)	157 (11.16)	84 (12.48)	26 (19.12)	2 (28.57)
Psychiatric disorders (SOC)	38 (2.70)	16 (2.38)	4 (2.94)	0
Vascular disorders (SOC)	98 (6.97)	56 (8.32)	13 (9.56)	0

CNS vascular disorders (SMQ)	9 (0.64)	12 (1.78)	3 (2.21)	0
Quality of life decreased (PT)	0	0	0	0
Fractures *a	14 (1.00)	12 (1.78)	6 (4.41)	0
Hypotension, falls, fractures (LCQ) *b	31 (2.20)	23 (3.42)	14 (10.29)	1 (14.29)

Due to the low number of subjects aged ≥85 years, it is virtually impossible to draw reliable conclusions on tolerability of TZP in this age group.

Regarding subjects <65, 65-74 and 75-84 years:

- The percentage of total TEAEs was numerically higher across all three age groups in the TZP_ALL group vs. pooled comparator. However, the SAEs were numerically reduced in the TZP_ALL vs. the pooled comparator group.
- Most event categories are numerically lower (or at least unchanged) in the TZP-treated patients (TZP_ALL) as compared to the pooled comparator group.
- However, the category "AEs leading to study drug discontinuation" is strongly increased in TZP-treated patients (TZP_ALL) as compared to the pooled comparator group, specifically in the higher age groups (e.g., 21.95 % discontinue TZP treatment due to AEs in the 75-84 age group, but only 10.29 % of this age group discontinue comparator treatment). It is suspected that this category may be driven by gastrointestinal events.
- It is reassuring that no event of the category "quality of life decreased" is listed for TZP-treated patients.

Gastrointestinal AEs in the elderly:
An additional analysis of gastrointestinal AEs across age groups in the TZP_ALL group (AS2 dataset) revealed a slightly increased frequency in patients aged 75-84 years than in younger patients (<65: 43.77%; 65-74: 42.80%; 75-84: 45.85%). This tendency was specifically visible for diarrhoea and vomiting:

AS2:
Diarrhoea: TZP_ALL: <65: 15.45% 65-74: 12.89% 75-84: 19.02 %
Vomiting: TZP_ALL: <65: 7.65% 65-74: 7.16% 75-84: 11.22 %

No such trend was visible for vomiting and diarrhoea in the comparator group.

Table 16 below shows that the percentage of patients discontinuing due to gastrointestinal AEs increased with age in the TZP_ALL group of dataset AS2, while no such trend occurred in the comparator group.

Table 16: Summary of GI-related and unrelated AEs leading to study drug discontinuation by age group (AS2 dataset)

AEs leading to discontinuation of study drug[a]	<65 years		65-74 years		75-84 years	
	TZP All (N = 3580)	Comp. (N =1407)	TZP All (N = 1327)	Comp. (N = 673)	TZP All (N = 205)	Comp. (N = 136)
	n (%)					
Total	226 (6.3)	44 (3.1)	162 (12.2)	35 (5.2)	45 (22.0)	14 (10.3)
GI-related	112 (3.1)	13 (0.9)	83 (6.3)	4 (0.6)	22 (10.7)	1 (0.7)
Not GI-related	114 (3.2)	31 (2.2)	79 (6.0)	31 (4.6)	23 (11.2)	13 (9.6)

Renal or hepatic insufficiency

In the clinical pharmacology study (I8F-MCGPGG), which investigated the PK of 5 mg of TZP (single s.c. dose) in subjects with varying levels of renal impairment, no clinically relevant effects of renal impairment on the PK of TZP were observed. Therefore, no dose adjustments were recommended in patients with renal impairment or in patients undergoing dialysis. There is only limited data on patients with eGFR <30 mL/min/1.73 m^2.

Patients with hepatic impairment were excluded from the Phase 3 program. To evaluate the use of TZP in patients with hepatic impairment, the clinical pharmacology study GPGQ was conducted, where no clinically relevant effects of hepatic impairment were observed on the PK of TZP. No long-term clinical data on hepatic impairment are available.

GI disease

No data on patients with severe GI disease are available.

2.6.8.7. Immunological events

Immunogenicity

The applicant provided an extensive analysis of anti-drug antibodies (ADA) as summarized in the following. The other aspects of immunogenicity, systemic hypersensitivity reactions and injection site reactions, are discusses as AEs of special interest in the respective section above. In this section the relationship between the presence of ADA and the incidence of hypersensitivity and injection site reactions will be summarized.

Analytical methods for ADA detection

Binding antibodies

The assay principle was a so-called affinity capture and elution (ACE) approach, which employs 2 TZP analogues, GIP735 with a single biotin in place of the fatty acid, and GIP740 with a single N-terminal biotin. This approach served to control the biotin placement and to minimize nonspecific labelling. The positive control material was isolated from cynomolgus monkeys hyperimmunised with ovalbumin-coupled TZP, yielding serum with an approximate titre of 1:102,400 against the drug.

The assay encompassed the following consecutive steps (tiers): **Tier 1** was a screening assay, where ADA was detected as described above without further control for specific binding. Any sample yielding a signal ratio ≥the Tier 1 floating cut point factor was transferred to Tier 2a; all other samples with lower signal ratios were reported as "not detected". In **Tier 2a**, an excess of unlabelled TZP was added to the assay to control for specific binding. Samples with a percent inhibition ≥ the Tier 2a cut point were reported as "detected," and further evaluated in tiers 2b, 2c and 3. In **Tier 2b**, an excess of unlabelled native GIP(1-42) was added to the biotin-labelled TZP analogue-containing detection solution to address cross-reactive binding to native GIP(1-42). Accordingly, in **Tier 2c** cross-reactive binding to native GLP-1(7-36) was addressed by adding excess unlabelled GLP-1(7-36). Finally, in **Tier 3**, confirmed positive samples were serially diluted to identify the highest sample dilution still yielding a response ≥ the titration cut point of the assay, which allowed titer quantitation of ADA confirmed in Tier 2a.

The validation strategy for this assay is summarised in **Table 17** below.

Table 17: Validation Strategy Table

		Ligand Binding ACE Assay				
Validation Experiment		**Tier 1**	**Tier 2a**	**Tier 2b**	**Tier 2c**	**Tier 3**
MRD		✓ →	→	→	→	
Cut Point	Screening	✓				
	Confirmation		✓			
	Cross-reactivity to native GIP			✓		
	Cross-reactivity to native GLP-1				✓	
	Titration					✓
Sensitivity		✓ →	→	→	→	
Drug Tolerance		✓ →	→	→	→	
Titration of a Positive Sample						✓
Precision	Screening Assay (ECL)	✓ →	→	→	→	
	Confirmation (percent inhibition)		✓			
Robustness		✓ →	→	→	→	
Stability		✓ →	→	→	→	
Serum Factor Interference		✓ →	→	→	→	
Quality Control Levels[a]		✓ →	→	→	→	
Quality Control Levels[b]			✓			
Positive Specificity	Positive QCs ECL signal	✓				
	Positive QCs percent inhibition with excess LY		✓			
Negative Specificity	Isotype-matched irrelevant antibody	✓				

Abbreviations: ACE = Affinity Capture and Elution; ECL = electrochemiluminescent; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; MRD = minimum required dilution; QC = quality control.

[a] QC ranges were set on limits of ±40% of the validated mean for each control.

[b] Tier 2 QCs are identical to those in Tier 1, but percent inhibition is monitored with excess tirzepatide.

Neutralising antibody (NAb) assay

For characterization of the neutralizing activity of ADA the following cell-based and in-silico assays were used:

1. Cell-based NAb assay to detect ADA that prevent TZP from activating the GIPR (Tier 4a).
2. Cell-based NAb assay to detect ADA that prevent TZP from activating the GLP1R (Tier 4b).
3. *In silico* classification using Tier 2b/4a results to detect ADA preventing GIPR activation by nGIP.
4. *In silico* classification using Tier 2c/4b results to detect ADA preventing GLP1R activation by nGLP-1.

The *in-silico* approach was chosen for NAbs cross-reacting with endogenous GLP-1 or GIP because the cell-based assays turned out to have a low drug tolerance (i.e. are affected by peptides present in the plasma samples).

The ***in-silico* classification** was performed as follows: Any patient sample with cross-reactivity to native GIP (Tier 2b) and capable of neutralising TZP activity on the GIPR (Tier 4a) will be considered positive for cross-reactive NAb against native GIP. Likewise, any samples positive for cross-reactive ADA to GLP-1 in Tier 2c and positive for NAb in Tier 4b will be considered positive for cross-reactive NAb activity against native GLP-1.

ADA Results

Overview

The evaluated ADA for the safety datasets **AS1** (placebo-controlled studies) and **AS2** (TZP-treated patients in Phase 3 studies). ADA were regarded as treatment-emergent (TE) if they were induced or boostered (i.e., increase in titre) during treatment.

In **AS1**, the following observations were made (similar results in **AS2**, which lacks the comparator group):

At baseline, 77 (8.3%) patients had pre-existing ADA (similar rates with TZP and placebo). The baseline ADA titres ranged from 1:10 to 1:640 (median 1:20). Post-baseline, 695 **TZP**-treated patients were evaluable for TE ADA during the planned treatment period. Of these, 352 (**50.6%**) were TE ADA+. Only a small fraction of ADA (~1%) were neutralising according to the laboratory tests.

In detail:

- 327 (47.1%) were classified as treatment induced
- 25 (3.6%) were classified as treatment boosted
- 226 (32.5%) patients were positive for cross-reactive binding ADA to nGIP
- 92 (13.2%) patients were positive for cross-reactive binding ADA to nGLP-1
- 8 (1.2%) patients were positive for NAb against TZP activity on GIPR
- 7 (1.0%) patients were positive for NAb against TZP activity on GLP-1R
- 5 (0.7%) patients were positive for cross-reactive NAb against nGIP
- 4 (0.6%) patients were positive for cross-reactive NAb against nGLP-1

The maximum titre ranged from 1:20 to 1:40960 (median **1:160**).

In the **placebo** group, 11 patients (**4.8%**) were TE ADA+ during the planned treatment period.

Time-to-First TE ADA+ Titre

The cumulative frequency of TZP-treated patients from each Phase 3 study who had developed TE ADA by specific time points shows that the Time-to-first TE ADA+ titre followed similar profiles across all Phase 3 studies; most ADAs developed within 40 weeks. In detail:

- 4.6 to 10.7% (median **7.2%**) developed TE ADA by **12** weeks,
- 19.9 to 38.2% (median **25.6%**) by **24** weeks,
- 31.4 to 58.4% (median **45.9%**) up to **40** weeks,
- 38.4 to 65.5% (median **50.5%**) up to **52** weeks, and
- 40.7 to 67.6% (median **54.2%**) up to **78** weeks (includes GPGH, GPGM, GPGO, and GPGP studies only).

The median titre was highest between Week 40 and Week 52 (up to 1:160) and decreased thereafter (1:80 or 1:40).

Persistence of ADA

Persistent ADA was defined as TE ADA detected at 2 or more sampling time points, with the first and last ADA+ samples separated by ≥16-weeks. Transient ADA was defined as TE ADA detected with the first and

last ADA+ samples separated by a period of <16 weeks and with TE ADA not detected at the last sampling time point. Other constellations were regarded as potentially persistent.

In the TE ADA+ patients, ADA were

- persistent in 72.3% of cases
- potentially persistent in 11.9%
- transient in 15.8 % of cases.

In absolute terms, of the patients treated with tirzepatide (any dose), 38.3 % developed persistent ADA.

Effect of ADA on PK (clearance)

No relationship between the presence of ADA and the clearance of TZP was detectable. The applicant also investigated the relationship between ADA titres and clearance, revealing a tendency to slightly lower TZP clearance with higher ADA titres, but the number of patients with high titres is low. Therefore, no firm conclusions are possible.

Effect of ADA on treatment outcome (HbA1c)

In mean, ADA+ patients displayed a slightly lower HbA1c reduction in most studies. In Studies **GPGL** and **GPGM** some patients had a very poor glycaemic control. Notably, these outliers were mainly found among the ADA+ patients. The applicant also presented an analysis on the relationship between ADA titre (≥1:5120 vs. <1:5120) and HbA1c level. According to this analysis, the outliers were in the low-titre group, i.e. the poor glycaemic control was not due to high ADA titres. Also, the applicant provides an evaluation of HbA1c level in relation to the presence of neutralising antibodies (as identified by the in-vitro assays described above). No meaningful conclusions can be drawn from this evaluation. This may be due to the low number of patients with NAbs.

In summary, a small effect of ADA on the efficacy of TZP cannot be excluded, but due to the small size, it is not considered clinically relevant.

Correlation of ADA and hypersensitivity reactions / injection site reactions

Of the 179 total TZP-treated patients with **hypersensitivity reactions** during the planned treatment period, 106 were TE ADA+ and 73 were TE ADA-. One ADA+ patient had a severe hypersensitivity reaction. The other events were mild or moderate in severity.

Of the 137 total TZP-treated TE ADA-evaluable patients with **injection site reaction** (prespecified MedDRA search) during the planned treatment period, 119 were TE ADA+ and 18 were TE ADA-.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Similar to established GLP1 receptor agonists, TZP delays gastric emptying and intestinal transit time. This may result in altered absorption of other orally administered concomitant medications, potentially altering PK parameters like C_{max} and T_{max}. The influence of TZP on gastrointestinal function was addressed in phase 1 study GBGA (acetaminophen as a probe to assess gastric emptying). Physiologically based PK modelling was conducted instead of drug-drug interaction studies for acetaminophen, lisinopril, metoprolol, digoxin, oral contraceptives, atorvastatin, sitagliptin, metformin and warfarin. In addition, the drug-drug interaction study GPGR was conducted to evaluate the interaction of TZP with combination oral contraceptives in healthy female subjects.

2.6.8.9. Discontinuation due to adverse events

In AS1, a higher percentage of TZP- than placebo-treated patients permanently discontinued study drug due to an AE (non-specific reasons excluded), with an incremental increase across TZP doses (TZP 5 mg: 11 [4.6%]; 10 mg: 16 [6.7%]; 15 mg: 21 [8.7%]; placebo: 6 [2.6%]). The most frequent AEs causing discontinuation were from the SOC *gastrointestinal disorders*. This was confirmed by AS2 (TZP 5 mg: 121 [7.11%]; 10 mg: 145 [8.52%]; 15 mg: 169 [9.85%]), with SOC gastrointestinal disorders (mostly nausea, diarrhoea and vomiting) responsible for ~50% of all discontinuations. The incremental increase across TZP doses (5 mg: n=2; 10 mg: n=33; 15 mg: n=42) in AS2 is illustrated by the Kaplan-Meier plot in **Figure 2**.

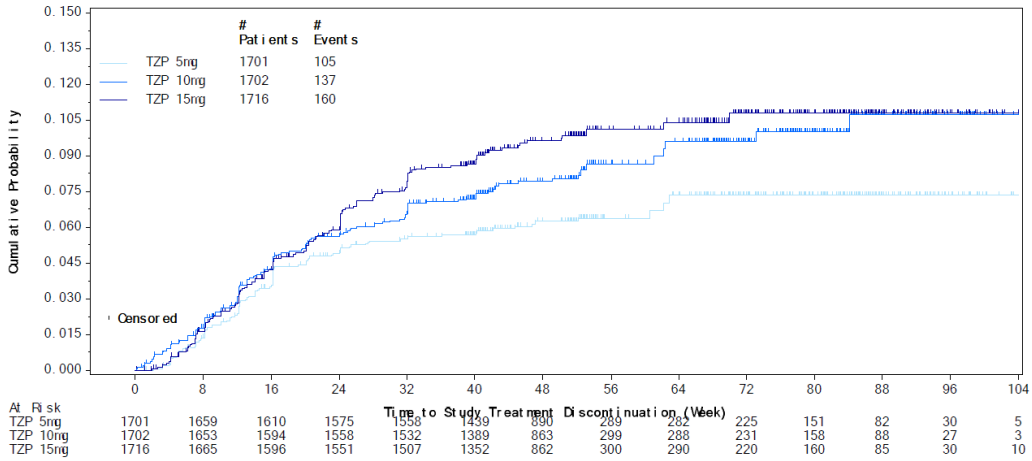


Figure 2: Kaplan-Meier plot of time to premature study treatment discontinuation due to AEs in AS2

It is noted that the curves in **Figure 2** separate at the end of the dose escalation period (i.e., after week 24). Across all TZP treatment groups, 53.1% of patients discontinued prior to receiving their maintenance dose. In GPGH, GPGM and GPGP, the option to de-escalate the dose (TZP 10 mg → 5 mg or TZP 15 mg → 10 mg) was used by 104 (14.4%), 101 (15.2%) and 34 (11.5%) patients, respectively. A comparison of the reasons for treatment discontinuation earlier in the study (0-24 weeks) vs. later (>24 weeks) confirms that gastrointestinal AEs play a larger role during the dose escalation phase. A similar effect can be seen for more unspecific AEs like "malaise" or "asthenia". Furthermore, two cases of "abnormal loss of weight" occurred as reasons for treatment discontinuation after >24 weeks.

As illustrated by **Table 16** above, the percentage of patients discontinuing due to gastrointestinal AEs increased with age in the TZP_ALL group of dataset AS2, while no such trend occurred in the comparator group.

Comparison with GLP1 agonists:
In study GPGL, more patients discontinued study drug due to gastrointestinal AEs in the TZP 10 mg (20 [4.3%]) and 15 mg (20 [4.3%]) group as compared to sema 1 mg (15 [3.2%]). In study GPGO (conducted in Japan), more patients discontinued due to a gastrointestinal AE with TZP (any dose group) than with dula 0.75 mg (TZP 5 mg: 7 [4.4%]; 10 mg: 4 [2.5%]; 15 mg: 11 [6.9%]; dula: 1 [0.6%]).

2.6.8.10. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

Safety analysis sets, exposure and discontinuations
The applicant has provided five safety analysis sets (AS). AS1 (phase 3) and AS4 (phase 2/3) only include placebo-controlled studies; AS2 and AS3 comprise all phase 3 and phase 2/3 studies, respectively. For AS1 and AS4, the applicant compares TZP *vs.* placebo, for AS2 an analysis TZP *vs.* comparator is presented. Moreover, AS2 compares the different TZP dose levels. For AS3, only a summary was presented, but no comparison was performed (neither between TZP dosing groups, nor between TZP and comparator). For AS5, which focuses on cardiovascular risk assessment, a comparison of TZP vs. comparator groups is provided.

The population exposed to TZP and the exposure duration (5415 patients received TZP for 4833.1 patient-years) is considered sufficient to detect AEs of reasonable frequency (0.5 - 5%) and to elucidate, whether frequently occurring AEs increase or decrease over time. Long-term exposure (>2000 patients exposed to TZP for ≥52 weeks) is considered adequate. Thus, exposure corresponds to the recommendations of the "Note for Guidance on Population Exposure" (CPMP/ICH/375/95).

As expected with a GLP1 receptor agonist, a large part of study drug discontinuations was due to gastrointestinal AEs, particularly in elderly subjects. In clinical reality, this would be addressed by dose reduction, an option, which was available and used in studies GPGH, GPGM and GPGP of the TZP program. The curves in the discontinuation Kaplan Meier Plot of AS2 separate at the end of the dose escalation period (week 24). A comparison of the reasons for treatment discontinuation earlier in the study (0-24 weeks) vs. later (>24 weeks) confirms that gastrointestinal AEs play a larger role during the dose escalation phase. A similar effect can be seen for more unspecific AEs like "malaise" or "asthenia". The occurrence of two cases of "abnormal loss of weight" as reasons for treatment discontinuation after >24 weeks underlines that caution should be exercised when treating non-overweight patients with TZP.

AEs, including AEs of special interest (AESIs)
Although TZP shows a safety profile similar to other GLP1 receptor agonists, the 10 mg and/or 15 mg dose caused more gastrointestinal, pancreatic, hypoglycaemic and systemic (such as asthenia) AEs and decreased blood pressure to a larger extent than semaglutide 1 mg or dulaglutide 0.75 mg. It should be noted, however, that, semaglutide and dulaglutide could have been under-dosed in relation to TZP because the GLP-1RAs were used in their antidiabetic dose, while TZP also caused marked weight reduction (which requires higher doses as known from liraglutide), precluding *on par* comparison with TZP.

The applicant has analysed the following AESIs: gastrointestinal AEs, dehydration, renal safety, metabolic acidosis, exocrine pancreas safety, thyroid safety, hypoglycaemia, severe persistent hyperglycaemia, cardiovascular safety, amputation or peripheral revascularization, hypersensitivity reactions, injection site reactions, immunogenicity, diabetic retinopathy complications, hepatobiliary disorders, malignancy and major depressive disorder/suicidal ideation or behaviour.

The most common TEAEs (≥5%) were gastrointestinal AEs, mostly nausea, vomiting and diarrhoea, occurring specifically during the phase 3 study dose escalation phase. However, the dose escalation effectively mitigated gastrointestinal AEs in comparison to phase 2, where no such phase was included. TZP did not increase severe GI TEAEs in comparison to placebo. It seems that the prevalence of vomiting remains increased with TZP 15 mg throughout the study duration as compared to the first 4 weeks, and GI AEs appear to persist for a longer time at safety follow-up. According to the applicant, the appearingly prolonged prevalence of vomiting is mainly driven by study GPGM, which had a longer duration than all other studies in AS2. In addition, the prevalence of vomiting may have additionally been prolonged by the study centres keeping an AE open in case of intermittent episodes of vomiting. It is noted that this may have led to an underestimation of the number of

AEs of vomiting. Regarding the persistence of vomiting during the safety follow-up, this could be explained with the long half-life of TZP, which may have prolonged the AE e.g., after study discontinuation due to GI AE.

In general, gastrointestinal AEs are considered not of major concern, as they would be managed in clinical reality by dose adjustment. It is noted that no data on patients with severe GI disease are available. However, a slight increase of the frequencies of diarrhoea and vomiting was observed in TZP-treated patients aged 75-84 years as compared to younger age groups. Moreover, the percentage of patients discontinuing due to gastrointestinal AEs increased with age in the TZP_ALL group of dataset AS2, while no such trend occurred in the comparator group. For elderly, electrolyte disturbance or dehydration caused by nausea and vomiting may be particularly hazardous. This is reflected in the SmPC.

TZP did not appear to significantly worsen kidney function in T2DM patients. However, it is noted that there is only limited data on patients with eGFR <30 mL/min/1.73 m^2. Two patients (both randomized to TZP 15 mg) showed a very fast decline in renal function. However, both patients had pre-existing conditions of diabetic nephropathy at baseline and received concomitant therapy with confounding medications (omeprazole and amoxicillin). Thus, it is difficult to conclude on a causative role of TZP. In general, the safety data generated in the TZP development program do not indicate a nephrotoxic effect of TZP or glomerular damage by ADA-containing immune complexes.

The PT of "renal cyst" was increased with TZP 10 and 15 mg as compared to control. However, it is noted that out of the 36 TZP-treated patients with renal cysts in AS2, 15 had a pre-existing condition of kidney-related disease. Renal cysts are often asymptomatic and only reported as incidental findings and their incidence is increased in patients with T2DM. Thus, it is difficult to firmly establish a connection with TZP treatment. No difference in the incidence of renal cysts as compared to placebo was observed in the placebo-controlled datasets AS1 and AS4.

Thyroid safety was a pre-defined AESI, since C cell hyperplasia and thyroid carcinomas were observed with TZP in rodents in line with what has been reported for other long-acting GLP-1 agonists. It is reassuring that no case of medullary thyroid carcinoma (MTC) or C-cell hyperplasia was reported in the phase 2/3 clinical studies. However, the risk for developing MTC cannot be fully explored from controlled data in the clinical trial program covering rather short observation periods. Moreover, it is noted that detection of C-cell hyperplasia would require special diagnostics so that it would not be detected and reported in most cases. The applicant has performed more detailed endocrinological evaluation in the small subset of patients with very high calcitonin levels.

Across the phase 3 study program, mean serum calcitonin levels were higher with TZP than with comparator. Of note, the comparators semaglutide 1 mg and dulaglutide 0.75 mg did not increase calcitonin, suggesting that the slight calcitonin increase is a peculiarity of tirzepatide. Furthermore, the PT "blood calcitonin increased" was also reported more frequently in TZP-treated patients as compared to control groups. Of note, the applicant's calcitonin assays did not show cross-reactivity with procalcitonin, and it is considered unlikely that procalcitonin was inadvertently detected during the calcitonin measurements. Procalcitonin was not determined in the TZP clinical program. Although the calcitonin elevations were usually reversible and not acutely clinically relevant (mostly within normal range), the long-term consequences (e.g. increased risk of C-cell malignancy) are currently unclear. An underlying mechanism could not be established. However, MTC has been adequately proposed to be included in the RMP, in line with other GLP-1 agonists. Serum amylase and lipase increased with TZP treatment, in line with what has been described with other incretin-based treatment. In the placebo-controlled dataset AS1, more TZP- than placebo-treated subjects exhibited an increase in serum amylase from normal (<1×ULN) levels at baseline to postbaseline values of >1×ULN to ≤3×ULN (15.9% *vs* 5.1% for TZP *vs* placebo) and of >3×ULN to ≤5×ULN (0.7% *vs* 0% for TZP vs placebo). Moreover, the proportion of subjects

reaching post-baseline lipase values of >3×ULN to ≤5×ULN (2.8% *vs* 0.9% for TZP *vs* placebo) and >5×ULN to ≤10×ULN (0.6% *vs* 0% for TZP *vs* placebo) was higher for TZP as compared to placebo.

TZP may increase the risk of pancreatitis; however, the number of cases was low, which is reassuring. In the phase 2/3 program, the incidence of acute pancreatitis was increased for TZP (0.24%) compared with the comparator group (0.13%; all treated with semaglutide). No adjudicated events of pancreatitis were identified in the integrated analysis of placebo-controlled phase 3 studies (AS1). Notably, many of investigator-reported cases of pancreatitis (47 patients) were adjudicated "no event", the majority (43) due to negative imaging results.

Two cases, #GPGH-109-2671 and #GPGI-300-5214, were adjudicated "no event", despite signs and symptoms of pancreatitis. Patient GPGH-109-2671 had negative imaging results and, according to one of the adjudicators, amylase and lipase were <3 x ULN. In case of patient GPGI-300-5214, symptoms were rather unspecific (dyspepsia) and amylase and lipase were < 3 x ULN, but sonography showed signs of subacute pancreatitis. It is somehow controversial, whether this patient should be considered "event" of acute pancreatitis or "no event" (i.e. pancreatitis, but not acute). A causal relationship between development of pancreatitis and TZP treatment cannot be excluded. Acute pancreatitis as well as increased amylase and increased lipase are labeled in the SmPC Section 4.4 and 4.8.

The hypoglycaemic risk profile of TZP essentially corresponds to the known risk profile of GLP1 receptor agonists. TZP increased hypoglycaemias of the category "BG <54 mg/dL or severe hypoglycaemia" mainly in combination with other glucose-lowering drugs (i.e., insulin glargine or SU), but did not appear to cause such events when used alone. Severe hypoglycaemia was uncommon with TZP treatment.

In AS1, an increase in pulse rate of 3.3-5.2 beats/ minute for TZP vs. 1.0 beat/minute for placebo was noted. In the phase 3 studies, the pulse rate increased in a dose-dependent manner (TZP 5 mg: 4.3 bpm; 10 mg: 4.9 bpm and 15 mg: 5.7 bpm). The magnitude of mean pulse rate was lower when excluding the Japanese studies (3.8 bpm, 4.0 bpm and 4.6 bpm for tirzepatide 5 mg, 10 mg and 15 mg, respectively). The magnitude of mean increase in pulse rate was highest for Japanese patients (6.1 bpm, 7.9 bpm and 9.5 bpm for tirzepatide 5 mg, 10 mg and 15 mg, respectively). Moreover, the incidence of patients who met threshold criteria for abnormal pulse was dose-dependently higher for TZP as compared to placebo. The incidence of patients who had a change of baseline pulse rate of >20 bpm was 9.7%, 12.2% and 15.0% for TZP 5 mg, 10 mg and 15 mg, respectively, compared with 6.4% for placebo. The incidence of patients that had a pulse rate of >100 at any visit was 7.2%, 9.7% and 16.3% for TZP 5 mg, 10 mg and 15 mg, respectively, compared with 6.8% for placebo. Increased pulse rate is therefore included in Section 4.8 of the SmPC. In this context, it is noted that for GLP1 receptor agonists, the maximum pulse rate increase occurs at rest (during the night), and the rate assessed by office measurements (and proposed for Section 5.1 of the SmPC) is not representative. Nevertheless, measuring the night time heart rate for patients treated with TZP is not considered necessary, since the CV safety assessment (AS5) suggests TZP does not lead to excess CV risk. Moreover, further data on cardiovascular safety are going to be gained in a dedicated head-to-head CVOT study between TZP and dulaglutide.

Comparing pooled TZP *vs.* pooled comparators in AS5, a HR of 0.81 (97.85% CI, 0.52 to 1.26) was attained at the interim analysis. Thus, the upper limit of the CI of the HR of MACE 4 for TZP vs. comparators was less than the regulatory-stipulated limit of 1.8 for submission, thereby fulfilling the pre-marketing safety requirement. The upper limit of the 2-sided 95% CI of the HR was also less than the regulatory stipulated limit of 1.3 and thus, demonstrated that treatment with TZP was not associated with excess CV risk. The results of the complete analysis (HR of 0.80; 95% CI, 0.57 to 1.11 for the primary MACE 4 composite endpoint), as well as analyses

of the composite endpoint of MACE-3 support the interim analysis. The result regarding MACE-4 was confirmed by MACE-3, which was tested in a sensitivity analysis.

The applicant is going to conduct the SURPASS-CVOT with MACE-3 as the primary efficacy outcome for ultimate conclusion of the CV efficacy and safety of TZP.

Data on CV safety and potential CV benefits of TZP will be provided from the currently ongoing CV outcome study (Study I8F MC GPGN, SURPASS-CVOT), with dulaglutide as an active comparator. This event-driven study is expected to enrol 12,500 patients with a history of CV disease, and will have an average treatment follow up of approximately 4 years. Of note, although the cardiovascular meta-analysis clearly excluded excess cardiovascular risk, a cardiovascular *benefit* has not been demonstrated yet, since the completion of SURPASS-CVOT is projected for 2025. Thus, TZP can only be approved for glycaemic control in T2DM based on the dossier submitted.

Immunological aspects of TZP treatment were covered by the AESIs "hypersensitivity reactions", "injection site reactions" and "immunogenicity". No anaphylactic reaction was observed. In AS1, the incidence of hypersensitivity reactions was increased for TZP (3.2%) compared with placebo (1.7%) in AS1. No potential immediate or non-immediate severe or serious hypersensitivity reactions were reported in AS1. A similar percentage of patients reported immediate and non-immediate hypersensitivity AEs across TZP dose groups in the total phase 3 dataset (AS2). Moreover, in AS2, a total of 4 (0.08%) TZP-treated patients reported potential severe or serious non-immediate hypersensitivity reactions (skin necrosis, urticaria, allergic rhinitis and eczema). Four of the six study discontinuations due to hypersensitivity reactions occurred in the Japan studies GPGO and GPGP, and one patient from Japan has repeatedly experienced throat tightness in association with TZP administration. However, in the comparator group (dulaglutide) of Study GPGO, the frequency of hypersensitivity reactions was also higher than in the comparator groups of the other phase 3 studies (study GPGP did not include a comparator group). This could indicate that Japanese patients are more susceptible to hypersensitivity reactions but does not appear to be a specific safety concern of TZP.

As to be expected with a non-physiological peptide like TZP, the frequency of injection site reactions (mainly erythema, pruritus, induration, pain and oedema) was increased with TZP *vs.* placebo. Most injection site reactions (78.35%) occurred > 6 hours after study drug administration, with 34.33% occurring from 24 hours to 14 days post-administration. It is reassuring that none of the injection site reactions identified from the predefined MedDRA search were severe or serious. However, analysis of the dedicated injection site reaction electronic case report forms (eCRFs) revealed severe signs and symptoms of "bright red erythema" (68 events in 10 patients [6.76%]) and one event of "severe induration" in 1 patient ([0.68%]) in AS2. Injection site reactions have adequately been proposed to be included in section 4.8 of the SmPC.

Immunogenicity of TZP was assessed by determining the new formation or increase in titre of anti-drug antibodies during treatment (TE ADAs). While the ADA+ status was comparable at baseline, the post-baseline TE ADA+ status was considerably increased with TZP *vs.* comparator; around 50% of the study participants in phase 3 developed TE ADA. Among the TE ADA+ patients, most of them (72.3%) developed persistent antibodies. In 15.8% of these patients, transient antibodies were found; the remainder was uncertain according to the applicant's criteria used for definition of persistence. Although there was a tendency to slightly lower TZP clearance with higher ADA titres, the small number of patients precludes firm conclusions on the relationship between ADA titres and clearance. A small effect of ADA at reducing efficacy of TZP cannot be excluded, but, due to the small size, it is not considered clinically relevant. There was a marked imbalance between ADA+ and ADA- subjects in regard to the incidence of hypersensitivity reactions and injection site reactions. These conditions mainly occurred in ADA+ patients. As the number of patients with and without TE ADA was nearly equal (around 50% TE ADA+), a similar incidence of hypersensitivity and injection site reactions

would be expected if ADA had no effect. Vice versa, this means that the presence of ADA is responsible for several of these reactions so that at least part of the observed hypersensitivity / injection site reactions were indeed related to tirzepatide treatment via ADA formation. Reassuringly, most of these reactions were not serious or severe and were self-limiting. Apparently, patients from Japan are more susceptible to develop TZP antibodies during therapy, which may favour the occurrence of hypersensitivity and injection site reactions in patients from Japan.

Analysis of ADA+ patients experiencing hypersensitivity reactions or injection site reactions revealed that in most cases (>85%) these patients had ADA of low titre (defined as less than 1:5120).

The AESI of diabetic retinopathy complications was pre-defined based on previous experience with the GLP1 agonist semaglutide. In SUSTAIN-6, a 2-year CVOT with semaglutide in patients with T2DM and a high cardiovascular risk, diabetic retinopathy complications occurred more frequently in patients treated with semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. No exclusion criteria regarding retinopathy were implemented in the CVOT for semaglutide. By contrast, in the phase 3 trials of the semaglutide programme, patients requiring active treatment for known proliferative retinopathy or maculopathy at baseline were excluded and diabetic retinopathy was reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%). Due to exclusion of respective risk patients in the TZP phase 3 program, TZP has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema. There is no experience with tirzepatide in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy. Therefore, tirzepatide should be used with caution in these patients, and regular monitoring should be performed. This is appropriately indicated in the SmPC. In the phase 3 studies, the incidence of potential diabetic retinopathy complications was slightly higher for the comparator group (0.99%; 22/2223) than for TZP (0.72%; 37/5119). Four TZP-treated subjects (2 retinal vein occlusion, 2 retinal detachment) in AS2 experienced a serious or severe event of a diabetic retinopathy complication. Worsening of fundoscopic examination (as recorded on eCRF) was noted in 0.35% (18/5119) of the tirzepatide-treated subjects and in 0.22% (5/2223) in the comparator group. No SAEs were reported. The ongoing SURPASS CVOT will further investigate the impact of TZP treatment on diabetic retinopathy progression.

AESI "hepatobiliary disorders": A numerically higher percentage of patients was affected by hepatobiliary TEAEs with TZP than with comparator in most phase 3 studies. This imbalance was probably driven by gallbladder complications. In the placebo-controlled studies (AS1), the proportion of subjects with gallbladder-related AEs was increased for TZP (0.6%) vs. placebo (0%). None of the events were serious or led to study discontinuation. In the phase 3 studies (AS2), the incidence of gallbladder-related AEs was 1.1% (n=18) for TZP 5 mg, 1.1% for TZP 10 mg (n=19), 0.8% (n=14) for TZP 15 mg and 0.8% (n=17) for comparator. The gallbladder-related AEs in the TZP group (n=51) were mainly driven by cholelithiasis (n=30). Sixteen (16) SAEs were reported, of which cholecystitis/acute cholecystitis (n=8) and cholelithiasis (n=5) were the most frequently reported SAEs.

The increased risk of cholelithiasis with TZP is in line with data from other GLP-1 agonists. Cholelithiasis has been included in Section 4.8 of the SmPC with the frequency "uncommon". Increased weight loss did not increase the risk of cholelithiasis.

In addition, a rapporteur's search for gallbladder-related PTs in the phase 3 studies revealed a slightly increased occurrence of "gallbladder polyp" with TZP 15 mg as compared to lower TZP doses and control groups in AS2. However, it is noted that 6 of the 11 patients affected in the 15 mg group were still in the dose escalation phase and 8 of the 11 cases of gallbladder polyp in the 15-mg group occurred in the Japan studies. Literature suggests that the prevalence of gallbladder polyps in adults may be higher in East Asian populations.

Nevertheless, the imbalance between TZP-treated and comparator treated patients remains unexplained (TZP_ALL: 14 [0.27%] vs. pooled comparator: 1 [0.04%). It is expected that gallbladder imaging will be performed in upcoming studies (due to the increased probability of cholelithiasis in TZP-treated patients so that gallbladder polyps will most likely be detected, possibly allowing a final conclusion on this AE.

In AS2, a numerically higher percentage of patients in the TZP 15 mg group as compared to lower TZP doses reached a post-baseline ALT/AST category of ≥3 x ULN and ≥5 x ULN. However, no clear conclusion on a potential causative role of TZP can be drawn, as some of these patients started already with increased enzyme levels at baseline and/or may have had a history of confounding hepatic diseases. Moreover, in some of the patients with ALT/AST elevations ≥3 x ULN, the high enzyme levels were only measured once and returned to the normal range during the study. Since none of the patients met the criteria for Hy's law (ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN), it is considered unlikely that TZP has a hepatotoxic effect. TZP may even have a beneficial effect on liver function (possibly a consequence of positive metabolic effects), as ALT, AST and ALP were more prominently reduced from baseline to week 52 at higher TZP doses as compared to lower doses.

The malignancy risk does not appear to be increased with TZP (TZP *vs.* placebo in phase 2/3: 1.02% *vs.* 1.60%). However, it is noted that the risk for developing malignancies cannot be fully explored from controlled data in the clinical trial program covering rather short observation periods. As discussed above in context of thyroid safety, the TZP-mediated elevation of calcitonin may be of concern, although no cases of MTC were identified in the clinical programme. Thyroid proliferative C-cell changes in rodents are a known class effect following GLP-1R activation by GLP-1R agonists and increases in thyroid C-cell tumours were identified in rodents treated with TZP. In total, 3 cases of pancreatic cancer occurred, of which 2 were identified in the TZP group and 1 in the placebo group. The 2 cases in the TZP group were adjudicated unrelated to TZP treatment. However, the number of cases in the TZP program is too low to draw firm conclusions about a TZP-associated pancreatic cancer risk. Thyroid C-cell tumours are included in the RMP as important potential risk in line with other GLP-1 agonists on the market. Pancreatic malignancies will be evaluated in further studies. Pancreatic malignancy is a potential risk that requires long-term surveillance.

AESI of major depressive disorder/suicidal ideation or behavior: TZP can cause loss of appetite, nausea and vomiting. Since eating might be a short-term compensatory behavior in some patients, which produces positive emotions and helps to cope with difficult life situations, it is conceivable that the gastrointestinal and appetite-reducing effects of TZP may precipitate or worsen depressive episodes in predisposed patients. It is noted that in AS2, TZP 15 mg was associated with more depressions than the 5 mg and 10 mg dose. Even when some of the affected patients may have been pre-disposed (e.g., life situation, previous depressive episodes), it cannot be excluded that TZP could have triggered a depressive episode in such persons. It should also be considered that depression may be associated with rather unspecific somatic symptoms like fatigue, back pain or sleeping problems ("masked" depression). Therefore, the applicant has analysed, whether the 6 PTs dizziness, asthenia, fatigue, vertigo, illness or malaise are associated with depression. There seems to be a weak relationship with depression, as in 5 patients with depression (all in the TZP group), 2 of the 6 aforementioned AEs were co-reported. By contrast, no such case was identified in the comparator group. Nevertheless, depression was generally not reported more frequently with TZP than with comparator.

In AS1, more patients in the TZP group (16.3%) compared with the placebo group (9.2%) shifted from normal/high haemoglobin to low haemoglobin. Haemoglobin values across the tirzepatide groups did not return towards baseline at the time of safety follow-up. Similar results were reported for the AS2 dataset. However, the between-group difference is very small and large standard deviations preclude a meaningful interpretation

of the results. A large part of the haemoglobin decrease is likely to be caused by the underlying condition of T2DM. The incidence of anemia was numerically increased for tirzepatide vs placebo (1.1% vs 0%).

Deaths and SAEs
There was no relevant imbalance between TZP dose groups or between TZP and comparator groups with regard to deaths. The majority of fatal cases in the TZP group (61%; 25/41) and the comparator group (90%; 35/39) occurred in patients from the study GPGM (patients with increased CV risk and/or impaired renal function).

Special groups
As described above for immunogenicity, hypersensitivity reactions, injection site reactions and increase in pulse rate, patients from Japan appear to be more susceptible to TZP AEs. This was confirmed by an analysis of the most common TEAEs by geographic region in AS2, revealing more GI AEs in patients from Japan and from Asia (excluding Japan) as compared to other regions.

A detailed treatment-by-subgroup interaction analysis of dataset AS1 revealed no relevant interactions.
Regarding AEs by age category, the applicant has provided the required table with an analysis of the TZP-treated patients in phase 2/3 safety analysis set AS3. Moreover, the applicant has presented a corresponding analysis for AS2, including a comparison with the pooled comparator groups and differentiating between TZP doses. Due to the low number of subjects aged ≥85 years, it is virtually impossible to draw reliable conclusions on tolerability of TZP in this age group.
The applicant has provided an AE analysis in different subgroups, including gender, race/ethnicity, baseline BMI and hepatic function. AEs were also analysed by weight reduction at study end. There were some numerical differences in the AE frequencies of these subgroups and conditions, but overall the analyses gave no hint for concern in any group or condition.

No specific issues were identified with regard to patients with renal or hepatic impairment. However, it is noted that long-term clinical data are limited for patients with hepatic impairment.

2.6.10. Conclusions on the clinical safety

Although TZP is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, its safety profile strongly resembles the safety profile of GLP1 receptor agonists. Specifically, the rate of gastrointestinal adverse events was dose-dependently higher with TZP compared with placebo. Among the subjects that experienced ≥1 GI event, more subjects in the TZP groups dose-dependently discontinued treatment permanently compared with placebo (up to 15% in the TZP 15 mg group). Moreover, serum amylase and lipase increased with TZP treatment. Furthermore, similar to GLP1 agonists, hypoglycaemias only occurred in combination with other glucose-lowering drugs, and TZP lowers blood pressure and dose-dependently increases pulse rate (up to 5.2 beats/minute for 15 mg TZP compared to 1.0 beats/minute with placebo).

However, it appears that unlike pure GLP1 receptor agonists, TZP increases calcitonin, and it is currently not clear, whether this may also be associated with C cell hyperplasia. No cases of MTC were identified across the phase 2 and 3 clinical studies; however, the risk for developing MTC cannot be fully explored from controlled data in the clinical trial program covering rather short observation periods. In non-clinical studies, thyroid C-cell tumour responses were identified in rodents, in line with what has been reported for other long-acting GLP-1 agonists.

About 50% of TZP-treated patients developed antibodies, of which about 4% were positive for neutralising antibodies against TZP activity on the GIPR and GLP-1 receptors, respectively. Most of the affected patients

developed persistent treatment-emergent antibodies. Injection site reactions were dose-dependently increased for tirzepatide 5 mg. A majority of the injection site reactions were identified in subjects that developed antibodies.

Worsening of fundoscopic examination results of diabetic retinopathy was noted in 0.35% of the tirzepatide-treated subjects and in 0.22% in the comparator group. TZP has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular oedema. There is no experience with TZP in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy. This is appropriately reflected in the SmPC.

The cardiovascular meta-analysis excludes an excessive cardiovascular risk. However, a cardiovascular benefit has not been demonstrated yet, since the completion of SURPASS-CVOT is projected for 2025. Thus, TZP can only be approved for glycaemic control in T2DM based on the dossier submitted.

2.7. Risk Management Plan

2.7.1. 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

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 - Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
Medullary Thyroid Carcinoma Surveillance Study (I8F-MC-B010) Planned	To determine the annual incidence of MTC in the US and to identify any possible increase related to the introduction of long-acting GLP-1 Ras, including tirzepatide, into	Important potential risk of medullary thyroid cancer	Submission of draft protocol outline	Within 6 months of the CHMP opinion.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	the US market			
Tirzepatide Pancreatic Malignancy Study (I8F-MC-B011) Planned	To evaluate the incidence of pancreatic malignancy among patients with T2DM treated with tirzepatide and to compare the incidence of pancreatic malignancy among patients treated with tirzepatide to patients treated with alternative treatments for clinical indications approved for GLP-1 Ras in Europe.	Important potential risk of pancreatic malignancy	Submission of draft protocol outline	Within 6 months of the CHMP opinion.
Retinopathy addendum to SURPASS-CVOT Study (I8F-MC-GPGN) Ongoing	To compare the effect of tirzepatide dose up to 15 mg QW with dulaglutide 1.5 mg QW on DR progression. To assess the safety of tirzepatide dose up to 15 mg QW when compared with dulaglutide 1.5 mg QW on DR.	Important potential risk of DR complications	Protocol submission	Provided in Annex 3 of this RMP
			Submission of CSR	Within 6 months after CSR approval (estimated CSR approval date: 04/01/2025)

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Medullary thyroid cancer	Routine risk minimisation measures: • SmPC Section 5.3 Additional risk minimisation measures: None
Pancreatic malignancy	Routine risk minimisation measures: • None Additional risk minimisation measures: None
Diabetic retinopathy complications	Routine risk minimisation measures: • SmPC Section 4.4 Additional risk minimisation measures: None
Use in pregnant and/or breastfeeding women	Routine risk minimisation measures: • SmPC Section 4.6

Safety Concern	Risk Minimisation Measures
	• PL Section 2 Additional risk minimisation measures: None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 13.05.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

Tirzepatide was proposed to be used in the following type 2 diabetes mellitus indication (wording initially proposed by the Applicant):
Tirzepatide (Mounjaro) is indicated for the treatment of adults with 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, weight and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

The indication wording has been modified throughout the procedure and the final approvable wording is provided in section 3.7.3.

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist which is administered subcutaneously once-weekly.

3.1.1. Disease or condition

Diabetes affects approximately 463 million adults worldwide, with T2DM accounting for approximately 90% of all diabetes worldwide (IDF 2019). Type 2 diabetes mellitus is characterized by a complex pathophysiology that causes chronic hyperglycaemia which, if left untreated or inadequately managed, can result in long-term damage, dysfunction, and failure of various organs, including the heart, kidneys, and eyes, as well as blood vessels and nerves (Alam et al. 2014). Arterial hypertension, dyslipidemia, and obesity all contribute to the development of chronic complications of T2DM (Van Gaal et al. 2006; ADA 2021e). Most subjects with T2D are overweight or obese, which is important in the aetiology as it increases insulin resistance and leads to persistent hyperglycaemia. The pathogenesis is seemingly heterogeneous and also involves environmental, lifestyle, and genetic components. All of these factors contribute to chronic hyperglycaemia which, if left untreated, is associated with β-cell failure and increased risk of long-term micro- and macrovascular complications. The typical presentation of diabetes includes polyuria and polydipsia. However, many patients with T2D are asymptomatic and are diagnosed with screening or general investigations of aspecific complaints like fatigue. The diagnosis is made by measurement of hyperglycaemia.

3.1.2. Available therapies and unmet medical need

The guidelines of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) for treatment of T2D have been developed in cooperation and are widely agreed. The major steps recommended for managing type 2 diabetes are lifestyle changes such as diet and exercise. For glycaemic control, primarily metformin, other non-insulin anti-diabetic agents and finally insulin are used, alone or in combination. Treatment is individualized to the individual patient's glycaemic target (for example, HbA1c <7.0%) and co-morbidities (for example, renal insufficiency), and risks of adverse effects (for example, increased risk of hypoglycaemia, body weight gain) (Pfeiffer and Klein 2014; Inzucchi et al. 2015; Davies et al. 2018; Buse et al. 2020; ADA 2021d). Besides anti-glycaemic therapy, antihypertensive, antithrombotic and lipid lowering treatments might be indicated to avoid other associated co-morbidities (e.g.

hypertension, obesity, dyslipidemia) and macrovascular complications (MI, stroke). Recently, SGLT-2 inhibitors and GLP-1 RAs have shown not only improvements in glycaemic control but also a reduction in body weight and CV events in patients with T2DM and high cardiovascular risk. There is no unmet medical need for tirzepatide.

3.1.3. Main clinical studies

The efficacy data supporting this application are from the five global pivotal phase 3 studies. Tirzepatide was compared with placebo or active comparators in a population of patients with T2DM, representing a broad range of patients who could be treated in clinical practice. Tirzepatide was assessed as monotherapy and as add-on treatment to OAMs or basal insulin. Key design elements are outlined in the table below.

Key design elements of the 5 global Phase 3 studies

	GPGK (SURPASS-1)	GPGL (SURPASS-2)	GPGH (SURPASS-3)	GPGM (SURPASS-4)	GPGI (SURPASS-5)
Study Design	Double-blind	Open-label[a]	Open-label	Open-label	Double-blind
TZP QW Maintenance Doses	5, 10, 15 mg	5, 10, 15 mg	5, 10, 15 mg	5, 10, 15 mg	5, 10, 15 mg
Comparator	PBO	Semaglutide 1 mg	Insulin degludec[b] (titrated)	Insulin glargine[b] (titrated)	PBO
Randomization Scheme	1:1:1:1	1:1:1:1	1:1:1:1	1:1:1:3	1:1:1:1
Treatment Period Duration	40 weeks	40 weeks	52 weeks	52 to 104 weeks	40 weeks
Total # Randomized and Treated with Study Drug	478	1878	1437	1995	475
# Randomized and Treated with TZP	363	1409	1077	995	355
Background Medications	None (lifestyle changes only)	Metformin	Metformin ± SGLT-2i	1 to 3 OAMs (± metformin ± SU ± SGLT-2i)	Insulin glargine[b] (titrated) ± metformin
HbA1c Inclusion Criterion	≥7.0 to ≤9.5% (≥53 to ≤80 mmol/mol)	≥7.0 to ≤10.5% (≥53 to ≤91 mmol/mol)	≥7.0 to ≤10.5% (≥53 to ≤91 mmol/mol)	≥7.5 to ≤10.5% (≥58 to ≤91 mmol/mol)	≥7.0 to ≤10.5% (≥53 to ≤91 mmol/mol)

Abbreviations: # = number; ± = with or without; HbA1c = glycosylated hemoglobin A1c; OAM = oral antihyperglycaemic medication; PBO = placebo; QW = once-weekly; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide.

[a] Investigators and patients were blinded to the dose of tirzepatide administered in Study GPGL.

[b] The insulin concentration was 100 units/mL (U100).

3.2. Favourable effects

Tirzepatide showed statistically superior and clinically relevant reductions from baseline in HbA1c compared with placebo, a GLP-1 receptor agonist (semaglutide 1mg), and basal insulin (insulin degludec, insulin

glargine). Basal insulin was titrated to a sufficiently high dose to achieve full antihyperglycaemic potential; 1 mg semaglutide is currently the highest semaglutide dose available.

For the treatment-regimen estimand, irrespective of adherence to study drug or initiation of another antihyperglycaemic medication, the mean changes in HbA1c from baseline to primary endpoint ranged from tirzepatide 5 mg: -1.75% (Study GPGK, 40 weeks) to -2.11% (Study GPGI, 40 weeks), tirzepatide 10 mg: -1.71% [Study GPGK, 40 weeks] to -2.40% [Study GPGI, 40 weeks], and tirzepatide 15 mg: -1.69% [Study GPGK, 40 weeks] to -2.41% [Study GPGM, 52 weeks]. Results for the efficacy estimand (study drug was taken as intended without use of rescue) results were consistent. Sustainability of the HbA1c lowering effect over 104 weeks was demonstrated.

Glycaemic benefit was further reflected by significantly greater proportions of patients achieving HbA1c targets of <7.0%, ≤6.5%, and <5.7%, the latter corresponding to normoglycemia, compared to placebo and all active comparators studied. The vast majority of patients who achieved a glycaemic goal of <5.7% did so without developing hypoglycaemia (93.6% to 100% of patients not on a background of insulin glargine; 85.9% of patients on a background of insulin glargine).

FSG and 7-point SMBG results further supported the effect of tirzepatide on HbA1c. Glycaemic control seemed to be improved throughout the day, including post-prandial glycaemic excursions. For the treatment-regimen estimand, the mean changes in FSG from baseline to primary endpoint ranged from -tirzepatide 5 mg: -39.6 mg/dL [Study GPGK, 40 weeks] to -58.2 mg/dL [Study GPGI, 52 weeks], -tirzepatide 10 mg: -39.8 mg/dL [Study GPGK, 40 weeks] to -64.0 mg/dL [Study GPGI, 40 weeks], and -tirzepatide 15 mg: -38.6 mg/dL [Study GPGK, 40 weeks] to -62.6 mg/dL [Study GPGI, 40 weeks].

Further, Tirzepatide led to significantly more time spent in the euglycaemic range (71-140mg/dL), as demonstrated through continuous glucose monitoring; this was not achieved at the expense of increased hypoglycaemia.

Tirzepatide demonstrated superior and clinically relevant (body weight loss >5% from baseline weight) reductions in body weight in all phase 3 studies compared with placebo, semaglutide and basal insulin (insulin degludec and insulin glargine): tirzepatide 5 mg: -5.4 kg (Study GPGI, 40 weeks) to -7.6 kg (Study GPGL, 40 weeks), tirzepatide 10 mg: -7.0 kg (Study GPGK, 40 weeks) to -9.6 kg (Study GPGH, 52 weeks), and tirzepatide 15 mg: -7.8 kg (Study GPGK, 40 weeks) to -11.3 kg (Study GPGH, 52 weeks).

Reductions in body weight were observed regardless of concomitant therapy with SU or insulin which are known to promote weight gain. Of note, weight loss did not plateau by the end of the 40 to 52 week treatment period. A reduction of the volume of visceral adipose tissue, and the volume of abdominal subcutaneous adipose tissue, as demonstrated in the MRI substudy, showed that weight loss was related to loss of fat mass.

Likewise, other cardiometabolic measures (waist circumference, lipid parameters, blood pressure, hepatic fat content) improved with tirzepatide.

3.3. Uncertainties and limitations about favourable effects

There are uncertainties with respect to the beneficial effect in subgroups. Weight loss exceeded the observational period in the phase 3 studies. Hence, some patients may struggle to keep their weight during chronic therapy. Further analyses had been requested in the subgroup of patients with baseline BMI between 23 and 24.9 kg/m2 (from studies GPGK and GPGI, as well as from the supportive study GPGO). These

subgroup analyses showed maintained efficacy and no significant safety concerns in patients with BMI ≥23 and 24.9 kg/m2 at baseline. A total of nine patients from studies GPGK (n=478), GPGI (n=475), and GPGO (n=636), which included seven patients with BMI ≥23 and <25 kg/m2 at baseline, had a BMI ≤18.5 kg/m^2 at the end of the study (Week 40 and Week 52, respectively), which is considered a low number. In clinical practice, the risk of underweight may even be lower, as the treating physician will not have to adhere to an assigned dose and will adjust the dose of tirzepatide according to the therapeutic needs and the tolerability of each patient.

Overall, the data do not justify implementing a BMI cut-off for the use of tirzepatide in the SmPC or a warning in the SmPC; this issue was resolved by adding weight loss as adverse event in section 4.8 of the SmPC.

There was some uncertainty as regards the benefit in patients with stages 4 and 5 chronic kidney disease. Except for study GPGM which had no exclusion criterion based on eGFR, the phase 3 studies had a lower limit of eGFR of 30 ml/min/1.73m2. The Applicant submitted a by-participant listing of the 32 participants enrolled in Study I8F-MC-GPGM who had a baseline eGFR <30 mL/min/1.73 m2 (11 treated with 5 mg, 2 on 10 mg, 3 on 15 mg, 16 treated with glargine). Efficacy seemed not to be lower in this subset compared to the overall study population, both with regard to HbA1c and weight. No unexpected safety issues occurred in these patients and no deterioration in renal function (eGFR) was noted. Results from the PK study GPGG showed a PK largely independent of renal function after administration of a single subcutaneous dose of 5 mg tirzepatide. Based on these data no dose adjustment of tirzepatide in patients with CKD stage 4 and 5 seems warranted. However, the applicant acknowledges the limited phase 3 data in patients with stage 4 and 5 kidney disease and has proposed the addition of a sentence in section 4.2 of the SmPC that "*Experience with the use of tirzepatide in patients with severe renal impairment or ESRD is limited. Caution should be exercised when treating these patients with tirzepatide.*"

Patients with hepatic impairment were excluded from the phase 3 studies. A clinical pharmacology study (Study GPGQ) was conducted in patients with hepatic impairment. No clinically relevant effects of hepatic impairment were observed on the PK of tirzepatide in this study. The applicant concluded that patients with hepatic impairment do not require different dosing regimens (and inserted a respective wording in section 4.2 of the SmPC); this needed to be further justified as long term clinical data in patients with hepatic impairment do not exist The Applicant pointed to published clinical data suggesting that tirzepatide may lead to improvements in liver-related clinical markers: a post-hoc analysis of a phase 2 study showed improvement in nonalcoholic steatohepatitis-related biomarkers after 26 weeks of treatment with tirzepatide (Hartman et al. 2020) and in a substudy of the Phase 3 SURPASS-3 study, patients treated with tirzepatide had a significantly greater decrease in liver fat content at Week 52 compared to insulin degludec (Gastaldelli et al. 2021).

However, the applicant has acknowledged the lack of clinical data following the use of tirzepatide in patients with severe hepatic impairment in the phase 3 studies and has proposed a revision to the text in section 4.2 which adequately reflects the lack of data.

3.4. Unfavourable effects

The safety profile for TZP is overall similar to what is known for the class of GLP-1 agonists. Gastrointestinal AEs were dose-dependently increased with TZP-treatment. More subjects in the TZP groups discontinued treatment permanently (up to 15% for TZP 15 mg) than for placebo. About 50% of the TZP-treated patients developed antibodies (<5% positive for neutralising antibodies), the majority of which were persistent

antibodies. Injection site reactions were dose-dependently increased for TZP, of which most cases were identified in subjects that developed antibodies. Pancreatic enzymes (serum amylase and lipase) were increased for TZP, which, however, was in general not associated with pancreatitis.

Pancreatitis occurred slightly more frequently with TZP than with comparator in the phase 2/3 program (0.24 *vs.* 0.17%). Moreover, unlike pure GLP1 receptor agonists, TZP appears to slightly increase serum calcitonin.

TZP does not exert major negative effects on renal and hepatic function.

TZP increased the frequency of general adverse events like dizziness, asthenia, fatigue, vertigo, illness and malaise.

Discontinuation from study drug due to GI AEs was <5%. During the initial dose escalation phase (0-24 weeks), the majority of discontinuations was due to GI AEs. After week 24, despite reduced frequency, GI AEs remain an important factor for discontinuations, specifically at higher TZP doses.

The data suggest that the presence of ADA is responsible for several of the hypersensitivity- and injection site reactions, most of which were not serious or severe and were self-limiting. The influence of TZP antibodies on TZP clearance and efficacy seems negligible.

There was no relevant imbalance between TZP dose groups or between TZP and comparator groups with regard to deaths.

In several instances (e.g., GI TEAEs, increase in pulse rate, hypersensitivity reactions, post-baseline TE ADA+), patients from Japan were more sensitive to TZP-associated TEAEs than patients from other parts of the world, which may partly be due to a higher TZP dose relative to body weight.

Hypoglycaemia events were low with TZP and mainly occurred in combination with other glucose-lowering background therapies like insulin or OADs.

3.5. Uncertainties and limitations about unfavourable effects

Some AEs (including typical AEs associated with GLP1 receptor agonism) occurred more frequently with TZP as compared to GLP1 receptor agonist comparators (semaglutide 1 mg and dulaglutide 0.75 mg). This is probably due to a relatively low GLP1 receptor agonist dose as compared to TZP, which precludes *on par* comparison of TZP and GLP1 receptor agonists.

According to the applicant, no C-cell hyperplasia occurred during the study program. However, the rapporteur considers the employed diagnostic methods insufficient to exclude C-cell hyperplasia, which is specifically emphasized in light of the serum calcitonin increase associated with TZP treatment. No MTC cases were observed in the TZP clinical programme, but the duration of the clinical studies does not allow identification of long-latency events, such as thyroid cancer.

Regarding pancreatitis, many of the investigator-reported cases of pancreatitis were not confirmed by the CEC. Two cases of pancreatic cancer were reported in TZP-treated patients of the phase 2/3 study program, both being adjudicated unrelated to TZP treatment. Based on the current data that are derived from a clinical study program with only limited duration, the risk for long-latency events like pancreatic cancer cannot be assessed. The applicant has not presented data on patients with a history of proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy that required acute treatment, as such patients were excluded in the phase 3 programme. However, it is to be expected that the ongoing dedicated addendum

study to SURPASS-CVOT (investigating the impact of TZP on diabetic retinopathy progression) will allow a more reliable estimation of the TZP-associated retinopathy risk.

The TZP-induced increase of the frequency of general adverse events like dizziness, asthenia, fatigue, vertigo, illness and malaise seems to weakly correlate with depression, but the number of cases is too low and no major imbalance with regard to depression is observed between TZP- and comparator group.

Due to limited data, no firm conclusion can be drawn on long-term hepatic safety. There is only limited data on patients with eGFR <30 mL/min/1.73 m^2. It seems that the PTs "renal cyst" and "gallbladder polyp" occurred with slightly increased frequency in TZP-treated patients, but due to confounding factors (background medical conditions) and the low number of cases, a clear causative role of TZP cannot be established.

No data on patients with severe GI disease are available.

3.6. Effects Table

Table 1. Effects Table for Mounjaro for type 2 diabetes mellitus (data cut-off: 2 June 2021).

Effect	Short Description	TZP 5 mg	TZP 10 mg	TZP 15 mg	Control	Study or Analysis Set	Strengths/Limitations/Uncertainties
Favourable Effects							
HbA1c Reduction	LS Mean CFB at 40 wks (%)	-1.87	-1.89	-2.07	+0.04 (PBO)	SURPASS-1	**Strength of evidence** • Phase 3 studies were adequately powered to show superior reductions in HbA1c and body weight in the target population: patients across the disease continuum with varying disease duration, background therapies, comorbidities, and complications. • Participants encouraged to remain in studies up to primary endpoint visit, whether or not they adhered to study treatment, resulting in high retention rates and minimal missing data • In all phase 3 studies, all 3 TZP doses statistically significantly reduced HbA1c and body weight relative to comparators using both the treatment-regimen estimand and efficacy estimand. • TZP was efficacious in reducing HbA1c and body weight across all subgroups evaluated, including age, gender, baseline BMI, and background oral diabetes meds. • Higher percentages of patients achieving HbA1c targets (<7%, ≤6.5%, <5.7%), and weight loss targets (≥10% and ≥15%) than with comparators. • FSG and 7-point SMBG support beneficial effect of tirzepatide on glycaemic control throughout the day, including postprandial glycaemic excursions. • TZP improved waist circumference, lipid parameters, and blood pressure in all global Phase 3 studies • Glycaemic control was achieved without clinically significant or severe hypoglycaemia for most tirzepatide-treated patients: for those achieving HbA1c <5.7% at the primary endpoint, 93.6% to 100% of tirzepatide-treated patients not on background of insulin and 85.9% of patients on background of insulin. **Limitations and uncertainties** • Limitation: no weight loss claim. Therefore, reference to "weight" in section 4.1 of the SmPC not acceptable.
		-2.09	-2.37	-2.46	-1.86 (Sema)	SURPASS-2	
		-2.23	-2.59	-2.59	-0.93 (PBO)	SURPASS-5	
	LS Mean CFB at 40 wks mmol/mol	-20.4	-20.7	-22.7	0.4 (PBO)	SURPASS-1	
		-22.8	-25.9	-26.9	-20.3 (Sema)	SURPASS-2	
		-24.4	-28.3	-28.3	-10.2 (PBO)	SURPASS-5	
	LS Mean CFB at 52 wks (%)	-1.93	-2.20	-2.37	-1.34 (IDeg)	SURPASS-3	
		-2.24	-2.43	-2.58	-1.44 (IGlar)	SURPASS-4	
	LS Mean CFB at 52 wks mmol/mol	-21.1	-24.0	-26.0	-14.6 (IDeg)	SURPASS-3	
		-24.5	-26.6	-28.2	-15.7 (IGlar)	SURPASS-4	
HbA1c Target of <7.0%	Proportion of patients at 40 wks (%)	86.8	91.5	87.9	19.6 (PBO)	SURPASS-1	
		85.5	88.9	92.2	81.1 (Sema)	SURPASS-2	
		93.0	97.4	94.0	33.9 (PBO)	SURPASS-5	
	Proportion of patients at 52 wks (%)	82.4	89.7	92.6	61.3 (IDeg)	SURPASS-3	
		81.0	88.2	90.7	50.7 (IGlar)	SURPASS-4	
Body Weight Reduction	LS Mean CFB at 40 wks (kg)	-7.0	-7.8	-9.5	-0.7 (PBO)	SURPASS-1	
		-7.8	-10.3	-12.4	-6.2 (Sema)	SURPASS-2	
		-6.2	-8.2	-10.9	+1.7 (PBO)	SURPASS-5	
	LS Mean CFB at 52 wks (kg)	-7.5	-10.7	-12.9	+2.3 (IDeg)	SURPASS-3	
		-7.1	-9.5	-11.7	+1.9 (IGlar)	SURPASS-4	
Body Weight Loss Target of ≥5%	Proportion at 40 wks (%)	66.9	78.0	76.7	14.3 (PBO)	SURPASS-1	
		68.6	82.4	86.2	58.4 (Sema)	SURPASS-2	
		53.9	64.6	84.6	5.9 (PBO)	SURPASS-5	
	Proportion at 52 wks (%)	66.0	83.7	87.8	6.3 (IDeg)	SURPASS-3	
		62.9	77.6	85.3	8.0 (IGlar)	SURPASS-4	
Unfavourable effects							
TEAEs	Number and proportion of patients	680 (70.7) (TZP_ALL)			190 (60.9)	AS4	**Strength of evidence** • Safety characterised in large number (5415) of patients on TZP
SAEs		37 (3.8) (TZP_ALL)			13 (4.2)		

Discontinuations from study drug due to AE	during the study (n [%])	68 (7.1) (TZP_ALL)			8 (2.6)		in Phase 2 and 3 studies (4833.1 patient-years of exposure). • Safety profile of TZP was mostly consistent with the known safety profiles of GLP-1 receptor agonists. • Acute pancreatitis showed a slight imbalance between TZP and comparator. GLP1 receptor agonists can increase pancreatic enzymes, but this is mostly not associated with pancreatitis. • GI events, the most common AEs for TZP, were more frequent during the dose-escalation period and were mostly mild to moderate in severity, and discontinuation from study drug due to GI AEs was <5%. • Hypoglycaemia events were low with TZP and dependend mostly on background therapy. **Limitations and uncertainties** • No data on patients with a history of proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy that required acute treatment. • No data on patients with severe GI disorders. • Limited data on patients with eGFR <30 mL/min/1.73 m^2. • TZP caused slight increases in serum calcitonin. A potential risk of C cell hyperplasia could not be excluded. • Duration of the clinical studies does not allow identification of long-latency events, such as thyroid cancer.
GI TEAEs		88 (37.1)	95 (39.6)	105 (43.6)	48 (20.4)	AS1	
Nausea		179 (18.6) (TZP_ALL)			15 (4.8)	AS4	
		224 (13.17)	312 (18.33)	381 (22.20)	135 (6.07)	AS2*	
Vomiting		85 (8.8) (TZP_ALL)			6 (1.9)	AS4	
		93 (5.47)	132 (7.76)	167 (9.73)	66 (2.97)	AS2*	
Diarrhoea		166 (17.3) (TZP_ALL)			22 (7.1)	AS4	
		224 (13.17)	268 (15.75)	272 (15.85)	144 (6.48)	AS2*	
Acute Pancreatitis (adjudication confirmed)		13 (0.24) (TZP_ALL)[a]			4 (0.17)	AS3	
		0 (0)	2 (0.4)	2 (0.4)	3 (0.6) (Sema)	SURPASS-2	
		3 (0.9)	2 (0.6)	1 (0.3)	0 (0) (IGlar)	SURPASS-4	
Blood calcitonin increased		9 (0.53)	11 (0.65)	16 (0.93)	5 (0.22)	AS2*	
Asthenia		27 (1.59)	23 (1.35)	51 (2.97)	11 (0.49)	AS2*	

Abbreviations: AE = adverse event; AS1 = placebo-controlled phase 3 safety analysis set; AS2 = safety analysis set 2 (all phase 3 studies); AS3 = Analysis Set 3 (integrated dataset for pooled tirzepatide doses across all Phase 2 and 3 studies); AS4 = placebo-controlled phase 2/3 safety analysis set; BG = blood glucose; BMI = body mass index; CFB = change from baseline; eGFR = estimated glomerular filtration rate; FSG = fasting serum glucose; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; GPGB = I8F-MC-GPGB; GPGO = I8F-JE-GPGO; HbA1c = glycated haemoglobin A1c; IDeg = insulin degludec (titrated); IGlar = insulin glargine (titrated); LS = least-squares; n = number of patients in the specified category; N/A = not applicable; OAM = oral antihyperglycaemic medicinal product; PBO = placebo; Sema = semaglutide 1 mg, subcutaneous injection; SMBG = self-monitored blood glucose; SURPASS-1 = Study I8F-MC-GPGK; SURPASS-2 = Study I8F-MC-GPGL; SURPASS-3 = Study I8F-MC-GPGH; SURPASS-4 = Study I8F-MC-GPGM; SURPASS-5 = Study I8F-MC-GPGI; TZP = tirzepatide; TZP_ALL = pooled across all tirzepatide doses; wks = weeks.

[a] Three of the tirzepatide-treated patients with adjudication-confirmed acute pancreatitis were from Phase 2 Study GPGB (tirzepatide 5 mg [n=2]) and Phase 3 Japan Study GPGO (tirzepatide 15 mg [n=1]).

* The results for the pooled comparator groups of safety analysis set AS2 were calculated by the rapporteur and may be updated, as soon as the applicant has submitted the corresponding analysis.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important effects observed are (in order of importance), superior and clinically meaningful reduction from baseline in HbA1c compared to placebo and to active comparators, significantly higher proportions of responders to HbA1c targets of (>7%, ≤6.5% and <5.7%= normoglycaemia), improvement of other glycaemic measures (FSG, 7-point SMPG, increased time in range), achievement of normoglycemia without a significant increase in the rate of hypoglycaemias, weight reduction, improvement of PRO scores, and improvement of other parameters related to cardiometabolic health (reduction of visceral fat mass, reduction of hepatic fat content, blood pressure, lipids).

The evidence of efficacy was considered statistically convincing and there is good concordance among efficacy endpoints and among subgroups. Some uncertainties with respect to efficacy in subgroups (patients with hepatic impairment, stage 4 and 5 CKD, and normal weight patients) have been addressed by a revised wording in the SPC. Their impact on the overall benefit of tirzepatide is considered small.

Importance of unfavourable effects:

Pancreatitis has been assigned the highest importance, because it may lead to severe complications.

The PTs "renal cyst" and "gallbladder polyp" are considered important, but a causal relation to TZP is difficult to conclude, based on the currently available data.

The importance of the systemic TEAEs dizziness, asthenia, fatigue, vertigo, illness is considered low, as they only weakly correlate with depression and there seems to be no association with dehydration and/or hypotension.

Although gastrointestinal TEAEs belong to the *most common* unfavourable effects, they are considered of minor importance, as they are mostly occurring temporarily and can be controlled by dose adjustment.

The effects of TZP on blood pressure and heart rate are also considered to be of minor importance, as they are well known from other GLP1 receptor agonists, and the CV meta-analysis suggests no increased risk of cardiovascular death.

Increase in pancreatic enzymes is deemed of minor importance, as it was not associated with pancreatitis in most of the cases and is an adverse event well known from established GLP1 receptor agonists.

Hypersensitivity- and injection site reactions are considered to be of low importance, since they were mostly not serious or severe and were self-limiting. Likewise, hypoglycaemia events are considered to be of low importance as they rarely occurred with TZP, mainly in combination with other glucose-lowering background therapies like insulin or OADs.

The relevance of the mild increases in serum calcitonin is unclear and will be followed up post-marketing.

3.7.2. Balance of benefits and risks

For the key benefits of glycaemic control and body weight reductions, tirzepatide was superior to placebo and all active comparators, including the GLP-1 receptor agonist, semaglutide. Glucose control with all tirzepatide doses could be achieved with only minimally increased risk of hypoglycaemia.

The safety and tolerability profile of tirzepatide was characterized in a patient population aligned with the target population for up to 104 weeks (in the longest study) and is considered acceptable. As expected, similar to the GLP-1 receptor agonist class, the most common AEs were GI-related. For the key risk of acute pancreatitis, adjudication-confirmed cases were low in frequency, but a slight imbalance was observed between TZP- and comparator-treated patients. The aetiology and potential long-term implications of the observed increases in serum calcitonin levels are not clear. Post-marketing follow-up is therefore necessary.

3.7.3. Additional considerations on the benefit-risk balance

Quality:

The major objections concerning the missing Notified Body Opinion for the prefilled pen, drug product manufacturing process validation data and risk evaluation report for nitrosamines have been solved.

Clinical:

Initial MO with respect to the indication wording, evolution of indication wording throughout the procedure: please refer to section 2.6.7 of this report.

The following wording is considered approvable:

Tirzepatide (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.

3.8. Conclusions

The overall benefit/risk balance of Mounjaro is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Mounjaro is favourable in the following indication(s):

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tirzepatide is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.