Statistical Analysis Plan: I8F-MC-GPHX

Disposition of [14C]-Tirzepatide Following Subcutaneous Administration in Healthy Male Subjects

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STATISTICAL ANALYSIS PLAN

Disposition of [^{14}C]-Tirzepatide Following Subcutaneous Administration in Healthy Male Subjects

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

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Covance CRU Study: 1001215-8409944

Clinical Phase I

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2. ABBREVIATIONS

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

%AUC(t_{last}-∞)	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
ADA	Anti-drug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate 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-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
BG	Blood glucose
BQL	Below the quantifiable lower limit of the assay
CL/F	Apparent total body clearance of drug calculated after extra vascular administration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CT	Computed tomography
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAP	Statistical Analysis Plan

SC	Subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure
$t_{1/2}$	Half-life associated with the terminal rate constant (λz) in non-compartmental analysis
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
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
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 18 February 2020).

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 Objective

To determine the disposition of radioactivity in healthy male subjects following subcutaneous (SC) administration of a single dose of approximately 4.1 mg (approximately 100 μCi) [^{14}C]-tirzepatide.

4.2 Secondary Objectives

- To determine the PK of tirzepatide in plasma and total radioactivity in plasma and whole blood.
- To assess the mass balance of tirzepatide by quantifying radioactivity recovered in urine, feces, and expired air (if applicable).
- To assess the metabolism of tirzepatide in plasma, urine, and feces (if applicable).
- To assess the safety and tolerability of a single dose of tirzepatide in healthy male subjects.

5. STUDY DESIGN

This is a Phase 1, open-label, single-center study in healthy male subjects following a single dose of approximately 4.1 mg tirzepatide containing approximately 100 μCi of [^{14}C]-tirzepatide administered as an SC injection.

Subjects will participate in a screening visit, a single study period, up to 7 follow-up visits and a follow-up telephone assessment. Subjects will be admitted to the clinical research unit (CRU) on the day prior to dosing (Day -1) and will receive a single SC injection of [^{14}C]-tirzepatide, administered by clinical site staff, on Day 1.

Subjects will remain resident in the CRU for 14 days postdose (Day 15), but, may be discharged earlier if both the following release criteria have been met:

- ≥90% of the administered radioactivity (based on the actual dose) has been recovered, AND
- 24-hour urine and fecal samples from 2 consecutive collections (where both collections have occurred) where each combined urine and feces collection has a radioactivity level <1.0% of the total administered radioactivity.

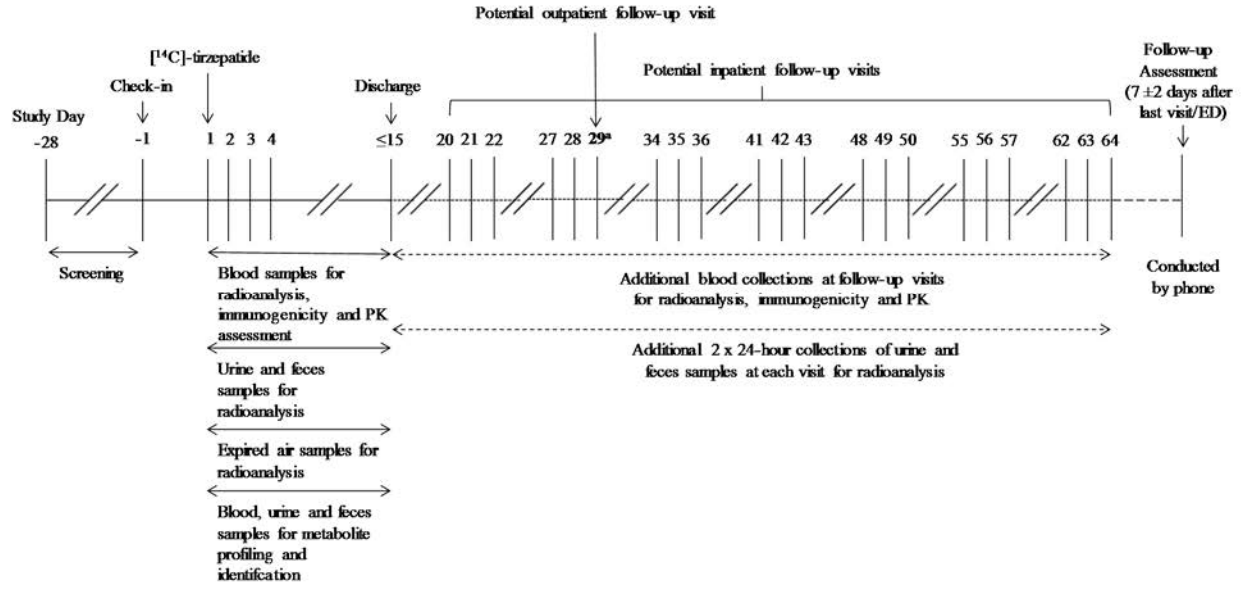
If subjects have not met both release criteria by 14 days postdose (Day 15), they will be required to return to the CRU for up to seven 48-hour residential inpatient follow-up visits. Samples will be collected for PK and the measurement of remaining radioactivity in urine and feces during the inpatient follow-up visits. Subjects will be required to attend all inpatient follow -up visits as scheduled until such time that the second release criterion (<1.0% total radioactivity in excreta) is met or up to a maximum of 63 days postdose (Day 64), whichever occurs first.

An immunogenicity and corresponding PK sample are required from all subjects on Day 29. If subjects have not previously met the release criteria and are returning for the Day 27 to 29 inpatient follow-up visit, then the immunogenicity and PK samples will be collected in the course of this visit. Subjects that have met the release criteria prior to the Day 27 to 29 inpatient visit will be required to attend a single outpatient visit on Day 29 for the collection of PK and immunogenicity samples.

A follow-up assessment will be conducted by telephone and will include recording of adverse events (AEs) and concomitant medication. The follow-up assessment will be performed 7 ± 2 days after each subject has completed the final study visit or following early discontinuation from the study.

Sequential urine and fecal samples will be obtained to determine the mass balance of tirzepatide by quantification of radioactivity and to identify metabolites. Samples of expired air will also be collected for the analysis of $^{14}CO_2$ at selected time points. If a significant amount of administered radioactivity is present in expired air samples, these data will be extrapolated to estimate the radioactive dose recovery. The percent of the dose eliminated in excreta will be estimated by measuring the amount of radioactivity in the urine and/or feces for each collection period.

Figure 1 illustrates the study design.



Abbreviations: ED = early discontinuation; PK = pharmacokinetic

Figure 1 Illustration of study design

6. TREATMENT

The study treatment will be a single dose of approximately 4.1-mg (approximately 100 μCi) [^{14}C]-tirzepatide. The treatment label presented in the TFLs will be 'X.X mg [^{14}C]-tirzepatide', where the TFLs will show the actual dosage level administered.

7. SAMPLE SIZE JUSTIFICATION

Up to 8 subjects will be enrolled. It is planned that up to 6 subjects will be dosed initially and 2 additional subjects will be dosed if needed, in order that a minimum of 4 subjects complete the study.

The sample size is customary for [^{14}C]-disposition studies[3] and is chosen to provide adequate PK data while limiting the number of subjects exposed to radiopharmaceuticals in non-therapeutic research.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of study drug.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of study drug 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 [AUCs] and maximum 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, 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

The PK parameter estimates will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, 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-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
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(t_{last}-∞)	%	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
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 (λ_z) 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 at steady state after extra-vascular administration
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration

The following pharmacokinetic parameters will be calculated for total radioactivity in plasma and whole blood:

Parameter	Units	Definition
AUC(0-∞)	ng equiv.h/mL	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	ng equiv.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(t_{last}-∞)	%	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	ng equiv/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 (λ_z) in non-compartmental analysis

Additional pharmacokinetic parameters may be calculated where appropriate.

The software and version used for the final analysis will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded in the raw data.

The ratio of total radioactivity in whole blood : plasma will be calculated for each time point.

The ratio of plasma tirzepatide : plasma total radioactivity will be calculated for each time point.

The ratio of total radioactivity in whole blood : plasma will be calculated based upon C_{max}, AUC(0-t_{last}) and AUC(0-∞).

The ratio of plasma tirzepatide : plasma total radioactivity will be calculated based upon C_{max}, AUC(0-t_{last}) and AUC(0-∞).

The percentage and cumulative percentage of radiolabeled dose excreted in expired air may also be presented, if applicable.

Analysis of the total radioactivity in faeces, urine, expired air, plasma and whole blood will be presented in a separate radioanalysis report. Cumulative recovery of total radioactivity in excreta will also be determined.

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 time point, t_{max} will be assigned to the first occurrence of C_{max}.

- Where concentration data are supplied in ng equiv/g a matrix density of 1g/mL will be used for pharmacokinetic calculation.

- 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}.

- 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. An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

- 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 predicted 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.

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 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 $n\geq6$, 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

No formal statistical analysis will be performed for this study.

PK parameters and concentrations for tirzepatide and total radioactivity in plasma and whole blood will be summarized and listed.

Ratios of PK concentrations (plasma tirzepatide to plasma total radioactivity and total whole blood radioactivity to plasma total radioactivity) and parameters will summarized and listed.

Plasma concentrations of tirzepatide and total radioactivity in plasma and whole blood will be graphically represented with an arithmetic mean plot and a concentration-time profile by subject.

Expired air data will be listed (if radioactivity is detected).

The percentage of radiolabeled dose excreted in feces, urine and expired air will be determined by the radioanalytical lab and reported in the radioanalysis report. Cumulative recovery of total radioactivity in excreta will also be determined.

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 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 Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 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 by the investigator. Any serious AEs will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose (BG) concentrations will be monitored for safety assessments. Glucose data will be listed and summarized by timepoint together with changes from baseline, where baseline is defined as Day 1 predose.

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual BG 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. Hypoglycemia is defined as follows:

- **Glucose Alert Level (Level 1):**
  - **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a plasma glucose (PG) level of ≤70 mg/dL (≤3.9 mmol/L).
  - **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).
  - **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

- **Clinically Significant Hypoglycemia (Level 2):**
  - **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a PG level of <54 mg/dL (<3.0 mmol/L).
  - **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG <54 mg/dL (<3.0 mmol/L).
  - **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG <54 mg/dL (<3.0 mmol/L).

- **Severe hypoglycemia (Level 3):**
  - **Severe hypoglycemia** is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. BG measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

- **Other hypoglycemia categories:**
  - **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

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 March 2020). Concomitant medication will be listed.

9.4.4 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter 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.

9.4.5 Vital signs

Vital signs data will be summarized by timepoint 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 parameter over time.

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 reported as an AE.

9.4.7 Body Weight

Body weight will be listed together with changes from baseline, where baseline is defined as the Screening assessment.

9.4.8 Hepatic Monitoring

Close hepatic monitoring

If a subject who had normal or near normal baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL) (i.e., <1.5× upper limit of normal [ULN]), experiences elevated ALT≥3× ULN, AST≥3× ULN, ALP≥2× ULN, or TBL≥2× ULN, laboratory tests should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyltransferase, and creatinine phosphokinase to confirm the abnormality and to determine if it is increasing or decreasing.

In subjects enrolled with elevated baseline ALT, AST, ALP or TBL (≥1.5× ULN), the thresholds for close monitoring are ALT≥2× baseline, AST≥2× baseline, ALP≥2× baseline, or TBL≥2× baseline.

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses, (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

Comprehensive hepatic evaluation

If a study subject, who had baseline ALT, AST, ALP, TBL<1.5× ULN, experiences elevated ALT≥5× ULN, AST≥5× ULN, ALP ≥3× ULN, TBL ≥2× ULN, or elevated ALT, AST ≥3× ULN with hepatic signs/symptoms (severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia>5%), a comprehensive evaluation should be performed to search for possible causes of liver injury.

In subjects who had elevated baseline ALT, AST, ALP, or TBL (≥1.5× ULN), the thresholds for performing this evaluation are ALT≥3× baseline, AST≥3× baseline, ALP≥2× baseline, TBL≥1.5× baseline, or ALT, AST ≥2× baseline with hepatic signs/symptoms.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio, viral hepatitis A, B, C, E, tests for autoimmune hepatitis, and an abdominal imaging study (for example, ultrasound or computed tomography [CT] scan).

Additional hepatic data collection in subjects who have abnormal liver tests during the study

Additional hepatic safety data collection should be performed in subjects who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests (if baseline ALT<1.5x ULN)
   - In subjects with baseline ALT≥1.5× ULN, the threshold is ALT≥3x baseline on 2 or more consecutive tests

2. Elevated TBL to ≥2× ULN (if baseline TBL <1.5× ULN)
   - In subjects with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2x baseline

3. Elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests (if baseline ALP <1.5× ULN)

- In subjects with baseline ALP≥1.5× ULN, the threshold is ALP ≥2× baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be an SAE

5. Discontinuation of the investigational produce due to a hepatic event

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.

9.4.9 Hypersensitivity reactions

All hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs.

For moderate-to-severe 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.

Additionally, unscheduled PK, immunogenicity, and laboratory data may be collected. All data will be included in the relevant listings.

9.4.10 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 and listed.

9.4.11 Immunogenicity Assessments

Immunogenicity data will be listed and frequency tables will be presented if analysed. 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.

9.4.12 Other assessments

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

9.4.13 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.

3. Penner N, Klunk LJ, Prakash C. Human radiolabeled mass balance studies: objectives, utilities and limitations. Biopharm. Drug Dispos. 2009;30(4): 185-203.

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

If there are no data for an individual subject listing, the listing will be presented with a message printed in the center. For example, if no serious adverse events are reported, the serious adverse events listing will display the message “No serious adverse events occurred for this study”. Summary tables will not be produced if there are no or insufficient data.

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