Statistical Analysis Plan Version 2 I8F-MC-GPHG

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

NCT04050553

Approval Date: 26-Oct-2021

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

LY3298176 for Type 2 Diabetes Mellitus

Phase 1, single-center, 2-period, crossover, randomized, patient- and investigator-blind study in patients with Type 2 Diabetes to compare tirzepatide 15 mg to placebo

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol I8F-MC-GPHG
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on 10 September 2020.
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 26-Oct-2021 GMT

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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved September 10, 2020.

This is SAP Version 2. The second version was approved before the final database lock. The overall changes made in this SAP are as follows:

- updated to address the changes made in Protocol Amendment (d)
- updated and clarified population for analyses
- added additional details for summaries of baseline patient characteristics, disposition, and concomitant therapy
- updated exposure and treatment compliance calculation, taking into account early termination
- added additional details for summaries of body weight, safety labs, and immunogenicity data
- updated and clarified details in treatment-emergent adverse event definition and special safety topics
- added additional details for summaries of vital signs and added criteria for treatment-emergent abnormal vital signs
- added algorithm details on lab measurement for values below or above the quantification limit, and
- made editorial changes and formatting corrections.

4. Study Objectives

Table GPHG.1 shows the objectives and endpoints of the study.

Table GPHG.1. Objectives and Endpoints

Objectives	Endpoints
Primary To compare the effect of tirzepatide 15 mg QW and placebo on glucagon response during hypoglycemia in T2DM patients following 12 weeks of treatment	Change in mean glucagon concentration during induced hypoglycemia from target PG concentration of 100 mg/dL to a nadir target of 45 mg/dL
Secondary To compare the effect of tirzepatide 15 mg QW and placebo in T2DM patients following 12 weeks of treatment on: • Other counter-regulatory hormone responses, and responses of insulin and C-peptide during hypoglycemia	• Change in mean glucagon concentration from target PG concentration of 100 mg/dL to 63 mg/dL and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean glucagon concentration from ambient PG to target PG concentrations of 100, 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL to 63 and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Time to hypoglycemia recovery	• Time from termination of insulin infusion at PG concentration of 45 mg/dL to reach recovery PG concentration (72 mg/dL) ($t_{PG\ nadir\text{-}72\ mg/dL}$)
• Clinical hypoglycemia	• Hypoglycemic symptoms score at PG concentrations of 100, 63, and 45 mg/dL and after recovery (PG concentration 72 mg/dL) from induced hypoglycemia • Hypoglycemia awareness at PG concentrations of 100, 63, and 45 mg/dL and after recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Vital signs during hypoglycemia	• Change in mean systolic and diastolic blood pressure and pulse rate from target PG concentration of 100 mg/dL, to 63, and 45 mg/dL, and to recovery (PG concentration 72 mg/dL) from induced hypoglycemia
• Additional safety and tolerability	• AEs • Incidence of hypoglycemia outside of the hypoglycemic clamps

Objectives	Endpoints
Exploratory To compare the effect of tirzepatide 15 mg QW and placebo in T2DM patients following 12 weeks of treatment on:	
• Other hypoglycemic clamp and recovery parameters	• Amount of insulin required to reach PG concentrations of 63 and 45 mg/dL from 100 mg/dL. • $AUC_{GIR,PG\_nadir\text{-}72\ mg/dL}$ • Proportions of patients who require glucose infusion to attain recovery (PG concentration 72 mg/dL) and associated G_{tot} • PG achieved at the end of spontaneous recovery
• Other safety parameters	• Frequency of treatment-emergent anti-tirzepatide antibodies

Abbreviations: AE = adverse event; $AUC_{GIR,PG\_nadir\text{-}72\ mg/dL}$ = area under the glucose infusion rate curve from time of termination of insulin infusion until recovery (PG concentration of 72 mg/dL); G_{tot} = total amount of glucose infused; PG = plasma glucose; QW = once-weekly; T2DM = type 2 diabetes mellitus.

Plasma glucose concentrations: 100 mg/dL = 5.5 mmol/L; 72 mg/dL = 4.0 mmol/L; 63 mg/dL = 3.5 mmol/L; 45 mg/dL = 2.5 mmol/L; ambient glucagon measured in the pre-prandial state prior to clamp initiation.

5. Study Design

5.1. Study Design and Treatment

This is a Phase 1, single-center, 2-period, crossover, randomized, patient- and investigator-blind study in patients with type 2 diabetes mellitus (T2DM). This study is designed to compare tirzepatide 15 mg once-weekly (QW) and placebo with respect to secretion of counter-regulatory hormones in response to a hypoglycemic stimulus and parameters of recovery from hypoglycemia.

Eligibility for this study will be assessed at screening (Visit 1) and confirmed at the beginning of the lead-in period (Visit 2). After eligibility is confirmed at Visit 2, patients will receive training and information on how to subsequently monitor their own diabetes condition. Where applicable, patients will be required to undergo a washout of oral antidiabetic medications (OAMs) other than metformin for at least 4 weeks between Visit 2 and Visit 3.

Following baseline assessments, eligible patients will be 1:1 randomized (Visit 3; Day 1) to treatment sequence. All patients will undergo 2 treatment periods (12 weeks of treatment), receiving tirzepatide in 1 period and placebo in the other, in a crossover fashion.

Tirzepatide 15 mg will be attained via step-wise dose escalation to reduce the risk of gastrointestinal adverse events (AE). Tirzepatide dosing will start at a dose of 2.5 mg QW for 2 weeks, followed by step-wise escalation to 5 mg QW for the next 2 weeks, 10 mg QW for the next 4 weeks, and 15 mg QW for the final 4 weeks.

There will be a washout period of at least 8 weeks (up to 10 weeks) between the last dose of study drug in Period 1 and the first dose in Period 2. The washout period will ensure sufficient washout of the study drug based on tirzepatide's elimination half-life of approximately 5 days.

At the end of each treatment period, patients will undergo a hypoglycemic clamp procedure (Day 79 ±2 [clamp run-in period] and Day 80 ±2 [hypoglycemic induction]). The hypoglycemic clamp procedure is detailed in protocol.

The planned study duration for an individual patient from screening through safety follow-up will be approximately 38 to 42 weeks.

Figure GPHG.1 illustrates the study design.

Figure GPHG.2 illustrates the hypoglycemic clamp procedure.

5.2. Determination of Sample Size

Approximately 38 patients are planned to be enrolled so that 30 patients complete the study assuming a 20% discontinuation rate. The calculation is based on the criterion that the width of the 95% confidence interval (CI) for the treatment comparison of the primary endpoint (change in glucagon from target plasma glucose concentration of 100 mg/dL to nadir target of 45 mg/dL) is within ±23.65 pg/mL with approximately 80% probability, provided that the within-subject variability is 40 pg/mL (Korsatko et al. 2018).

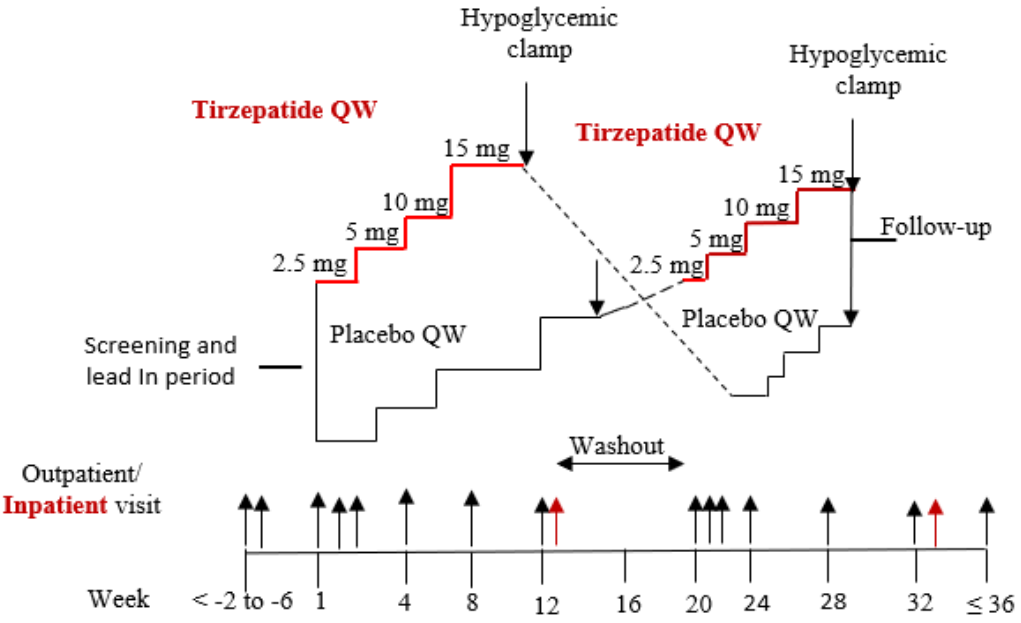
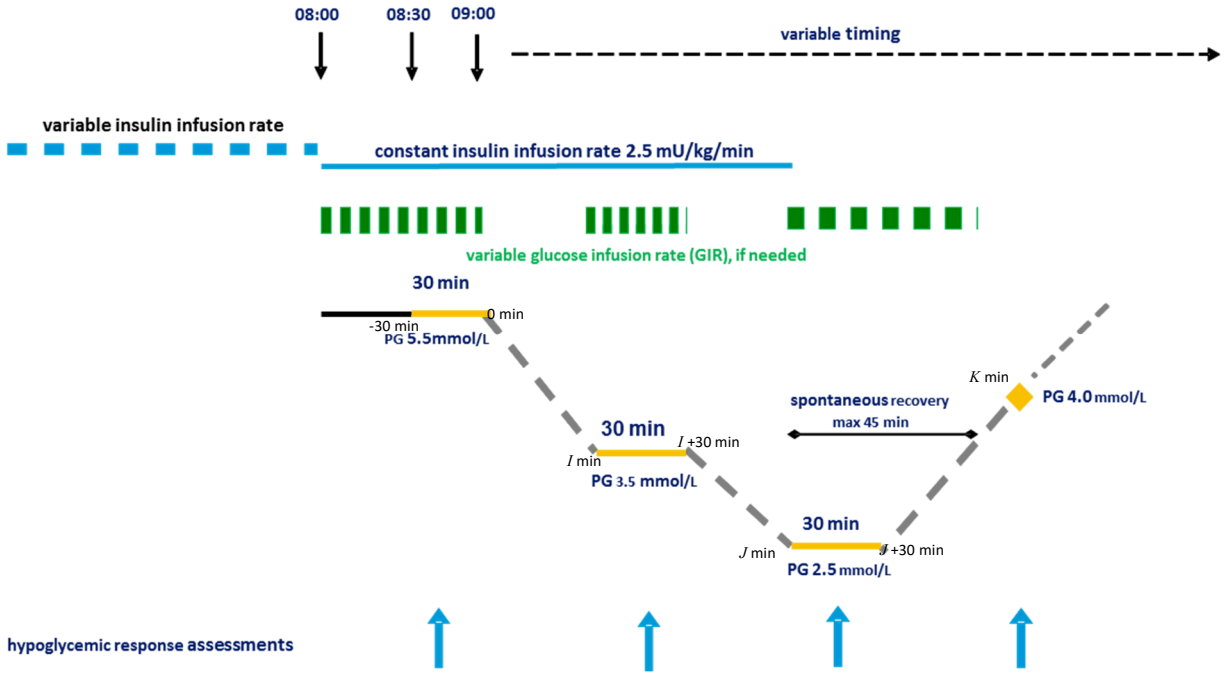


Figure GPHG.1. Illustration of study design for Protocol I8F-MC-GPHG.



Abbreviations: PG = plasma glucose.
Glucagon, insulin, C-peptide, cortisol, growth hormone, adrenaline, and noradrenaline measured at 10, 20 and 30 minutes of each clamp plateau and once PG 72 mg/dL (4.0 mmol/L) is reached.
Blood pressure and pulse rate measured at 0 and 30 minutes of each plateau and once PG 72 mg/dL (4.0 mmol/L) is reached.
Hypoglycemic symptom score and hypoglycemia awareness assessed at 0 and 30 minutes of each plateau and once PG 72 mg/dL (4.0 mmol/L) is reached.

Figure GPHG.2. Hypoglycemic clamp.

6. A Priori Statistical Methods

6.1. Populations for Analyses

For the purpose of analysis, Table GPHG.2 defines 3 analysis sets.

Table GPHG.2. Analysis Populations/Data Sets

Population/Data Set	Definition
All randomized population	All patients who are randomly assigned to a treatment sequence.
Safety population	All randomized patients who are exposed to at least 1 dose of study drug (tirzepatide or placebo), regardless of whether they completed all protocol requirements.
PD analysis set *	Evaluable PD data from all randomized patients who are exposed to at least 1 dose of study drug and complete both hypoglycemic clamp procedures.

Abbreviations: PD = pharmacodynamic.

* Protocol deviations will be considered for their severity/impact and taken into consideration whether subjects should be excluded from PD analysis set for hypoglycemic clamp data related analyses.

6.2. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. Any change to the statistical methods described in the protocol will require a protocol amendment only if it changes a principal feature of the protocol. Any other change to the statistical analyses and the justification for the change will be documented in this SAP.

Unless otherwise specified, safety analyses will be conducted on safety population (Table GPHG.2) and pharmacodynamic (PD) analyses will be conducted on PD analysis set (Table GPHG.2).

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the CI will be calculated at 95%, 2-sided.

If deemed necessary, additional analyses (e.g. linear mixed-effect models) of the endpoints on log transformed data will be conducted.

6.3. Patient Characteristics

The following patient demographic and clinical characteristics at study baseline (measurement collected at screening Visit 1 or during Period 1 Visit 3 Day 1 before first dose; details see below) will be summarized for the safety population and for PD analysis set by treatment sequence (i.e. tirzepatide/placebo and placebo/tirzepatide) and overall.

- age (years)
- age (<65, ≥65 years)
- sex (male, female)

- race
- ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- height (cm)
- duration of diabetes (years)

Note: for above parameters, the measurement collected at screening Visit 1 will be used.

- body weight (kg)
- body mass index (BMI) (kg/m^2)
- BMI groups (<30, ≥ 30 to <35, and ≥ 35 kg/m^2) and (<27, ≥ 27 kg/m^2)
- hemoglobin A1c (% and mmol/mol)
- fasting glucagon
- fasting insulin
- fasting C-peptide
- fasting glucose
- systolic blood pressure
- diastolic blood pressure
- pulse rate

Note: for above parameters, the measurement collected during Period 1 Visit 3 Day 1 before first dose will be used.

In addition, the following patient clinical characteristics at baseline for each period will be summarized for the safety population and for the PD analysis set by treatment for each period, and by treatment (i.e. placebo: overall, period 1, period 2; tirzepatide: overall, period 1, period 2).

- body weight (kg)
- body mass index (BMI) (kg/m^2)
- hemoglobin A1c (% and mmol/mol)
- fasting glucagon
- fasting insulin
- fasting C-peptide
- fasting glucose
- systolic blood pressure
- diastolic blood pressure

- pulse rate

Note: for above parameters, the measurements collected during Period 1 Visit 3 Day 1 before first dose and Period 2 Visit 10 Day 1 before first dose will be used.

6.4. Patient Disposition

A listing of patient disposition for the randomized population will be provided. Patient disposition will be summarized by treatment sequence and period.

A listing of patients who discontinue from the study for any reason for the randomized population will be provided, and the extent of their participation in the study will be reported. The reason for their discontinuation from study will be reported. The listing will also include age, sex, race, treatment, and study period.

6.5. Concomitant Therapy

Concomitant medication will be listed and summarized by World Health Organization Drug Dictionary Medication Class and Preferred Term for the safety population.

A listing of rescue medication for hyperglycemia will be provided.

6.6. Treatment Exposure and Compliance

6.6.1. Treatment Exposure

The duration of exposure to study medication (tirzepatide or placebo) in each treatment period is defined as:

Date of last dose of study medication - date of first dose of study medication +7 days

The duration of exposure to study medication for each treatment period will be listed and summarized by treatment for each treatment period and by treatment only using the safety population

6.6.2. Treatment Compliance

Treatment compliance will be assessed using the safety population. Treatment compliance for each patient will be listed, including the percent compliance for 12-week treatment period taking into account early termination. Percent compliance and treatment compliance will be summarized by treatment for each period and by treatment only.

The percent compliance will be calculated as:

$$(Number\ of\ injections\ administered\ [regardless\ of\ actual\ dose\ in\ mg\ administered] \div total\ number\ of\ injections\ expected\ to\ be\ administered) \times 100$$

Patients will be considered treatment compliant if taking ≥75% of their scheduled doses for 12-week treatment period taking into account early termination (specifically excluding the period after early termination).

When assessing treatment compliance, the missed doses and interrupted doses will be taken into consideration as described in protocol (Section 7.2.1 Selection and Timing of Doses and Section 8.1.2 Temporary Interruption of Study Drug).

6.7. Important Protocol Deviations

Important protocol deviations (IPDs) are defined as deviations from the study protocol that may significantly compromise the data integrity and/or patients' safety. The details of identification of IPDs is provided in a separate document (i.e., the trial issue management plan). A listing/table of IPDs will be provided by the study manager after database lock.

6.8. Pharmacokinetic Analyses

6.8.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic (PK) samples will be collected across the study duration. Tirzepatide concentrations will be determined to support an understanding of tirzepatide exposure over the treatment duration to compare with expected tirzepatide PK.

6.8.2. Pharmacokinetic Statistical Inference

No non-compartmental analysis dependent PK parameters will be derived, thus no statistical analyses of PK parameters are planned.

6.9. Pharmacodynamic Analyses

6.9.1. Pharmacodynamic Parameter Estimation

Hypoglycemic Clamp Procedure Measurements

The clamp procedure will be initiated on Day 79 (clamp run-in period) and the hypoglycemic induction will be performed on Day 80 at the end of both treatment periods. The patient will be asked to attend the clinical research unit at approximately 18:00 hours in the evening of Day 79 and will be served a standardized dinner at approximately 19:00 hours and thereafter will be fasted until the end of the clamp procedure on Day 80.

Pharmacodynamic assessments will include counter-regulatory hormone responses (glucagon, growth hormone, cortisol, adrenaline, and noradrenaline), and responses of insulin and C-peptide before and/or during the clamp, as well as clinical hypoglycemia (hypoglycemic symptom score and hypoglycemia awareness), time to hypoglycemia recovery, vital signs during induced hypoglycemia, and other hypoglycemic clamp and recovery parameters.

During the hypoglycemic clamp, for safety considerations, if the target PG concentrations are not achieved within 30 minutes of completion of the previous step, a higher PG concentration will be accepted as the PG concentration at which assessments are conducted. In case PG nadir 45 mg/dL (2.5 mmol/L) target cannot be reached or symptoms of hypoglycemia are unacceptable, nadir at a higher PG concentration will be accepted (decision will be made by site personnel conducting the test) and data will be included in the analyses.

Hypoglycemic clamp

Clamp interventions are based on the mean PG reading (recorded in eCRF) as one blood sample will be measured twice. The actual times (24 hour clock) of each stage of clamp procedure for each patient are provided through eCRF. These actual times, corresponding to key clamp timepoints (see Table GPHG.3 for details) will be identified by programming.

Table GPHG.3. Key Timepoints of Hypoglycemic Clamp Procedure On Day 80

Clamp PG Level	Planned Key Timepoints	eCRF Clamp Procedure Stage Comment
100 mg/dL (5.5 mmol/L)	-30 minutes	Start plateau 5.5 mmol/L
End of 100 mg/dL (5.5 mmol/L)	0 minutes	Stop plateau 5.5 mmol/L
Reaching 63 mg/dL (3.5 mmol/L)	*I* minutes	Start plateau 3.5 mmol/L
End of 63 mg/dL (3.5 mmol/L)	*I*+30 minutes	Stop plateau 3.5 mmol/L
Reaching 45 mg/dL (nadir; 2.5 mmol/L)	*J* minutes	Start plateau nadir Stop constant insulin infusion
End of 45 mg/dL (nadir; 2.5 mmol/L)	*J*+30 minutes	Stop plateau nadir Start recovery
Reaching 72 mg/dL (4.0 mmol/L)	*K* minutes	Timepoint 4.0 mmol/L reached

* The PG level and duration of each plateau may vary due to patient's conditions as described in Safety Considerations for Assessment Plateaus in Appendix 6 of Protocol.

Counter-regulatory hormone responses, and responses of insulin and C-peptide to hypoglycemic clamp

Glucagon, growth hormone, cortisol, adrenaline, noradrenaline, insulin, and C-peptide concentrations at target PG levels of 100 mg/dL (5.5 mmol/L), 63 mg/dL (3.5 mmol/L), and 45 mg/dL (2.5 mmol/L) will be measured 3 times during each of these 3 plateaus (see Table GPHG.4 for details).

- Mean concentrations at target PG levels of 100 mg/dL (5.5 mmol/L), 63 mg/dL (3.5 mmol/L), and 45 mg/dL (2.5 mmol/L) will be calculated from the 3 measurements taken during each of these 3 plateaus for PD analyses. If there is one missing measurement, the average value between 2 measurements will be used as the mean measurement. If there is only one value, it will be used as the measurement.

The concentrations are measured once at ambient PG (glucagon only) and upon recovery to 72 mg/dL (4.0 mmol/L) (see Table GPHG.4 for details).

Table GPHG.4. Measurements of Glucagon, Insulin, C-peptide, Growth Hormone, Cortisol, Adrenaline, and Noradrenaline from Blood Sampling During Hypoglycemic Clamp Procedure on Day 79 and Day 80

Study Period Day	Clamp PG Level	Planned Timepoints* of Blood Sampling
Day 79		Only glucagon at ambient PG sample was measured in pre-prandial state prior to clamp initiation
Day 80	100 mg/dL (5.5 mmol/L)	-20 minutes -10 minutes 0 minutes
Day 80	63 mg/dL (3.5 mmol/L)	*I* + 10 minutes *I* + 20 minutes *I* + 30 minutes
Day 80	45 mg/dL (nadir; 2.5 mmol/L)	*J* + 10 minutes *J* + 20 minutes *J* + 30 minutes
Day 80	72 mg/dL (4.0 mmol/L)	*K* minutes

* The Planned Timepoints of blood sampling during clamp will be collected in eCRF.

Clinical hypoglycemia

Hypoglycemic symptom score

Symptoms of hypoglycemia will be measured with a subjective, validated questionnaire, the Edinburgh Hypoglycemia Symptom Scale (EHSS), which measures the intensity of commonly experienced hypoglycemic symptoms on a 7-point Likert scale (1 = No symptom, 2 = very mild, 3 = mild, 4 = mild to moderate, 5 = moderate, 6 = moderate to severe, and 7 = Severe). These symptoms have been grouped previously into neuroglycopenic symptoms (cognitive dysfunction and neuroglycopenia), and autonomic symptoms (McCrimmon et al. 2003).

In this study, 13 questions are used to measure hypoglycemic symptoms. These data will be recorded in eCRF.

- **Neuroglycopenic symptoms (10)**
    - **Cognitive dysfunction (6):** inability to concentrate, blurred vision, anxiety, confusion, difficulty speaking, and double vision
    - **Neuroglycopenia (4):** drowsiness, tiredness, hunger, and weakness
- **Autonomic symptoms (3):** sweating, trembling, and warmness

The subscores of neuroglycopenic symptoms (cognitive dysfunction and neuroglycopenia), and autonomic symptoms, and the overall score (means of non-missing values) will be calculated and used for PD analyses based on responses to 13 questions, where lower score indicates fewer symptoms.

The EHSS questionnaire will be administered twice (0 and 30 minutes) at each of the 3 plateaus (target levels of PG of 100 mg/dL [5.5 mmol/L], 63 mg/dL [3.5 mmol/L,] and PG of 45 mg/dL [2.5 mmol/L]) (see Table GPHG.5 for details).

- The subscores and overall score (means of non-missing values) will be calculated for both collection timepoints in each plateau. Mean hypoglycemic symptoms subscores and overall score at each plateau (mean of the 2 measurements taken) will be calculated and used for analyses.

The EHSS questionnaire will be administered once when recovery PG of 72 mg/dL (4.0 mmol/L) is reached (see Table GPHG.5 for details). The subscores and overall score for this single recovery collection timepoint will be used for analyses.

Table GPHG.5. Hypoglycemic Symptom Score and Hypoglycemia Awareness During Hypoglycemic Clamp Procedure on Day 80

Clamp PG Level	Planned Timepoints of Collecting Hypoglycemic Symptom Score and Hypoglycemia Awareness
100 mg/dL (5.5 mmol/L)	-30 minutes 0 minutes
63 mg/dL (3.5 mmol/L)	*I* minutes *I* + 30 minutes
45 mg/dL (nadir; 2.5 mmol/L)	*J* minutes *J* + 30 minutes
72 mg/dL (4.0 mmol/L)	*K* minutes

Hypoglycemia awareness

Hypoglycemia awareness will be evaluated based on the patients' response (yes/no) to the question "Do you feel hypoglycemic?" during induced hypoglycemia. These data will be recorded in eCRF.

Hypoglycemia awareness will be assessed twice (0 and 30 minutes) at each of the 3 plateaus (target levels of PG of 100 mg/dL [5.5 mmol/L], 63 mg/dL [3.5 mmol/L], and PG of 45 mg/dL [2.5 mmol/L]) (see Table GPHG.5 for details).

- If the patient answered "yes" at least once when the question was asked twice in the same plateau, the patient is aware of hypoglycemia during induced hypoglycemia at that target PG level. If the patient answered "no" to the question when asked twice in that plateau, the patient is unaware of hypoglycemia. If there is only one non-missing value, it will be used as the measurement.

Hypoglycemia awareness will be assessed once when recovery PG of 72 mg/dL (4.0 mmol/L) is reached (see Table GPHG.5 for details).

Vital signs

Vital signs (that is, systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature) at target PG of 100 mg/dL (5.5 mmol/L), 63 mg/dL (3.5 mmol/L), and 45 mg/dL (2.5 mmol/L) will be measured twice at each of the 3 plateaus (see Table GPHG.6 for details).

- Mean vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) at target PG of 100 mg/dL (5.5 mmol/L), 63 mg/dL (3.5 mmol/L), and 45 mg/dL (2.5 mmol/L) will be calculated as the mean of the 2 measurements taken at each of these 3 plateaus for PD analyses. If there is only one non-missing value, it will be used as the measurement.

Vital signs will be measured once when recovery PG of 72 mg/dL (4.0 mmol/L) is reached (see Table GPHG.6 for details).

Table GPHG.6. Vital Signs During Hypoglycemic Clamp Procedure on Day 80

Clamp PG Level	Planned Timepoints of Collecting Vital Signs
100 mg/dL (5.5 mmol/L)	-30 minutes 0 minutes
63 mg/dL (3.5 mmol/L)	*I* minutes *I* + 30 minutes
45 mg/dL (nadir; 2.5 mmol/L)	*J* minutes *J* + 30 minutes
72 mg/dL (4.0 mmol/L)	*K* minutes

6.9.2. Pharmacodynamic Statistical Inference

The counter-regulatory hormone responses (glucagon, growth hormone, cortisol, adrenaline, and noradrenaline), and responses of insulin and C-peptide will be reported in the International System of Units and conventional units.

6.9.2.1. Primary Pharmacodynamic Analysis

Glucagon counter-regulatory response during induced hypoglycemia

The primary PD parameter to assess the effect of tirzepatide 15 mg versus placebo will be the change in mean glucagon concentration from the target PG concentration of 100 mg/dL (5.5 mmol/L) to the nadir target 45 mg/dL (2.5 mmol/L) (i.e., glucagon at nadir PG – glucagon at PG of 100mg/dL) during induced hypoglycemia. This will be evaluated using a linear mixed-effect model, with treatment, treatment period, and treatment sequence as fixed effects, and patient as a random effect using restricted maximum likelihood (REML) method in PD analysis set.

Note: See Section 6.9.1 for calculation details. Mean concentrations of glucagon at target PG levels of 100 mg/dL (5.5 mmol/L) and 45 mg/dL (2.5 mmol/L) will be calculated from the 3

measurements taken during these plateaus, respectively. If there is one missing measurement, the average value between 2 measurements will be used as the mean measurement. If there is only value, it will be used as the measurement.

Inferential statistics will include least squares (LS) means and standard error of glucagon concentration change for tirzepatide versus placebo, the treatment difference (tirzepatide - placebo), 95% CI, and associated p-values.

Sensitivity analyses on primary endpoint among patients who reached nadir target PG of 45 mg/dL (2.5 mmol/L) will be conducted in a similar manner if deemed appropriate, otherwise summary statistics will be sufficient. Patients who reached nadir are defined as the ones whose mean PG is ≤45 mg/dL at *J* minutes (Start plateau nadir).

- The actual PG level at nadir (*J* minutes) will be summarized by treatment. The frequency and proportion of patients who did not reach target nadir will be summarized.

6.9.2.2. Secondary Pharmacodynamic Analysis

The following measurements will be secondary PD measures in the study. See Section 6.9.1 for data collection and calculation details.

Counter-regulatory hormone responses, and responses of insulin and C-peptide during induced hypoglycemia

Secondary PD measures to assess the effect of tirzepatide 15 mg versus placebo on counter-regulatory hormones, insulin, and C-peptide concentrations during induced hypoglycemia:

Glucagon

- Change in mean glucagon concentration from target PG concentration of 100 mg/dL (5.5 mmol/L)
    - to target PG concentration of 63 mg/dL (3.5 mmol/L)
    - to target recovery PG concentration 72 mg/dL (4.0 mmol/L)
- Change in mean glucagon concentration from ambient PG (see Table GPHG.4 for details)
    - to target PG concentration of 100 mg/dL (5.5 mmol/L)
    - to target PG concentration of 63 mg/dL (3.5 mmol/L)
    - to target PG nadir 45 mg/dL (2.5 mmol/L)
    - to target recovery PG concentration of 72 mg/dL (4.0 mmol/L)

Insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline

- Change in mean insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG concentration of 100 mg/dL (5.5 mmol/L)

- to target PG concentration of 63 mg/dL (3.5 mmol/L)
- to target PG nadir 45 mg/dL (2.5 mmol/L)
- to target recovery PG concentration of 72 mg/dL (4.0 mmol/L)

The secondary PD parameters collected during hypoglycemic clamp procedure listed above (counter-regulatory responses) will be analyzed in a manner similar to the primary PD analysis using a linear mixed-effect model, respectively.

Additional assessments on counter-regulatory response are described in Section 6.9.2.3 as exploratory endpoints.

Time to hypoglycemia recovery

Secondary PD measures to assess the effect of tirzepatide 15 mg versus placebo on time to recovery from induced hypoglycemia:

- Time from termination of insulin infusion at PG concentration of nadir 45 mg/dL (2.5 mmol/L) to reach recovery PG concentration (72 mg/dL [4.0 mmol/L])
  - That is, $t_{PG\_nadir\text{-}72\ mg/dL}$ [from Stop constant insulin infusion (*J* minutes) to the Timepoint 4.0 mmol/L reached (*K* minutes)]
  - The actual times (24 hour clock), corresponding to *J* and *K* minutes (see Table GPHG.3 for details) will be identified by statistical programming, and the time interval will calculated for PD analyses.

The $t_{PG\_nadir\text{-}72\ mg/dL}$ will be analyzed in a manner similar to the primary PD analysis using a linear mixed-effect model.

Clinical hypoglycemia

Secondary PD measures to assess the effect of tirzepatide 15 mg versus placebo on clinical hypoglycemia during induced hypoglycemia:

- Hypoglycemic symptoms score (subscores and overall score) at the following times:
  - at target PG concentration of 100 mg/dL (5.5 mmol/L)
  - at target PG concentration of 63 mg/dL (3.5 mmol/L)
  - at target PG concentration of nadir 45 mg/dL (2.5 mmol/L)
  - at target recovery PG concentration of 72 mg/dL (4.0 mmol/L)

  The hypoglycemic symptom subscores and overall score at each of 4 target PG levels (i.e., 5.5 mmol/L, 3.5 mmol/L, nadir [2.5 mmol/L], and recovery [4.0 mmol/L]) during hypoglycemic clamp will be analyzed respectively in a manner similar to the primary PD analysis using a linear mixed-effect model.
- Hypoglycemia awareness (binary) at the following times:
  - at target PG concentration of 100 mg/dL (5.5 mmol/L)

- at target PG concentration of 63 mg/dL (3.5 mmol/L)
- at target PG concentration of nadir 45 mg/dL (2.5 mmol/L)
- at target recovery PG concentration of 72 mg/dL (4.0 mmol/L)

The hypoglycemia awareness at each of 4 target PG levels (i.e., 5.5 mmol/L, 3.5 mmol/L, nadir [2.5 mmol/L], and recovery [4.0 mmol/L]) during hypoglycemic clamp will be analyzed with nonparametric McNemar test at each target PG level to examine if there is difference in hypoglycemia awareness in comparison of tirzepatide 15 mg versus placebo.

The above PD parameters (hypoglycemic symptom scores and hypoglycemia awareness) collected at 4 target PG levels will be summarized by treatment using descriptive statistics. Corresponding plots on the hypoglycemic symptom scores with mean and standard deviations of PD parameters of these target PG levels will be provided by treatment.

Vital signs during induced hypoglycemia

Secondary PD measures to assess the effect of tirzepatide 15 mg versus placebo on vital signs during induced hypoglycemia:

- change in mean systolic blood pressure, diastolic blood pressure, and pulse rates from target PG concentration of 100 mg/dL (5.5 mmol/L)
  - to target PG concentration of 63 mg/dL (3.5 mmol/L)
  - to target PG nadir 45 mg/dL (2.5 mmol/L)
  - to target recovery PG concentration of 72 mg/dL (4.0 mmol/L)

The above changes in vital signs during induced hypoglycemia will be summarized by treatment, and will be analyzed respectively in a manner similar to the primary PD analysis using a linear mixed-effect model.

6.9.2.3. Exploratory Pharmacodynamic Analysis

AUC will be calculated using trapezoidal rule. See Section 6.9.1 for data collection and calculation details.

Additional hypoglycemic clamp and recovery parameters

Insulin infusion related parameters

The human soluble insulin lispro (40 IU insulin lispro [100 IU/mL] in 99.6 mL saline) is used for intravenous infusion (insulin 40 IU/100 mL). Between 0 minutes [Stop plateau 5.5 mmol/L], *I* minutes [Start plateau 3.5 mmol/L], and *J* minutes [Start plateau nadir, Stop constant insulin infusion], insulin is infused at a constant flow 2.5 mU/kg/min, based on the patient body weight at Day 78 predose of each period. Insulin infusion is terminated once PG reaches nadir 45 mg/dL.

Unit conversion of insulin infusion rate (IIR) [mL/hour] to IIR [mU/min/kg]:

*IIR [mL/hour] * concentration 0.4 IU/mL * 1000 mU/IU ÷ (60 min/hour) ÷ body weight [kg]*

Exploratory PD measures to assess the effect of tirzepatide 15 mg versus placebo on the amount insulin needed include:

- Amount of insulin [i.e. AUC of IIR; mU/kg] required to reach PG concentration of 63 mg/dL (3.5 mmol/L) from 100 mg/dL (5.5 mmol/L)
    - The time interval from Stop plateau 5.5mmol/L (0 minutes) to Start plateau 3.5mmol/L (*I* minutes) is of interest, where insulin is infused at a constant rate.
- Amount of insulin [i.e. AUC of IIR; mU/kg] required to reach PG concentration of nadir 45 mg/dL (2.5 mmol/L) from 100 mg/dL (5.5 mmol/L)
    - The time interval from Stop plateau 5.5mmol/L (0 minutes) to Start plateau Nadir (*J* minutes) is of interest, where insulin is infused at a constant rate.

Glucose infusion related parameters

The glucose 20% (200 mg/mL) is used for intravenous infusion. At *J* minutes [Start plateau nadir, Stop constant insulin infusion], variable glucose infusion started, if needed to maintain nadir PG 45 mg/dL. At *J*+30 minutes [Stop plateau nadir, Stary recovery], glucose infusion if switched off, and will be restarted if PG falls below 40 mg/dL until 45 mg/dL is reached. At *J*+45 minutes, if PG doesn't recover to 72 mg/dL, constant glucose infusion flow (5.5 mg/kg/min) is started [Start constant glucose infusion] until PG ≥ 72 mg/dL (at *K* minutes: Timepoint 4.0 mmol/L reached), based on the patient body weight at Day 78 predose of each period.

Unit conversion of glucose infusion rate (GIR) [mL/hour] to GIR [mg/min/kg]:

*GIR [mL/hour] * concentration 20 g/100 mL * 1000 mg/g ÷ (60 min/hour) ÷ body weight [kg]*

Exploratory PD measures to assess the effect of tirzepatide 15 mg versus placebo on glucose infusion related parameters include:

- Area under the glucose infusion rate curve from time of termination of insulin infusion until recovery (PG of 72 mg/dL [4.0 mmol/L]), $AUC_{GIR,PG\_nadir\text{-}72\ mg/dL}$ [mg/kg]
    - The time interval from Stop constant insulin infusion (*J* minutes) to Timepoint 4.0 mmol/L reached (*K* minutes) is of interest.
- The total amount of glucose infused to attain recovery (PG of 72 mg/dL [4.0 mmol/L]), G_{tot} [mg/kg] (i.e. AUC of GIR)
    - The time interval from Start recovery (*J* +30 minutes) to Timepoint 4.0 mmol/L reached (*K* minutes) is of interest.
- The proportion of patients who require glucose infusion to attain recovery (PG concentration 72 mg/dL [4.0 mmol/L])
    - If the above calculated G_{tot} >0, the patient required glucose infusion to attain recovery. If G_{tot} = 0, the patient attained recovery without glucose infusion.

- Average glucose infusion rate [mg/min/kg] from Start plateau 5.5 mmol/L (-30 minutes) to Stop constant insulin infusion (*J* minutes)
- Average glucose infusion rate [mg/min/kg] from Stop constant insulin infusion (*J* minutes) to Timepoint 4.0 mmol/L reached (*K* minutes)

Hypoglycemia recovery parameters

Exploratory PD measure to assess the effect of tirzepatide 15 mg versus placebo on the recovery from hypoglycemia include:

- PG achieved at the end of the spontaneous recovery period
    - This is the PG level at 45 minutes after termination of the insulin infusion (*J* minutes [Stop constant insulin infusion] + 45 minutes). At *J*+45 minutes, if PG doesn't recover to 72 mg/dL, Start constant glucose infusion.
- The proportion of patients who recovered spontaneously 45 minutes after termination of the insulin infusion (*J*+45 minutes)
- If the PG level at *J*+45 minutes ≥72 mg/dL, the patient recovered spontaneously at *J*+45 minutes.

The above other hypoglycemic clamp and recovery exploratory PD parameters (except the proportion of patients who require glucose infusion to attain recovery and the proportion of patients who recovered spontaneously at *J*+45 minutes) will be analyzed in a manner similar to the primary PD analysis using a linear mixed-effect model.

The status of whether patients require glucose infusion to attain recovery and whether patients recovered spontaneously at *J*+45 minutes will be analyzed in a similar manner to the secondary analyses on hypoglycemia awareness with nonparametric McNemar test.

Counter-regulatory hormone responses, and responses of insulin and C-peptide, and vital signs during induced hypoglycemia

- Change in mean glucagon, insulin, C-peptide, growth hormone, cortisol, adrenaline, and noradrenaline concentrations from target PG nadir of 45 mg/dL (2.5 mmol/L) to 72 mg/dL (4.0 mmol/L)

The above changes in counter-regulatory responses will be analyzed in a manner similar to the primary PD analysis using a linear mixed-effect model.

- Change in vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) from target PG nadir of 45 mg/dL (2.5 mmol/L) to 72 mg/dL (4.0 mmol/L)

The above changes in vital signs during induced hypoglycemia will be analyzed in a manner similar to the primary PD analysis using a linear mixed-effect model.

Additional exploratory PD parameters (counter-regulatory responses, vital signs, and AUC_{GIR}) for analyses

The following PD parameters collected at ambient PG sample (only glucagon), three 30-min target PG plateaus (5.5 mmol/L, 3.5 mmol/L, and nadir [2.5 mmol/L]) and recovery [4.0 mmol/L] on Day 80 will be summarized by treatment using descriptive statistics. Corresponding plots of mean and standard deviations of these PD parameters over the target PG levels will be provided by treatment.

These PD parameters will be analyzed in a manner similar to the primary PD analysis using a linear mixed-effect model.

- Counter-regulatory hormone responses (glucagon, growth hormone, cortisol, adrenaline, and noradrenaline), and responses of insulin and C-peptide to induced hypoglycemia
    - Only glucagon will also collected at ambient PG sample under pre-prandial state, prior to clamp initiation on Day 79
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) during induced hypoglycemia
- AUC_{GIR} [mg/kg]
    - It will be calculated at each of the 3 plateaus (30 minutes each), and at recovery period (*J*+30 minutes to *K* minutes).

6.9.3. Body Weight

Weight will be measured at multiple visits in both treatment periods before dosing. Descriptive summaries of body weight will be provided for actual values of Day 1, Day 29, Day 57, Day 78 by treatment for each period, and by treatment only, and change from Day 1 values by treatment for each period, and by treatment only. Plots of mean body weight and mean changes from Day 1 over time will be provided by treatment for each period, and by treatment only.

6.10. Safety Analyses

Safety measures include, but not limited to, AEs, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), vital signs, and safety laboratory measures.

Unless specified otherwise, safety analyses will be performed on the safety population.

Unless specified otherwise, safety listings will display values/events during all study periods (i.e., treatment periods, washout, and follow-up period). Listings of AEs, death, SAE may include (but not limited to): patient identification (ID) number, age, sex, race, treatment, dose, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), Preferred Term (PT), and time of onset from the first dose of study drug, duration of the AE, seriousness, severity, relatedness to study drug, action taken, and outcome, as appropriate. Additional safety listings will be provided for safety parameters other than AEs in related sections below. Treatment, and treatment period will be displayed in listings.

For safety measurements, summary statistics will be provided by treatment. A summary will be provided for AEs with frequency ≥10 patients with such event.

6.10.1. Adverse Events

A listing of adverse events for the safety population will be provided, which includes MedDRA SOC, and PT.

6.10.2. Treatment-Emergent Adverse Events

A TEAE is defined as an AE which first occurs post first dose of study drug (of Period 1) or which is present prior to first dose of study drug (of Period 1) and becomes more severe post first dose. The maximum severity for each AE during the baseline period (prior to first dose of Period 1) including ongoing medical history will be used as baseline severity.

Treatment-emergent adverse events will be summarized by treatment, severity and relationship with study drug.

For TEAEs in wash-out period, the treatment arm from Period 1 will be used for summary. For TEAEs in follow-up period, the treatment arm from Period 2 will be used.

6.10.3. Serious Adverse Events (SAEs)

A listing of patients with SAEs (including death) will be produced.

6.10.4. Adverse Events Leading to Discontinuation

A listing of patients with AEs leading to discontinuation from study will be provided.

6.10.5. Special Safety Topics

A listing of patients with all AESIs defined in Section 6.10.5 will be provided.

6.10.5.1. Severe/Serious Gastrointestinal Adverse Events

A listing of patients with severe/serious gastrointestinal AEs, such as nausea, vomiting, and diarrhea will be provided.

Only the PTs in the gastrointestinal SOC MedDRA with serious/severe cases will be considered as AESIs.

6.10.5.2. Hypoglycemia

Only hypoglycemic events outside of hypoglycemic clamp procedure are applicable here. A listing of clinically significant hypoglycemia (plasma glucose <54 mg/dL) and severe hypoglycemia events will be provided. A listing of patients with hypoglycemic events will be provided. The category of hypoglycemic events (see Table GPHG.7 for details) will be presented. A summary will be provided by treatment. The incidence of hypoglycemia will be reported.

Severe/Serious hypoglycemia will be considered as AESIs.

Table GPHG.7. Definitions of Hypoglycemic Event Categories

	Symptoms and/or Signs of Hypoglycemia	Plasma Glucose Level
Glucose alert value	Yes/No/Unknown	≤70 mg/dL (3.9 mmol/L)
Documented symptomatic hypoglycemia	Yes	
Documented asymptomatic hypoglycemia	No	
Documented unspecified hypoglycemia	Unknown	
Clinically significant hypoglycemia	Yes/No/Unknown	<54 mg/dL (3.0 mmol/L)
Documented symptomatic hypoglycemia	Yes	
Documented asymptomatic hypoglycemia	No	
Documented unspecified hypoglycemia	Unknown	

Severe hypoglycemia: defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemia will be reported as an SAE.

Nocturnal hypoglycemia: defined as any hypoglycemic event that occurs between bedtime and waking.

To avoid duplicate reporting, all consecutive plasma glucose values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event.

6.10.5.3. Severe, Persistent Hyperglycemia

Data on episodes of severe, persistent hyperglycemia will be reported by the investigator during the study. Events of interest related to hyperglycemia are those that require rescue therapy, per the criteria in Protocol Section 9.2.2.3.

A listing of rescue medication for hyperglycemia will be provided (also noted in Section 6.5).

6.10.5.4. Pancreatitis

A listing of patients with pancreatitis (including investigator-reported and adjudicated) will be provided. Adjudication assessment results will be reported in the listing.

Treatment-emergent adjudication-confirmed pancreatitis will be considered as AESI.

6.10.5.5. Thyroid Malignancies and C-Cell Hyperplasia

A listing of patients with thyroid malignancies and C-cell hyperplasia (search criteria provided in Appendix 1) will be provided.

Thyroid malignancies and C-cell hyperplasia will be considered as AESI.

6.10.5.6. Major Adverse Cardiovascular Events (MACE)

A listing of patients with MACE (including investigator-reported and adjudicated) will be provided. Adjudication assessment results will be reported in the listing.

Only positively adjudicated MACE will be considered as AESI.

6.10.5.7. Arrhythmias and Cardiac Conduction Disorders

A listing of patients with arrhythmias and cardiac conduction disorders (search criteria provided in Appendix 1) will be provided.

Severe/serious treatment-emergent arrhythmias and cardiac conduction disorders will be considered as AESI. The cardiovascular events will include clinically relevant rhythm and conduction disorders.

6.10.5.8. Hypersensitivity Events

A listing of patients with hypersensitivity reactions (search criteria provided in Appendix 1) will be provided.

Only the serious/severe cases of hypersensitivity will be considered as AESIs.

6.10.5.9. Injection Site Reactions

Injection-site assessments for local tolerability will be conducted, when reported as an AE from a patient, or a clinical observation from an investigator.

A listing of patients with reported injection-site reactions (e.g., edema, erythema, induration, itching, and pain) will be provided. Detailed search criteria can be found in Appendix 1.

Only the severe/serious injection site reactions (e.g., abscess, cellulitis, erythema, hematomas/hemorrhage, exfoliation/necrosis, pain, subcutaneous nodules, swelling, indurating, inflammation) will be considered as AESIs.

6.10.5.10. Diabetic Retinopathy Complications

A listing of patients with diabetic retinopathy complications (search criteria provided in Appendix 1) will be provided.

The cases with repeat fundoscopy during the course of the trial, based on clinical suspicion of worsening retinopathy that have either findings of de novo retinopathy or progression of retinopathy, and severe/serious adverse events from the PTs for diabetic retinopathy complications (search criteria provided in Appendix 1), will be classified as an AESI.

6.10.5.11. Hepatobiliary Disorders

A listing of patients with events of biliary colic, cholecystitis, or other suspected events related to gallbladder disease will be provided. Detailed search criteria are provided in Appendix 1.

Severe/serious hepatobiliary disorders will be considered as AESIs.

6.10.5.11.1. Hepatic Monitoring

The patients' liver disease history and associated person liver disease history data will be listed. Concomitant medications acetaminophen/paracetamol, that have potential to cause hepatotoxicity, will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be listed, and it will be summarized by treatment if ≥10 patients with such data. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual patient data listings.

6.10.5.12. Acute Renal Events

A listing of patients with acute renal events (search criteria provided in Appendix 1) will be provided.

Severe/serious acute renal events will be considered as AESI.

6.10.5.13. Metabolic Acidosis, Including Diabetic Ketoacidosis

A listing of patients with metabolic acidosis (search criteria provided in Appendix 1) will be provided.

Severe/serious Metabolic Acidosis, including Diabetic Ketoacidosis will be captured as AESIs.

6.10.5.14. Amputation/Peripheral Revascularization

A listing of patients with amputation and peripheral revascularization (search criteria provided in Appendix 1) will be provided.

Amputation/Peripheral revascularization will be considered as AESIs.

6.10.5.15. Major Depressive Disorder/Suicidal Ideation

A listing of patients with major depressive disorder/suicidal ideation (search criteria provided in Appendix 1) will be provided.

The severe/serious major depressive disorder/suicidal ideation or behavior will be captured as AESI.

6.10.6. Vital Signs

Descriptive summaries of vital signs will be provided for actual values of Day 1, Day 8, Day 15, Day 29, Day 57, Day 78 by treatment for each period, and by treatment only, and change from Day 1 values by treatment for each period, and by treatment only. Plots of mean vital signs and mean changes from Day 1 over time will be provided by treatment for each period.

The treatment-emergent abnormal vital signs will be listed. The criteria for identifying patients with treatment-emergent vital sign abnormalities are stated in Table GPHG.8.

Table GPHG.8. Categorical Criteria for Treatment-Emergent Abnormal Blood Pressure and Pulse Measurements

Parameter	Low	High
Systolic BP (mmHg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mmHg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15

Abbreviations: BP = blood pressure; bpm = beats per minute.

For PD parameters of systolic, diastolic blood pressure, and pulse rate during hypoglycemic clamp procedures, see Section 6.9 for analyses details.

6.10.7. Electrocardiogram

Electrocardiograms will be performed for safety monitoring purposes only. Any clinically significant ECG findings entered as AEs will be included in AE summaries.

6.10.8. Safety Laboratory Parameters

All laboratory data will be reported in the International System of Units and conventional units.

Descriptive summaries of clinical chemistry, hematology, and endocrine (calcitonin) data will be provided for actual values of Day 1 predose, Day 29, Day 78, and their changes from Day 1 will by treatment for each period, and by treatment only.

Additionally, clinical chemistry, hematology, urinalysis, and endocrine (calcitonin) data outside the reference ranges will be listed.

If any safety lab measurements are (1) below the quantification limit (e.g. < QL), ½ × QL may be used for the calculation of summary statistics; (2) above the quantification limit (e.g. > QL), 1.1 × QL may be used for the calculation of summary statistics, if deemed appropriate.

6.11. Evaluation of Immunogenicity

Baseline immunogenicity sample is collected on Day 1 pre-dose of period 1. The immunogenicity tables will be presented with only one overall column. The listings will report treatment and period.

For the treatment-emergent (TE) antidrug antibody (ADA)-positive patients, the distribution of maximum titers may be described.

The frequency and percentage of patients with preexisting ADA and with TE ADA-positive (TE-ADA+) to tirzepatide may be tabulated.

If cross-reactive antibodies to native GIP and GLP-1, neutralizing antibodies against tirzepatide activity on GIP and GLP-1 receptors, or neutralizing antibodies against native GLP-1 and GIP are performed, the frequency and percentage of each may be tabulated.

A listing will be provided of immunogenicity assessments. This includes the tirzepatide concentration from a simultaneous pharmacokinetic sample and the clinical interpretation result (ADA Present, ADA Not Present, ADA Inconclusive, or Missing). A listing of TEAE for patients with TE ADA+ or Injection Site Reaction or Potential Hypersensitivity may be provided.

Cases of TE-ADA+ that are associated with AEs of either severe/serious hypersensitivity or severe/serious injection site reaction will be classified as AESI.

6.12. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, clinical research physician, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

7. Unblinding Plan

The blinding/unblinding plan is not part of this SAP. The approved blinding/unblinding plan is stored in Leo.

8. Changes from the Protocol Specified Statistical Analyses

Changes from the protocol specified statistical analyses are as follows:

- Protocol Section 10 states "Safety analyses will be conducted for all enrolled patients whether or not they completed all protocol requirements" and "Pharmacodynamic analyses will be conducted on data from all patients who complete both hypoglycemic clamp procedures." In this SAP, it is clarified that safety population includes all randomized patients, who are exposed to at least 1 dose of the study drug (tirzepatide or placebo), regardless of whether they completed all protocol requirements, and PD analysis set includes evaluable PD data from all randomized patients who are exposed to at least 1 dose of study drug and complete both hypoglycemic clamp procedures.

9. References

Korsatko S, Jensen L, Brunner M, Sach-Friedl S, Tarp MD, Holst AG, Heller SR, Pieber TR. Effect of once-weekly semaglutide on the counterregulatory response to hypoglycaemia in people with type 2 diabetes: A randomized, placebo-controlled, double-blind, crossover trial. *Diabetes Obes Metab*. 2018;20(11):2565-2573.

McCrimmon RJ, Deary IJ, Gold AE, Hepburn DA, MacLeod KM, Ewing FM, Frier BM. Symptoms reported during experimental hypoglycaemia: effect of method of induction of hypoglycaemia and of diabetes per se. *Diabetic Medicine*. 2003 Jun;20(6):507-509.

10. Appendices

Appendix 1. Search Criteria For Adverse Events of Special Safety Topics

The search criteria for AEs of special safety topics and AESIs are stored in CLUWE:\statsclstr\qa\ly3298176\common\AESI_Lab\Search criteria AESIs_TZP.xlsx

Leo Document ID = f86a6ca7-e5ba-482d-94a2-d23a79b52c05

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