Statistical Analysis Plan: I8F-MC-GPGR

Effect of Tirzepatide on Oral Contraceptive Pharmacokinetics in Healthy Female Subjects

NCT04172987

Approval Date: 31-Jan-2020

STATISTICAL ANALYSIS PLAN

Effect of Tirzepatide on Oral Contraceptive Pharmacokinetics in Healthy Female Subjects

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 29 January 2020

Study Drug: Tirzepatide (LY3298176)

Sponsor Reference: I8F-MC-GPGR
Covance CRU Study: 1001215-8399709

Clinical Phase I

Approval Date: 31-Jan-2020 GMT

1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ADA	Anti-drug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-τ)	Area under the concentration versus time curve during one dosing interval
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the lower limit of quantitation
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
EE	Ethinyl Estradiol
GE	Gastric emptying
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography

NGM	Norgestimate
NGMN	Norelgestromin
OC	Oral contraceptive
PG	Plasma glucose
PK	Pharmacokinetic(s)
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TBL	Total bilirubin
TE ADA	Treatment-emergent antidrug antibody
TFLs	Tables, Figures, and Listings
$t_{½}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}/F	Apparent volume of distribution at steady state 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 18 October 2019) and Protocol Amendment (a) (final version dated 06 December 2019).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) 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. For open-label studies, this SAP must be signed off prior to first subject visit for this study. 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

To evaluate the effect of a single subcutaneous (SC) dose of tirzepatide on the PK of a combination oral contraceptive (OC) in healthy female subjects.

4.2 Secondary

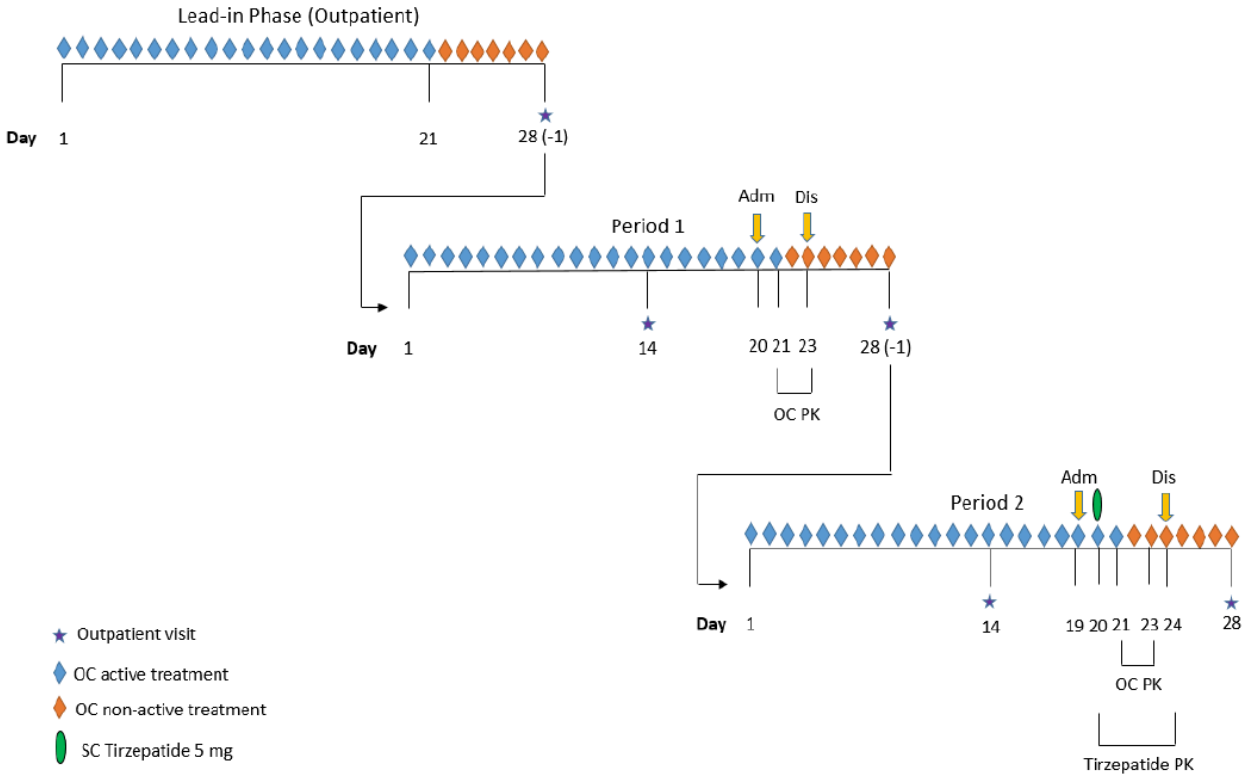
To evaluate the safety and tolerability of a single SC dose of tirzepatide when coadministered with an OC in healthy female subjects.

5. STUDY DESIGN

This is a single-center, open-label, 2-period, fixed sequence study with a lead-in period, in healthy female subjects. Subjects may already have been on OC medication prior to screening or be OC naïve. Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to Day 1 of the lead-in period. A final follow-up visit will occur on Day 49 ± 1 day (i.e. 28 days ± 1 day after tirzepatide dosing). During each treatment period, the PK of individual components of the OC combination will be assessed on Day 21 to enable evaluation

of OC PK alone. During period 2, tirzepatide will be administered on Day 20 such that peak exposure by Day 21 (tirzepatide time of maximum observed drug concentration [t_{max}] ~ 24 hours postdose) can be attained when OC PK is evaluated on Day 21 (norgestimate [NGM] and ethinyl estradiol [EE] are rapidly absorbed after oral administration). This will permit studying the influence of tirzepatide on OC PK, in the presence of maximum exposure; i.e. with greatest impact on gastric emptying (GE).

Figure GPGR.1 illustrates the study design.



Abbreviations: Adm = admission to the clinical research unit; CRU = clinical research unit; Dis = discharge from the clinical research unit; OC = oral contraceptive; PK = pharmacokinetic

Figure GPGR.1. Illustration of study design

6. TREATMENTS

The following is a list of the study treatment abbreviations that will be used in the TFLs.

Study Treatment Name	Abbreviation	Treatment order in TFL
0.035 mg EE / 0.25 mg NGM	OC	1
0.035 mg EE / 0.25 mg NGM + 5 mg tirzepatide SC	OC + 5 mg tirzepatide SC	2

7. SAMPLE SIZE JUSTIFICATION

Approximately 42 subjects will be enrolled so that a minimum of 28 subjects complete the study.

For EE area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}), the intra-subject variability (coefficient of variation [CV]) was estimated to be 18.2% and 14.2%, respectively (derived from study H9X-MC-GBCQ). Based on this assumption, 28 subjects will provide a precision of 0.10 and 0.08 on a log-scale for AUC and $C_{max,}$ respectively. This would result in a 90% probability that the half-width of the 90% confidence interval (CI) of the ratio of geometric least square means for AUC and C_{max} is no larger than 9.3% and 7.3%, respectively.

For norelgestromin (NGMN) AUC and C_{max}, the intra-subject variability (CV) was estimated to be 16.3% and 20.0% respectively (derived from study H9X-MC-GBCQ). Based on this assumption, 28 subjects will provide a precision of 0.09 and 0.11 on a log-scale for AUC and C_{max}, respectively. This would result in a 90% probability that the half-width of the 90% CI of the ratio of the geometric least square means for AUC and C_{max} is no larger than 8.3% and 10.2%, respectively.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of OC or tirzepatide, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of OC or tirzepatide and have evaluable PK 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: AUCs and C_{max}) the geometric mean and geometric 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, race, ethnicity, body weight, height and body mass index will be summarized and listed.

All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

Plasma concentrations of NGM, NGMN and EE will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-τ)	h*pg/mL	Area under the concentration versus time curve during one dosing interval
C_{max}	pg/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{½}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration
V_z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration

Plasma concentrations of tirzepatide will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	h*ng/mL	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	h*ng/mL	Area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{½}$	h	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration
V_z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}/F	L	Apparent volume of distribution at steady state after extra-vascular administration

Additional PK parameters may be calculated, as appropriate. Plasma concentrations of tirzepatide will be listed and summarized.

The software and version used for the final analyses will be specified in the CSR. 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. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, 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 concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- 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 the predicted last quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (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 time points 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.

- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be C_{min} for the dosing interval.

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 time point 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 PK 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.

<u>Data within an Individual Profile</u>

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

- For PK 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≥6, 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 ≥ 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

PK parameters will be evaluated to estimate the effect of tirzepatide on the PK of OC (NGM, NGMN and EE); OC administered alone will be the reference treatment and OC coadministered with tirzepatide will be the test treatment. Log-transformed AUC(0-τ) and C_{max} of NGM, NGMN and EE will be analyzed using a paired t-test. The treatment differences between the test and reference arm will be back-transformed to present the ratio of geometric means, corresponding 90% CI, and p-value from the paired t-test.

Example SAS code:

```
proc ttest data=<data in> alpha=0.1;
    by analyte param;
    paired test*ref;
run;
```

The t_{max} will be analyzed using a Wilcoxon signed rank test for the same comparison. Estimates of the median of differences, the 90% CI for the median of differences, and p-value from the Wilcoxon signed rank test will be calculated.

The PK parameters for each treatment and analyte will be summarised and listed. Furthermore, the geometric mean and 90% CI of AUC(0-τ) and C_{max} of NGM, NGMN and EE will be plotted, along with the individual values, against treatment. For t_{max}, the median and individual values will be plotted against treatment.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse Events

A pre-existing condition is defined as an adverse event (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 OC dosing in the lead-in phase. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

The assignment of TEAEs to treatments will be as follows:

- A TEAE occurring during or after Day 1 dosing in the lead-in phase and prior to tirzepatide dosing on Day 20 in Period 2 will be assigned to OC.
- A TEAE occurring during or after tirzepatide dosing on Day 20 in Period 2 will be assigned to OC + 5 mg tirzepatide SC.

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the AE will be reported in the listings. The following rules will be applied in summary tables:

- If an AE increases in severity, the AE will only be counted once at the maximum severity with the exception of the following:
    - If an AE occurs during or after Day 1 dosing in the lead-in phase and increases in severity during or after tirzepatide dosing on Day 20 in Period 2; the AE will be counted twice (at the maximum severity for each treatment).
- If an AE decreases in severity at any time, the AE will be counted once at the maximum severity.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment (including overall), 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 day of onset will be presented.

Discontinuations due to AEs will be listed.

9.4.2 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), Plasma Glucose (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.).

<u>Other Hypoglycemia:</u>

- **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.

9.4.3 Concomitant Medication

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

9.4.4 Clinical Laboratory Parameters

All clinical chemistry and hematology data will be summarized by parameter and treatment, and listed. Urinalysis data will be listed. Changes from baseline (Day -1 in the lead-in phase) will also be presented. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual subject data listings.

9.4.5 Serum Progesterone

Compliance with the OC during the lead-in period will be assessed by serum progesterone testing on Day 21 of the lead-in period. These data will be listed.

9.4.6 Vital Signs

Vital signs data will be summarized by treatment and timepoint. Values for individual subjects will be listed.

Temperature will be listed only.

9.4.7 Body Weight and Height

Body weight and height will be listed.

9.4.8 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.

9.4.9 Immunogenicity Assessments

Immunogenicity data will be listed and frequency tables will be presented. The frequency and percentage of subjects with pre-existing anti-drug antibody (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 20 predose in Period 2.

If cross-reactivity with native GLP-1 and 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.

9.4.10 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 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.

9.4.11 Hypersensitivity Reactions

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

These data will be listed.

9.4.12 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 listed.

9.4.13 Other Assessments

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

9.4.14 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim analyses are planned for this study.

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.”

Leo Document ID = ec030875-e054-4ffd-8738-d02e4c6b07dd

Approver: PPD

Approval Date & Time: 30-Jan-2020 13:18:13 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 30-Jan-2020 14:16:44 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 30-Jan-2020 16:43:22 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 31-Jan-2020 18:33:11 GMT

Signature meaning: Approved