Statistical Analysis Plan

Effect of Injection Site on the Relative Bioavailability of a Single Dose of Tirzepatide in Subjects with Low and High Body Mass Indices

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STATISTICAL ANALYSIS PLAN

Effect of Injection Site on the Relative Bioavailability of a Single Dose of Tirzepatide in Subjects with Low and High Body Mass Indices

Statistical Analysis Plan Status: Final
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Study Drug: Tirzepatide (LY3298176)

Sponsor Reference: I8F-MC-GPHI
Covance CRU Study: 1000071-8399702

Clinical Phase I

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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]).

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
ADA	Anti-drug antibody
AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
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
BMI	Body mass index
BQL	Below the lower limit of quantitation
CI	Confidence interval
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
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
DEXA	Dual energy x-ray absorptiometry
EC	Early Clinical
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
LLOQ	Lower limit of quantitation
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
$t_{½}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TFLs	Tables, Figures, and Listings

t_{max}	Time of maximum observed drug concentration
TOST	Two one-sided t-tests
ULN	Upper limit of normal
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 27 June 2019).

This SAP describes the planned analysis of the pharmacokinetic (PK), safety and tolerability 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 between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first subject administration 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 between Eli Lilly and Company and Covance EC Biometrics 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 determine the relative bioavailability of subcutaneous (SC) tirzepatide 5-mg injection into the thigh and upper arm compared to the abdomen.

4.2 Secondary Objectives

- To determine the relative bioavailability of SC tirzepatide 5-mg injection in subjects with different body mass indices (BMIs).

- To evaluate the safety and tolerability of SC tirzepatide 5-mg injection.

4.3 Exploratory Objective

- To explore the relationship between adiposity at injection site with tirzepatide exposure.

5. STUDY DESIGN

This is a single-center, open-label, 3-period, 3-sequence, randomized, crossover study conducted in overtly healthy male and female subjects in 2 BMI groups (low and high). The BMI groups will be as follows:

- Low BMI: 18.5 to 27.0 kg/m^2
- High BMI: 27.1 to 45.0 kg/m^2 – every effort will be made to enroll subjects so that approximately half of this group have a BMI above 35.0 kg/m^2

Subjects will be admitted to the clinical research unit (CRU) on Day -1 and will receive a single SC injection of tirzepatide 5 mg into 1 of 3 injection sites on Day 1, of each of the 3 treatment periods, with injection site sequence determined by the randomization.

The injection sites are:

- upper arm (Test 1)
- thigh (Test 2)
- abdomen (Reference)

Subjects will remain in the CRU until the scheduled assessments have been completed on Day 8. Subjects may be required to remain inpatient for a longer period if deemed necessary by the investigator for safety monitoring reasons. Subjects will attend 3 outpatient visits on Days 15, 21, and 36 of each treatment period for safety monitoring and PK sampling. The Day 36 visit of Treatment Period 3 will be considered the final follow-up visit.

There will be a washout period of at least 35 days between tirzepatide injections.

Figure GPHI.1 illustrates the study design. This tirzepatide injection sequence shown is an illustrative example only. Each subject enrolled will be assigned a treatment sequence according to the actual randomization schedule provided to the site.

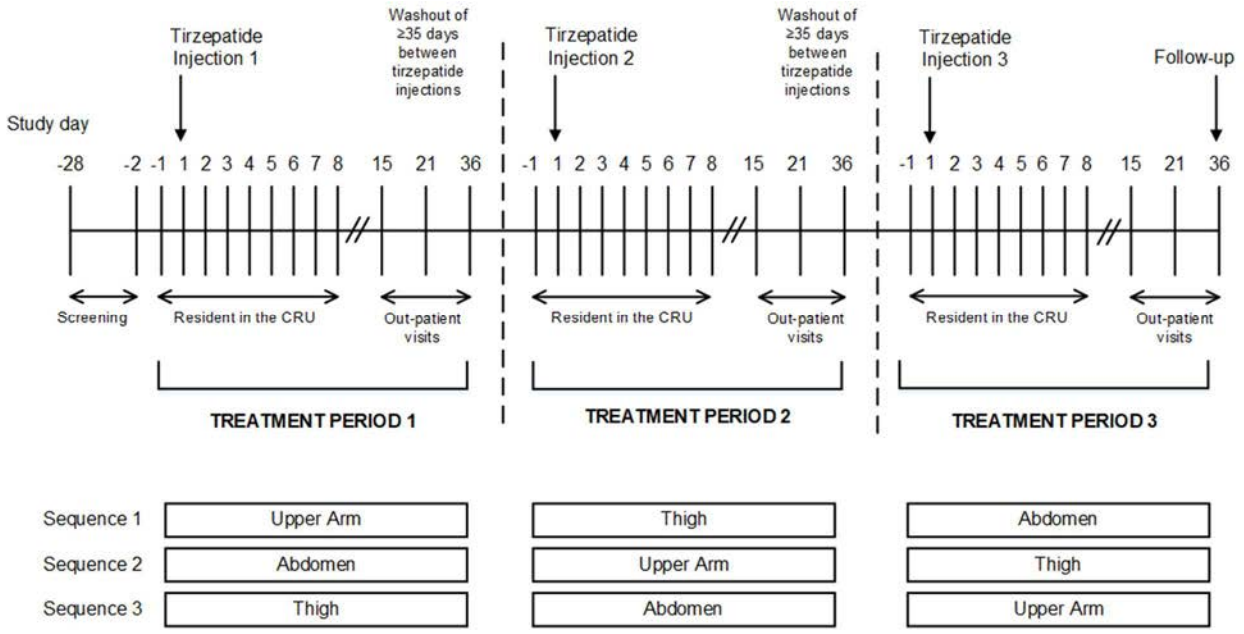

Figure GPHI.1. Illustration of Study Design

6. TREATMENTS

The TFLs will include a subheader for treatment (5 mg tirzepatide SC) throughout. The TFLs will also be presented by BMI group (Low BMI, High BMI, and Overall). The following is a list of the injection sites that will be used in the TFLs.

Injection site	Order in TFL
Abdomen	1
Upper Arm	2
Thigh	3

7. SAMPLE SIZE JUSTIFICATION

Approximately 54 subjects will be enrolled to ensure that at least 36 evaluable subjects complete the study, with at least 12 subjects completing per treatment sequence. With 36 subjects, we expect the two one-sided t-tests (TOST) for equivalence applied to the log-normal mean ratio to have a power of at least 98% for each of the 4 tests on the primary objective. This assumes a nominal expected mean ratio of 1.05, a coefficient variation of 19.6%, and significance level of 0.05 of each one-sided test when testing against an upper limit of 1.25 and lower limit of 0.80. The source of the choice of coefficient of variation is from the final results of study I8F-MC-GPGE. For balance and the evaluation of the secondary objective of effect of BMI, the 54 subjects will be enrolled according to their BMI category such that each category enrolls approximately 27 subjects and retains 6 completers per treatment sequence.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least 1 dose of tirzepatide, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received at least 1 dose of 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: area under the concentration versus 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.

Where specified in the sections below, safety data will be summarised by BMI group (Low, High and Overall) and also by injection site location (Abdomen, Upper Arm and Thigh), but not by injection site within BMI group. For the secondary objective, the PK data will be presented by injection site within BMI group.

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 and BMI will be summarized by BMI group and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

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

Plasma concentrations of tirzepatide (LY3298176) will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/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-∞)	ng.h/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 (λz) 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. The PK parameters will be summarized by injection site and BMI group (Low BMI, High BMI, and Overall).

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 concentrations above the lower limit of quantitation (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 last observed 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.

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

Pharmacokinetic parameter estimates will be evaluated to delineate effects of injection site. Log-transformed AUC(0-∞) and C_{max} will be evaluated in a linear mixed-effects model[3] with fixed effects for injection site, period, and sequence. Subject nested within sequence will be fitted as a random effect.

For the primary endpoints, the following comparisons will be assessed:

Ratio of AUC(0-∞) (90% confidence interval [CI]) and C_{max} (90% CI) for:

- Upper arm (Test 1) : Abdomen (Reference)
- Thigh (Test 2) : Abdomen (Reference).

Differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CI.

Example SAS code:

```
proc mixed data=DATAIN alpha=0.1;
  by parameter;
  class site period sequence subject;
  model log_pk = site period sequence / cl residual ddfm=kr;
  random subject(sequence);
  lsmeans site / pdiff=control alpha=0.1;
run;
```

For the secondary endpoint, BMI group and the BMI group-by-injection site interaction term will be added to the above model. Subject nested within sequence and BMI group will be fitted as a random effect. The effect of BMI group will be assessed overall, within each injection site, and between injection sites. The comparisons that will be assessed are the following:

Ratio of AUC(0-∞) (90% CI) and C_{max} (90% CI) for:

- Low BMI group (Test) : High BMI group (Reference) - Overall
- Low BMI group (Test) : High BMI group (Reference) - Abdomen
- Low BMI group (Test) : High BMI group (Reference) - Upper Arm
- Low BMI group (Test) : High BMI group (Reference) - Thigh
- Upper arm (Test 1) : Abdomen (Reference) - Low BMI
- Upper arm (Test 1) : Abdomen (Reference) - High BMI
- Thigh (Test 2) : Abdomen (Reference) - Low BMI
- Thigh (Test 2) : Abdomen (Reference) - High BMI

Example SAS code:

```
proc mixed data=DATAIN alpha=0.1;
  by parameter;
  class site period sequence subject BMI;
  model log_pk = site period sequence BMI BMI*site / cl residual
ddfm=kr;
  random subject(sequence*BMI);
  lsmeans BMI / pdiff=control alpha=0.1;
  lsmeans BMI*site / pdiff=control alpha=0.1;
run;
```

Injection site will be deemed to show no evidence of a difference if the 90% CI is fully contained within the 0.80 to 1.25 range.

In addition, AUC(0-t_{last}) will also be analyzed as an exploratory parameter using the same methodology.

The t_{max} will be analyzed, analyzed through non-parametric methods for all of the above comparisons. Estimates of the median difference, 90% CIs, and p-values from the Wilcoxon signed rank test will be calculated.

Relationship between exposure to tirzepatide and adiposity/body composition parameters (i.e., skinfold thickness and fat deposition) at the injection sites and waist, thigh, and upper arm circumference may be explored if deemed appropriate. Scatter plots of AUC(0-∞) and C_{max} versus skinfold thickness, fat percentage, lean mass percentage, waist circumference, thigh circumference, and upper arm circumference will be presented by injection site along with the Pearson's correlation coefficient and the associated p-value.

Additional analyses, such as subgroup analyses, may be carried out if appropriate.

9.4 Safety and Tolerability Assessments

9.4.1 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 BMI group, injection site (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 BMI group, injection site, Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 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. Any serious AEs will be listed.

9.4.2 Concomitant medication

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

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter, BMI group and injection site, and listed. Urinalysis data will be listed. Changes from baseline will also be presented, where baseline is defined as Day -1 in each Period. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values outside the reference ranges will be flagged on the individual subject data listings

9.4.4 Glucose Monitoring and Hyperglycemia/Hypoglycemia Reporting

During the study, blood glucose concentrations will be monitored for safety assessments. Glucose data will be listed and summarized by BMI group and injection site together with changes from baseline, where baseline is defined as Day 1 predose in each Period.

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 BMI group and injection site.

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

- **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.

9.4.5 Vital signs

Vital signs data will be summarized by BMI group and injection site together with changes from baseline, where baseline is defined as the Day 1 predose in each Period assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by BMI group and injection site.

Furthermore, values for individual subjects will be listed.

9.4.6 Electrocardiogram (ECG)

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be recorded as AEs.

9.4.7 Injection-site Assessments

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 and summarized by BMI group and injection site in frequency tables.

9.4.8 Fat Disposition

Total tissue mass, tissue fat percentage, fat mass and lean mass will be measured at each injection site using a dual energy x-ray absorptiometry (DEXA) scan.

The lean mass percentage will be derived as follows:

$$\text{Lean mass (\%)} = \frac{\text{Lean mass}}{\text{Total tissue mass}} \times 100$$

Fat mass percentage will be derived in a similar manner.

All parameters will be listed and summarized by BMI group.

9.4.9 Waist, Upper Arm, and Thigh Circumference

Circumference of the injection site will be listed and summarized by BMI group.

9.4.10 Skinfold Thickness

Skinfold thickness at each injection site will be listed and summarized by BMI group.

9.4.11 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 medication of acetaminophen/paracetamol will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan, and a biopsy assessment will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by BMI group and injection site, 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.

9.4.12 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.

9.4.13 Immunogenicity

Immunogenicity data will be listed and frequency tables will be presented. The frequency and percentage of patients 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 1 predose in Period 1.

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 (or absence) of antibodies and clinical parameters (AEs) will be assessed. Likewise, the relationship between the presence of antibodies and the PK parameters may be assessed if deemed appropriate.

9.4.14 Other assessments

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

9.4.15 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

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

Neither the Lilly study team nor the investigator is blinded as the study is open-label. Data may be accessed while the trial is ongoing, but no changes to the study design 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.

3. Brown H, Prescott R. *Applied Mixed Models in Medicine*. Chichester: John Wiley & Sons, 1999.

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 centre of the table, such as, “No serious adverse events occurred for this study.”

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