Statistical Analysis Plan: I8F-MC-GPHV

A Safety, Tolerability and Pharmacokinetic Study of Tirzepatide for the Treatment of Pediatric Participants (6 years to 11 years) with Obesity

NCT05696847

Approval Date: 23-Jan-2024

STATISTICAL ANALYSIS PLAN

A Safety, Tolerability and Pharmacokinetic Study of Tirzepatide for the Treatment of Pediatric Participants (6 years to 11 years) with Obesity

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Version: 2.0
Statistical Analysis Plan Date: 18JAN2024

Investigational Medicinal Product: Tirzepatide (LY3298176)

Protocol Reference: I8F-MC-GPHV
Fortrea Study: 8492131

Clinical Phase I

1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ADA	Anti-drug antibody
AUC	Area under the concentration versus time curve
$AUC_{0\text{-}tau}$	Area under the concentration versus time curve from time 0 to the end of the dosing interval
C_{max}	Maximum concentration
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
IBT	Intensive behavioral therapy
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PD	Pharmacodynamics
PK	Pharmacokinetic
QW	Once Weekly
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TFLs	Tables, Figures, and Listings
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol Amendment (e) (final version dated 16th November 2023).

This SAP describes the planned analysis of the safety, tolerability and 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.

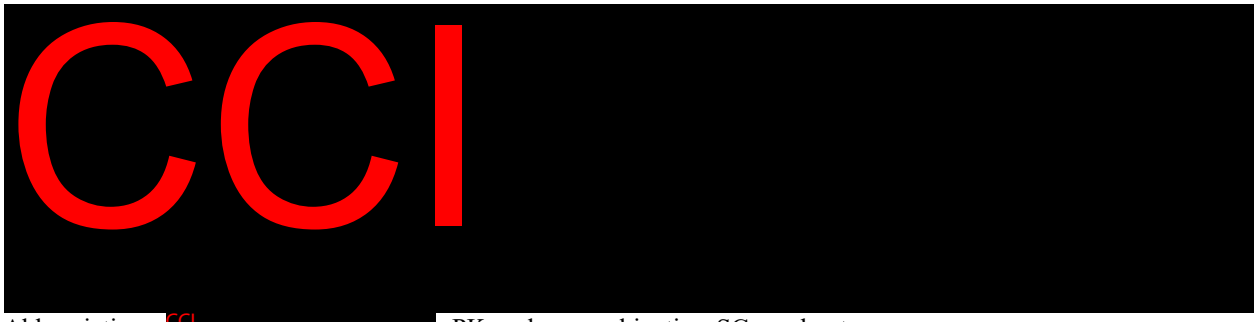
The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to first participant visit. 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

Objectives	Endpoints
Primary • To evaluate tirzepatide safety and tolerability following the subcutaneous (SC) injections of tirzepatide in pediatric participants with obesity	• Number of treatment-emergent adverse events and serious adverse events
Secondary • To evaluate the PK profile of tirzepatide following SC injections in pediatric participants with obesity	• Tirzepatide area under the concentration versus time curve (AUC) from time 0 to the end of the dosing interval ($AUC_{0\text{-}tau}$), maximum concentration (C_{max}) from population PK model



Abbreviations: CCI ; PK = pharmacokinetics; SC = subcutaneous.

5. STUDY DESIGN

This is a randomized, placebo-controlled, participant and investigator blinded, 8-week treatment Phase 1 study in pediatric participants with obesity who do not have diabetes mellitus. Potential pediatric participants will be screened to assess their eligibility to enter the study within 28 days prior to Day 1. Participants enrolled will be partitioned as follows:

- Cohort 1: Higher weight cohort – screening body weight ≥50 kg
- Cohorts 2: Lower weight cohort – screening body weight <50 kg, and
- Cohort 3: Screening body weight between 40 to 60 kg, inclusive.

The schematic of the study is shown in Figure 1. Initially, CCI participants are planned to be enrolled into the higher body weight (Cohort 1). Participants will be randomized on Day 1 to tirzepatide or placebo (CCI ratio) after the confirmation of eligibility. Placebo is included as the control in a blinded manner for investigator, site staff, and participants to allow an unbiased assessment of the safety and tolerability data generated, which will allow a more robust comparison between tirzepatide and placebo.

Safety and tolerability data will be reviewed by the unblinded sponsor clinical pharmacologist, clinical research physician / clinical research scientist, and blinded investigator. Decisions for commencing dosing in Cohort 2 (lower body weight participants) will be made based on the following:

- the completion of at least 5 treatment doses from at least CCI participants in Cohort 1, and
- the review of safety/tolerability data through Day 36, including safety clinical laboratory.

Likewise, the dosing of Cohort 3 participants (body weight 40 to 60 kg inclusive) will proceed only after the satisfactory review of safety and tolerability data from at least CCI participants who received at least 5 treatment doses in Cohort 2 as shown in Figure 1. PK samples will be collected, and exposure data for tirzepatide will be analyzed during the study to support dose-escalation decisions where possible. Sentinel dosing will be used for CCI participants in the specific body weight range of 40 to 50 kg in Cohort 3 (CCI). If safety and tolerability after 1 week are acceptable in the CCI sentinel participants, as clinically assessed by the investigator, the remainder of the participants in Cohort 3 (CCI tirzepatide and CCI placebo) in the 40 to 60 kg range can be randomized and dosed.

A final follow-up visit will occur after participants complete the final dosing or discontinue prematurely.

Starting at Visit 2 (baseline visit), all participants will be offered intensive behavioral therapy (IBT) sessions which will continue through the study period and until the final follow up.

CCI

6. BLINDING

This is a randomized participant- and investigator-blind study. All measures possible must be taken to maintain the blind; access to the blinding information will be restricted to authorized personnel as described in the protocol. Staff who prepare the study intervention will not be blinded to treatment allocation.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. In such cases, the unblinding is to be conducted according to the protocol.

The Fortrea biometrics and Eli Lilly study teams will be unblinded throughout the study.

7. TREATMENTS

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

Cohort	Study Treatment Name	Treatment order in TFL
1	Placebo QW (BW ≥50 kg)	1
	[redacted] mg tirzepatide QW (BW ≥50 kg)	2
2	Placebo QW (BW <50 kg)	3
	[redacted] mg tirzepatide QW (BW <50 kg)	4
3	Placebo QW (BW 40 to 60 kg)	5
	[redacted] mg tirzepatide QW (BW 40 to 60 kg)	6

Abbreviations: BW = body weight; QW = once weekly

8. SAMPLE SIZE JUSTIFICATION

Approximately [redacted] participants may be enrolled. This will allow PK characterization in at least [redacted] participants each, exposed to tirzepatide, for each of the 3 cohorts. Evaluable participants are participants who receive at least 1 dose of the study intervention and have at least 1 evaluable PK sample. The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK, and is not powered on the basis of any a priori statistical hypothesis testing for efficacy.

Participants who do not complete all the study procedures may be replaced to achieve the planned number of completers.

Note: Enrolled means a participant's parent or their legally acceptable representative's, agreement to participate in a clinical study following the completion of the informed consent process and assent where applicable and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled. A participant will be considered as enrolled if the informed consent is not withdrawn prior to participating in any study activity after the screening visit.

9. DEFINITION OF ANALYSIS POPULATIONS

"Full analysis set" will consist of all enrolled participants. Participants will be included in the analyses according to the planned intervention.

The "Safety" population will consist of all participants who received at least 1 dose of tirzepatide or placebo. Participants will be analyzed according to the intervention they actually received.

The "Pharmacokinetic" population will consist of all participants 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 participants are assigned to analysis populations.

10. STATISTICAL METHODOLOGY

10.1 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, minimum, maximum and number of observations; for log-normal data (e.g. the PK parameters: AUCs and 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 participants up to the point of withdrawal from study, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

For change from baseline summary statistics, each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at that time point. The individual participants' change from baseline values will be used to calculate the summary statistics (arithmetic mean, arithmetic SD, median, minimum, maximum and number of observations) using a SAS procedure such as Proc Univariate.

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

10.2 Demographics and Participant Disposition

Participant disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment (if more than one), site ID (if more than one), body weight, height, body mass index and waist circumference will be summarized by treatment and listed. All other demographic variables will be listed only.

10.3 Pharmacokinetic Assessment

Pharmacokinetic analysis will be the responsibility of Lilly's PK/PD group. Tirzepatide concentration data will be analyzed using a population PK approach using nonlinear mixed-effects modelling techniques implemented on the NONMEM® software to determine the C_{max} and $AUC_{0\text{-}tau}$ of tirzepatide by each cohort and dose.

Derivation of the PK parameters and TFL production will be the responsibility of Eli Lilly.

10.4 Pharmacodynamic Assessment

10.4.1 Pharmacodynamic Analysis

The exploratory PD parameters are:

- Body weight, body mass index, and waist circumference

10.4.2 Pharmacodynamic Statistical Methodology

Body weight, body mass index, and waist circumference data and changes from baseline, where baseline is defined as the last non-missing value prior to dosing, will be summarized by treatment and listed. Figures of mean body weight and mean changes from baseline profiles will be presented by treatment. Percent changes from baseline will also be presented.

[redacted] An unstructured covariance structure will be used to model the covariance between a participant's multiple observations, with an alternative structure to be used if the model fails to converge. Follow-up data will not be included in the model.

Treatment in the model will be defined as per Section 7 with the following comparisons presented:

- [redacted] mg tirzepatide QW (BW ≥50 kg) versus Placebo QW (BW ≥50 kg)
- [redacted] mg tirzepatide QW (BW <50 kg) versus Placebo QW (BW <50 kg)
- [redacted] mg tirzepatide QW (BW 40 to 60 kg) versus Placebo QW (BW 40 to 60 kg)

In addition, treatment may also be defined as Placebo QW, [redacted] mg tirzepatide QW, or [redacted] -- mg tirzepatide QW in an additional model, with the following comparisons presented:

- [redacted] mg tirzepatide QW versus Placebo QW
- [redacted] mg tirzepatide QW versus Placebo QW

If the above model does not converge, treatment may be defined as Pooled placebo QW or Pooled tirzepatide QW, with the following comparison presented:

- Pooled tirzepatide QW versus Pooled placebo QW

The difference in LS means at each post-dose timepoint, along with the 90% confidence interval, will be reported.

Example SAS code:

[redacted]

10.5 Safety and Tolerability Assessments

10.5.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (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 a condition that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

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

Discontinuations due to AEs will be listed.

10.5.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose concentrations will be monitored for safety assessments. Glucose data will be listed and summarized by treatment.

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

- **Level 1 hypoglycemia:**
  - **Glucose <70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L):** Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

- **Level 2 hypoglycemia:**
  - **Glucose <54 mg/dL (3.0 mmol/L):** Level 2 hypoglycemia is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

- **Level 3 hypoglycemia:**
  - **Severe hypoglycemia (in adults)**: A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For

example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as a serious AE.

- **Other hypoglycemia categories:**
  - **Nocturnal hypoglycemia** is a hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

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

10.5.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (version is documented in the DMP). Concomitant medication will be listed.

10.5.4 Clinical laboratory parameters

All clinical chemistry, hematology and lipid data will be summarized by treatment and time point together with change from baseline, where baseline is defined as Day 1 predose, and listed. Urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

10.5.5 Vital signs

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

Values for individual participants will be listed.

10.5.6 Electrocardiogram (ECG)

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

10.5.7 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.7.1 of the protocol, additional 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 participants' liver disease history and associated person liver disease history data will be listed. Use of acetaminophen during the study, which has potential for hepatotoxicity, 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 participant data listings.

10.5.8 Immunogenicity Assessments

Immunogenicity data will be listed and frequency tables will be presented if analysed. The frequency and percentage of participants with pre-existing antidrug 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.

The frequency of neutralizing antibodies, if assessed, and cross-reactivity to native GIP and GLP-1 may also be tabulated in TE ADA+ participants if deemed appropriate.

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

10.5.9 Hypersensitivity reactions

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

These data will be listed.

10.5.10 Injection-Site Reactions

Injection-site reaction data (erythema, induration, categorical pain, pruritus, and edema) will be listed and summarized by treatment in frequency tables.

10.5.11 Elevated Lipase or Amylase

If a patient experiences elevated serum amylase or lipase values ≥3× ULN, additional monitoring and tests will be performed to confirm the abnormality, even in asymptomatic participants.

The frequency of serum amylase or lipase values ≥3× ULN will be summarized by treatment and listed.

10.5.12 Tanner Staging

Female participants' pubertal status will be assessed using Tanner Staging. These data will be listed.

10.5.13 Other assessments

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

10.5.14 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11. INTERIM ANALYSES

No interim analyses are planned for this study.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. 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.

14. DATA PRESENTATION

14.1 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. Number of observations 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.

14.2 Missing Data

Missing data will not be displayed in listings.

14.3 Insufficient Data for Presentation

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

15. Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Final Version 2.0	18JAN2024	Following Protocol Amendment e, Cohort 3 has been updated to be conducted in participants with a screening body weight of 40 to 60 kg, inclusive. Sentinel dosing will be used for [redacted] participants in the body weight range of 40 to 50 kg in Cohort 3. The study design, treatment labels and statistical analysis comparisons have been updated accordingly.

NA = not applicable

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Approval	PPD 18-Jan-2024 16:21:01 GMT+0000

Approval	PPD 19-Jan-2024 03:22:03 GMT+0000

Approval	PPD 19-Jan-2024 10:25:29 GMT+0000

Approval	PPD 23-Jan-2024 20:03:00 GMT+0000

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