Statistical Analysis Plan: I8F-MC-GPGQ

A Single Dose Pharmacokinetic Study of Tirzepatide in Subjects With Varying Degrees of Hepatic Impairment

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STATISTICAL ANALYSIS PLAN

A Single Dose Pharmacokinetic Study of Tirzepatide in Subjects with Varying Degrees of Hepatic Impairment

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

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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
ANCOVA	Analysis of covariance
AUC	Area under the concentration versus time curve
AUC(0-tlast)	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-∞)	Area under the concentration versus time curve from time zero to infinity
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
CP	Child-Pugh
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
INR	International normalized ratio
LLOQ	Lower limit of quantitation
PD	Pharmacodynamic
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
T2DM	Type 2 diabetes mellitus
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

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 01 April 2019).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) 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 evaluate the PK of a single subcutaneous (SC) dose of tirzepatide in subjects with mild, moderate, and severe hepatic impairment compared to control subjects with normal hepatic function.

4.2 Secondary Objective

- To evaluate the safety and tolerability of a single SC dose of tirzepatide in subjects with mild, moderate, and severe hepatic impairment compared to control subjects with normal hepatic function.

4.3 Exploratory Objective

- To evaluate the formation of anti-drug antibodies (ADA) to tirzepatide after a single 5-mg SC dose administered to subjects with mild, moderate, or severe hepatic impairment compared to control subjects with normal hepatic function.

5. STUDY DESIGN

This will be a multicenter, parallel, single-dose, open-label, single-period study of tirzepatide in subjects with normal hepatic function and subjects with mild, moderate, and severe hepatic impairment. Subjects who have a concomitant type 2 diabetes mellitus (T2DM) diagnosis will not be specifically excluded.

Subjects will be enrolled within the following groups:

- Group 1: at least 6 subjects and up to 12 subjects with normal hepatic function (Control).
- Group 2: at least 6 subjects with mild hepatic impairment (Child-Pugh [CP] A).
- Group 3: at least 6 subjects with moderate hepatic impairment (CP B).
- Group 4: up to 6 subjects with severe hepatic impairment (CP C).

Efforts will be made to achieve 6 completers with severe hepatic impairment (Group 4); however, acknowledging the difficulty in recruiting this subject population, 2 to 3 subjects with severe hepatic impairment may be an acceptable target.

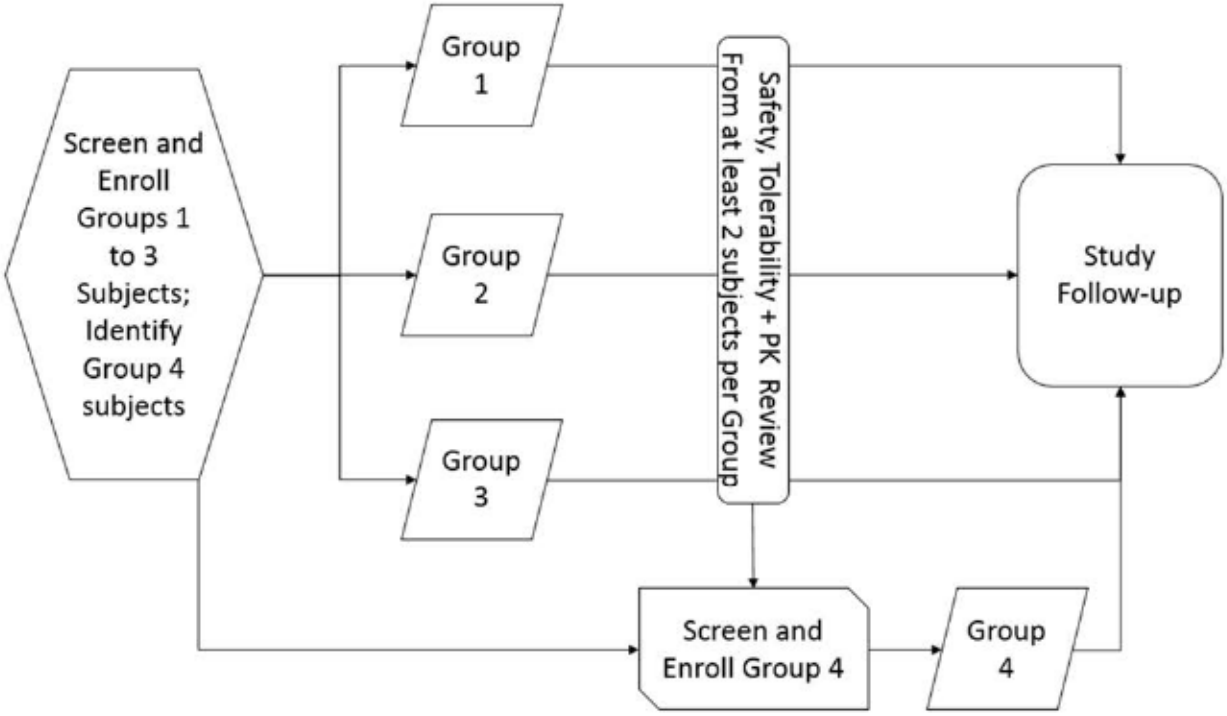
The Child-Pugh classification is described in Section 5.1.

Subjects enrolled in Group 1 (normal hepatic function) will be matched by weight (±10 kg), age (±10 years), and sex to subjects in Groups 2 through 4, as far as practically possible. Subjects with normal hepatic function cannot be matched to more than 1 hepatically-impaired subject within an impairment group; however, subjects with normal hepatic function may be matched to 1 subject from more than 1 hepatic impairment group, therefore requiring fewer subjects to be enrolled to Group 1 (minimum of 6). Subjects who withdraw before completing all study procedures may be replaced at the discretion of the investigator in discussion with the sponsor.

Subjects will undergo a screening examination within 28 days prior to enrollment, check in to the clinical research unit (CRU) on Day -1, and receive a single SC dose of 5 mg tirzepatide on Day 1, following an overnight fast of at least 8 hours. Subjects will remain at the CRU until discharge on Day 5, and return to the CRU on Days 8 and 15 for PK blood sampling and other study procedures. Each subject will be required to return to the CRU for a follow-up visit and final PK blood sample collection at least 28 days postdose.

PK blood sampling and safety assessments, including vital sign measurement, physical examination, clinical laboratory tests, electrocardiograms (ECGs), and adverse event (AE) recording, will be performed.

Subjects with normal hepatic function and with mild and moderate hepatic impairment (Groups 1 to 3) can be dosed concurrently (Figure GPGQ.1). Dosing of the first subject in Group 4 (severe hepatic impairment) may proceed only after satisfactory review of safety, tolerability, and PK data from at least 2 subjects in Group 2 (mild hepatic impairment), at least 2 subjects in Group 3 (moderate hepatic impairment), and at least 2 subjects in Group 1 (appropriate matched-control subjects with normal hepatic function). Based on continuous review of safety and tolerability data, the dose of tirzepatide may be reduced to 2.5 mg for the remainder of subjects in Groups 2 and 3 (mild and moderate impairment) and all subjects in Group 4 (severe impairment), as well as for control subjects in Group 1.



Note: dosing of the first subject with severe hepatic impairment (Group 4) may proceed only after satisfactory review of safety, tolerability and PK data from at least 2 subjects with mild hepatic impairment (Group 2), and at least 2 subjects with moderate hepatic impairment (Group 3), and at least 2 subjects in Group 1 (appropriate matched-control subjects with normal hepatic function).

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

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 8 weeks.

5.1 Child-Pugh Classification

Hepatic impairment is classified using the Child-Pugh system. The classification parameters will be collected at screening to determine the CP class for each subject prior to tirzepatide dose administration (Table GPGQ.1).

Table GPGQ.1. Child-Pugh Classification

Parameter	1 point	2 points	3 points
Serum Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total Serum Bilirubin (mg/dL)	<2	2 to 3	>3
Prothrombin Time (sec. prolonged) or	<4	4 to 6	>6
Prothrombin Time INR	<1.7	1.7 to 2.3	>2.3
Ascites [a]	Absent	Slight	Moderate
Hepatic Encephalopathy [b]	None	1 or 2 Or current treatment with lactulose or neomycin or other antibiotics	3 or 4 Or continued encephalopathy while receiving treatment with lactulose and/or neomycin or other antibiotics

Child Pugh A (mild): 5 or 6 points; Child Pugh B (moderate): 7 to 9 points; Child Pugh C (severe): 10 to 15 points. Adapted from Child and Turcotte[3] and Pugh et al.[4].
Abbreviations: INR = international normalized ratio.
[a] Absent: no detectable ascites.
Slight: no distension; ascites are only detectable by ultrasound examination.
Moderate: ascites causing moderate symmetrical distension of the abdomen.
[b] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity.

6. TREATMENTS

The TFLs will include a subheader for treatment (5 mg tirzepatide SC) throughout. The following is a list of the group abbreviations that will be used in the TFLs.

Group	Order in TFL
Control (normal hepatic function)	1
Mild hepatic impairment	2
Moderate hepatic impairment	3
Severe hepatic impairment	4

7. SAMPLE SIZE JUSTIFICATION

It is planned that up to 30 subjects may be enrolled. To support the planned analyses, at least 6 subjects in the mild and moderate hepatic impairment groups (Groups 2 and 3), at least 6 and up to 12 control subjects (Group 1) are expected to complete the study. Efforts will be made to achieve 6 completers with severe hepatic impairment (Group 4); however, acknowledging the difficulty in recruiting this subject population, 2 to 3 subjects with severe hepatic impairment may be an acceptable target.

This sample size is based on the FDA guidance[5], which advises that at least 6 subjects in each study arm (group) are required to provide evaluable data. The sample size was not selected to satisfy an a priori statistical requirement.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who received tirzepatide and have evaluable PK data.

The "Pharmacodynamic" population will consist of all subjects who received tirzepatide and have evaluable PD 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.

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, country of enrolment, site ID, body weight, height, body mass index, and Child-Pugh score will be summarized by group 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 procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

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

Parameter	Units	Definition
AUC(0-tlast)	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 (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 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 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}.

- 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 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.

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 $n \geq 6$ 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

The primary PK analysis is the evaluation of log-transformed AUC(0-∞) and C_{max} using an analysis of covariance (ANCOVA) model with hepatic function group as fixed factor and body weight as covariate. The geometric least squares means for each group, geometric least squares mean ratios between each hepatic impairment level versus the control group, and the corresponding 90% confidence intervals (CIs) will be estimated from the ANCOVA model. In the event of dose adjustment based on the interim analyses results, dose normalized PK parameters may be used in the above model.

Example SAS code:

```
proc mixed data=DATAIN alpha=0.1;
  by parameter;
  class group;
  model log_pk = group weight / cl residual ddfm=kr;
  lsmeans group / pdiff=control('Control') alpha=0.1;
run;
```

The analysis of t_{max} will be based on a nonparametric method. Medians and differences in medians for hepatic function groups and the p-value from a Wilcoxon rank sum test will be presented.

The relationship between the PK parameters and Child-Pugh Classification parameters (serum albumin concentration, total bilirubin concentration, and prothrombin time) will be assessed graphically. The PK parameters AUC(0-∞), C_{max}, and CL/F will be plotted against each Child-Pugh Classification parameter separately. A regression line and corresponding 90% CI from a simple linear model will be plotted, if appropriate.

Similarly, the PK parameters versus Child-Pugh Score will be assessed graphically. The control group will be kept in the analysis (with Child-Pugh score set to 0).

Additional PK parameters may be analyzed if deemed appropriate following a review of the data.

Additional exploratory analysis (such as metabolism work, protein binding, or bioanalytical method cross-validation) may be performed at a later date. Such analysis will be detailed in a separate analysis plan.

9.4 Pharmacodynamic Assessment

9.4.1 Immunogenicity

Immunogenicity data will be listed and frequency tables will be presented. The frequency and percentage of patients with pre-existing ADA and with treatment-emergent ADAs (TE ADAs) will be presented. TE ADAs are those that are induced or boosted 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.

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.

9.5 Safety and Tolerability Assessments

9.5.1 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 group, 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 group, Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 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. Any serious AEs will be listed.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2018). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

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

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

9.5.4 Glucose Monitoring and Hyperglycemia/Hypoglycemia Reporting

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 event (defined in Section 9.4.2.1 of the Protocol) will be listed and summarized by group.

Blood glucose levels will be listed for individual patients and summarized by group.

9.5.5 Vital signs

Vital signs data will be summarized by group 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 group.

Furthermore, values for individual subjects will be listed.

9.5.6 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.

9.5.7 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 group in frequency tables.

9.5.8 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 group 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.

9.5.9 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.

9.5.10 Other assessments

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

9.5.11 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

One interim analysis is planned to occur during Study GPGQ. Two subjects each from Groups 2 and 3 (subjects with mild and moderate hepatic impairment, respectively) and at least 2 subjects in Group 1 (appropriate matched-control subjects with normal hepatic function) will be enrolled in parallel and dosed with 5 mg tirzepatide, followed by an interim analysis to evaluate safety, tolerability, and PK data. Based on this interim analysis, dosing will either continue at 5 mg or be reduced to 2.5 mg for the remaining subjects subjects in Groups 2 and 3 (mild and moderate impairment) and all subjects in Group 4 (severe impairment), as well as for control subjects in Group 1. The final dose determinations will be made by the investigator and the Lilly study team.

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. Child CG, Turcotte JG. Surgery and portal hypertension. The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders;1964:50-64.

4. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-654.

5. [FDA, 2003] US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for industry: Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. May 2003.

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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