Statistical Analysis Plan I8F-MC-GPHT(b)

A Multiple Dose Titration Study in Chinese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Tirzepatide

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STATISTICAL ANALYSIS PLAN

A Multiple Dose Titration Study in Chinese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Tirzepatide

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

7p-SMPG	7-point self-monitored plasma glucose
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-168)	Area under the concentration versus time curve from time zero to 168 hour postdose
BQL	Below the lower limit of quantification
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical research unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
ICH	International Conference on Harmonisation
IP	Investigational Product
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
OAM	Oral antidiabetic medication
PD	Pharmacodynamic
PG	Plasma glucose

PK	Pharmacokinetic
QW	Once weekly
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
T2DM	Type 2 Diabetes Mellitus
TBL	Total bilirubin
TE	Treatment emergent
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
VAS	Visual analog scale
V_{ss}/F	Apparent volume of distribution as steady state after extravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 13 March 2019) and Protocol Amendment (a) (final version dated 14 February 2020).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and efficacy data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

To investigate the safety and tolerability of tirzepatide after multiple subcutaneous (SC) doses administered to Chinese patients with Type 2 Diabetes Mellitus (T2DM).

4.2 Secondary Objective

To characterize the PK of tirzepatide after multiple SC doses in Chinese patients with T2DM.

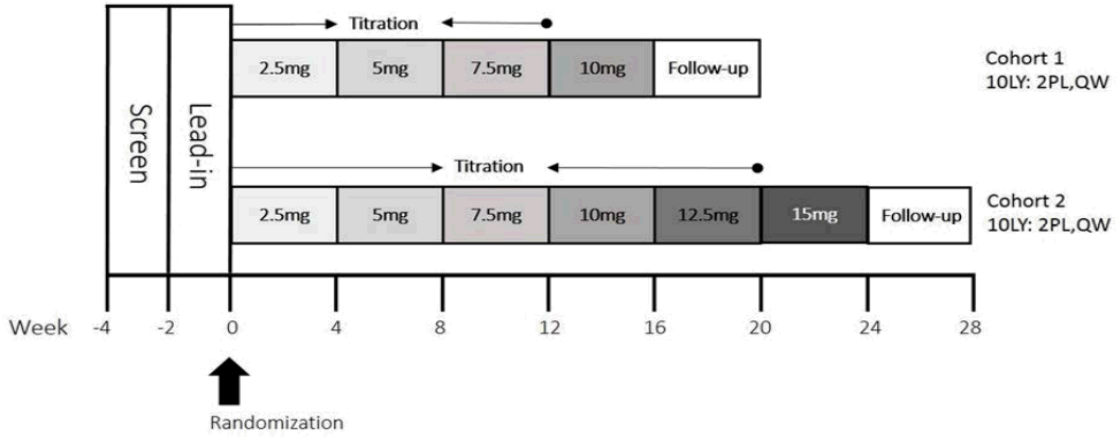
4.3 Exploratory Objectives

- To investigate the efficacy of tirzepatide after multiple SC doses administered to Chinese patients with T2DM
- To investigate the exploratory PD effects of tirzepatide after multiple SC doses administered to Chinese patients with T2DM
- To evaluate the formation of anti-drug antibodies (ADAs) to tirzepatide after multiple SC doses administered to Chinese patients with T2DM

5. STUDY DESIGN

Study GPHT is a Phase 1, single-site, patient- and investigator-blind, placebo-controlled, randomized, multiple dose titration study in Chinese patients with T2DM.

Figure 1 illustrates the study design.



Abbreviations: LY = tirzepatide; PL = placebo; QW = once weekly.

Figure 1. Illustration of study design

Patients will be administered either 16 or 24 weekly SC doses of tirzepatide or placebo.

Screening (Visit 1)

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2. Before performing any study procedures, the patient will sign the informed consent form.

Lead-in (Visit 2 to Visit 3)

At Visit 2, patients and their caregiver(s), if applicable, will receive a glucometer, study diaries, and training on how to perform self-monitoring of plasma glucose (PG) and record blood glucose values, hypoglycemic events, medications, and adverse events (AEs). Patients will also be trained on disease management and study procedures; this training can be repeated at subsequent visits as deemed appropriate.

Patients will conduct the 7-point self-monitored plasma glucose (7p-SMPG) approximately every 3 days since Day -13 during the lead-in period and will record readings in patient diary. Prior oral antidiabetic medication (OAM) should be discontinued during the lead-in period. Additionally, site personnel will require patients who were taking OAM at screening to monitor their PG in the morning before breakfast during the lead-in period.

Treatment Period

Cohort 1

Patients in Cohort 1 will receive either tirzepatide with titration regimen starting from 2.5 mg for Weeks 0 through 3 followed by 5 mg for Weeks 4 through 7, 7.5 mg for Weeks 8 through 11, and 10 mg for Weeks 12 through 15, or corresponding volume-matched placebo. During clinical research unit (CRU) visits 3a, 4, 5, 6a, 7, 8, 9, 10 and 11a, site staff will administer SC doses of tirzepatide or placebo. Patients may either self-administer or visit the CRU to have staff administer SC doses of tirzepatide or placebo at the beginning of Weeks 2, 3, 5, 6, 9, 10, and 11.

Cohort 2

Patients in Cohort 2 will receive either tirzepatide with titration regimen starting from 2.5 mg for Weeks 0 through 3 followed by 5 mg for Weeks 4 through 7, 7.5 mg for Weeks 8 through 11, 10 mg for Weeks 12 through 15, 12.5 mg for Weeks 16 through 19, and 15 mg for Weeks 20 through 23, or corresponding volume-matched placebo. During CRU visits 3a, 4, 5, 6a, 7, 8, 9, 10, 11, 12 and 13a, site staff will administer SC doses of tirzepatide or placebo. Patients may either self-administer or visit the CRU to have staff administer SC doses of tirzepatide or placebo at the beginning of Weeks 2, 3, 5, 6, 9, 10, 11, 13, 14, 15, 17, 18, and 19.

Follow-Up Period

Visits for safety follow-up and PK sampling will occur on 2 separate visits. These visits will be approximately 7 and 28 days after the last dose of investigational product (IP).

6. TREATMENTS

The following is a list of the study treatment labels that will be used in the safety, PD, and efficacy TFLs.

Cohort	Study Treatment Name	Treatment order in TFL
All	Placebo QW SC	1
1	2.5-10 mg tirzepatide QW SC*	2
2	2.5-15 mg tirzepatide QW SC**	3

Abbreviations: QW = once weekly; SC = subcutaneous
* Patients receive 2.5 mg for Weeks 0 through 3, 5 mg for Weeks 4 through 7, 7.5 mg for Weeks 8 through 11, and 10 mg for Weeks 12 through 15
** Patients receive 2.5 mg for Weeks 0 through 3, 5 mg for Weeks 4 through 7, 7.5 mg for Weeks 8 through 11, 10 mg for Weeks 12 through 15, 12.5 mg for Weeks 16 through 19, and 15 mg for Weeks 20 through 23

The following is a list of the study treatment labels that will be used in the PK TFLs, where a full profile is collected.

Cohort	Study Treatment Name	Treatment order in TFL
1	2.5 mg tirzepatide QW SC	1
	5 mg tirzepatide QW SC	2
	10 mg tirzepatide QW SC	3
2	2.5 mg tirzepatide QW SC	4
	5 mg tirzepatide QW SC	5
	15 mg tirzepatide QW SC	6

Abbreviations: QW = once weekly; SC = subcutaneous

For predose (trough) PK samples, the treatment labels will be consistent with the safety, PD and efficacy TFLs.

7. SAMPLE SIZE JUSTIFICATION

The sample size for the study was chosen to provide sufficient data to evaluate the primary objective of this study and is not intended to achieve any priori statistical requirements.

Approximately 24 Chinese patients with T2DM may be enrolled so that approximately 16 patients complete the study with compliant defined dosing regimen. Patients will be administered either 16 (Cohort 1) or 24 (Cohort 2) weekly SC doses of tirzepatide or placebo in a ratio of 10 tirzepatide:2 placebo for both cohorts.

Replacement of discontinued patients is not planned because the sample size is determined considering the expected drop-out rate.

8. DEFINITION OF ANALYSIS POPULATIONS

Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

The Pharmacokinetic population will consist of all patients who received at least 1 dose of the IP and have evaluable PK data.

The Pharmacodynamic population will consist of all patients who received at least 1 dose of the IP and have evaluable PD data.

The Efficacy population will consist of all patients who received at least 1 dose of the IP and have evaluable efficacy data.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, min, max and n; for log-normal data (e.g. the PK parameters: area under the concentration-time curve [AUC] and Maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed.

The demographic variables age, sex, race, ethnicity, body weight, height, body mass index, hemoglobin A1c (HbA1c), duration of diabetes and OAM use will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) to the plasma concentrations of tirzepatide will be used to determine the following pharmacokinetic parameters, when possible, on Days 1 (Week 0), 50 (Week 7), 106 (Week 15 [Cohort 1 only]) and 162 (Week 23 [Cohort 2 only]):

Parameter	Units	Definition
AUC(0-168)	ng.h/mL	area under the concentration versus time curve from time zero to 168 hour postdose
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
V_{ss}/F	L	apparent volume of distribution as steady state after extravascular administration
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration

Additional pharmacokinetic parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- Half-life ($t_{½}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate pharmacokinetic parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a subject or from a subsequent dose period following a suitable wash-out period.

    - The timepoints occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the final study report.

- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the timepoint have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all pharmacokinetic analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

Data within an Individual Profile

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For pharmacokinetic profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If $n<6$, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If $n\geq6$, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

All PK parameters will be summarized by treatment and PK profile day, and listed.

Trough concentrations will be summarized by cohort and timepoint, and listed.

9.4 Pharmacodynamic Assessments

9.4.1 Lipids Assessment

Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides data will be listed and summarized by treatment and timepoint. Changes from baseline will be presented, where baseline is defined as the Day 1 predose assessment.

9.4.2 Meal Intake and Appetite

The subjective rating of appetite sensations is measured using a 100-mm visual analogue scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption before and 4 to 5 hours after the standardized lunch and dinner meals.

Overall appetite score is calculated as the average of the 4 individual scores – satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4. The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

The data will be listed and summarized by treatment and timepoint. Changes from the assessment before food consumption will also be presented.

9.5 Efficacy Assessments

The efficacy of tirzepatide to reduce glucose and weight will be assessed. Efficacy measures that will be assessed include HbA1c, body weight, fasting PG, and 7p-SMPG.

All parameters will be listed and summarized by treatment and timepoint. Changes from baseline will be presented, where baseline is defined as the Day 1 predose assessment (HbA1c, body weight, fasting PG) or the Day -1 assessment (7p-SMPG).

The individual observed and mean time profile of the postdose efficacy parameters will be plotted by treatment group.

9.6 Safety and Tolerability Assessments

9.6.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any serious AEs will be listed. AEs by week of onset will be presented.

Discontinuations due to AEs will be listed.

9.6.2 Glucose Monitoring and Hypoglycemia

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual blood glucose value, if measured, will be recorded in the CRF, together with any treatments administered. Each category of hypoglycemic events (defined below) will be listed and summarized by treatment. Hypoglycemia is defined as follows:

- **Documented Glucose Alert Level (Level 1), PG ⩽70 mg/dL (3.9 mmol/L):**
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG ⩽70 mg/dL (3.9 mmol/L)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG ⩽70 mg/dL (3.9 mmol/L)
  - **Unspecified hypoglycemia:** an event during which PG ⩽70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded

- **Documented Clinically Significant Hypoglycemia (Level 2) PG ⩽54 mg/dL (3.0 mmol/L):**
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG ⩽54 mg/dL (3.0 mmol/L)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG ⩽54 mg/dL (3.0 mmol/L)

  - **Unspecified hypoglycemia:** an event during which PG ⩽54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded.

- **Severe hypoglycemia (Level 3):** an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (⩽70 mg/dL [3.9 mmol/L]).
  - **Severe hypoglycemia requiring medical attention**: a severe hypoglycemic event when subjects require therapy by health care providers (emergency medical technicians, emergency room personnel, etc.).

Other Hypoglycemia:

- **Nocturnal hypoglycemia:** any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking
- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, which do not require the assistance of another person, are accompanied by PG >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold
- **Overall (or total) hypoglycemia:** this optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is counted only once in this category
- **Probable symptomatic hypoglycemia:** an event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by PG ⩽70 mg/dL (3.9 mmol/L).

Investigator review of glucose results clinically indicative of hypoglycemia will be required.

9.6.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2019). Concomitant medication will be listed.

9.6.4 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter, treatment, and timepoint together with changes from baseline, where baseline is defined as the Day -1 assessment. All clinical chemistry, hematology and urinalysis data will be listed.

Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual subject data listings.

9.6.5 Pancreatic Enzymes

Pancreatic amylase and lipase will be measured to monitor pancreatic safety. All parameters will be listed and summarized by parameter and treatment together with changes from baseline, where baseline is defined as the Day -1 assessment. Data outside the reference range will also be listed and flagged on individual subject data listings.

9.6.6 Thyroid Malignancies and C-Cell Hyperplasia

The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy including medullary thyroid carcinoma and papillary carcinoma and measurements of calcitonin.

Calcitonin data will be summarized by treatment and timepoint together with changes from baseline, where baseline is defined as the Day 1 predose assessment.

9.6.7 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual subjects will be listed.

9.6.8 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

9.6.9 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× ULN, liver tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen 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 summarized by treatment and listed. 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 subject data listings.

9.6.10 Immunogenicity Assessments

Immunogenicity data will be listed and frequency tables will be presented. The frequency and percentage of subjects with pre-existing ADA and with treatment-emergent ADAs (TE ADAs) will be presented. TE ADAs are those that are boosted or induced by exposure to study drug, with a 4-fold increase in titer compared to baseline if ADAs were detected at baseline or a titer 2-fold greater than the minimum required dilution (1:10) if no ADAs were detected at baseline, where baseline is defined as Day 1 predose.

If cross-reactivity with native glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) or a neutralization assay is performed, the frequency of each will be determined.

The relationship between the presence of antibodies and PK parameters of tirzepatide may be assessed if deemed appropriate.

9.6.11 Hypersensitivity reactions

For all drug hypersensitivity reactions that occur, additional follow-up data will be collected to assess the patient’s medical history, alternative causes, and symptoms.

These data will be listed.

9.6.12 Injection-Site Reactions

Injection-site assessments for local tolerability will be conducted, when reported as:

- an AE from a subject, or
- a clinical observation from an investigator.

Injection site assessment data (erythema, induration, categorical pain, pruritus, and edema) will be summarized by treatment and listed.

9.6.13 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

9.6.14 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

13. DATA PRESENTATION

13.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

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