Statistical Analysis Plan Version 1 -I8F-MC-GPIP

A Bioequivalence Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by a Fixed-Dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

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Title Page

Protocol Title: A Bioequivalence Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by a Fixed-Dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

Protocol Number: I8F-MC-GPIP

Compound Number: LY3298176

Short Title: Bioequivalence Study to Compare the PK of Tirzepatide Administered by Fixed-dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

GPIP

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

Registry	**ID128801**

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Version history

The statistical analysis plan for GPIP is based on the protocol dated 10/21/2022.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Original version

1. Introduction

This document is the SAP for Study I8F-MC-GPIP.

The purpose of this study is to evaluate the PK of tirzepatide bioequivalence between fixed-dose multi-use prefilled pen (MUPFP) (test) versus a single-dose pen (SDP) (reference).

This SAP supersedes all statistical considerations and analyses described in Protocol GPIP.

1.1. Objectives, Endpoints

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence between the MUPFP (test) and the SDP (reference), as assessed using tirzepatide PK in healthy participants	• C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$
Secondary	
• To evaluate the additional PK parameter • To evaluate the safety and tolerability of a single subcutaneous dose of tirzepatide administered through MUPFP (test) versus SDP (reference)	• tmax • Incidence of AEs

1.2. Study Design

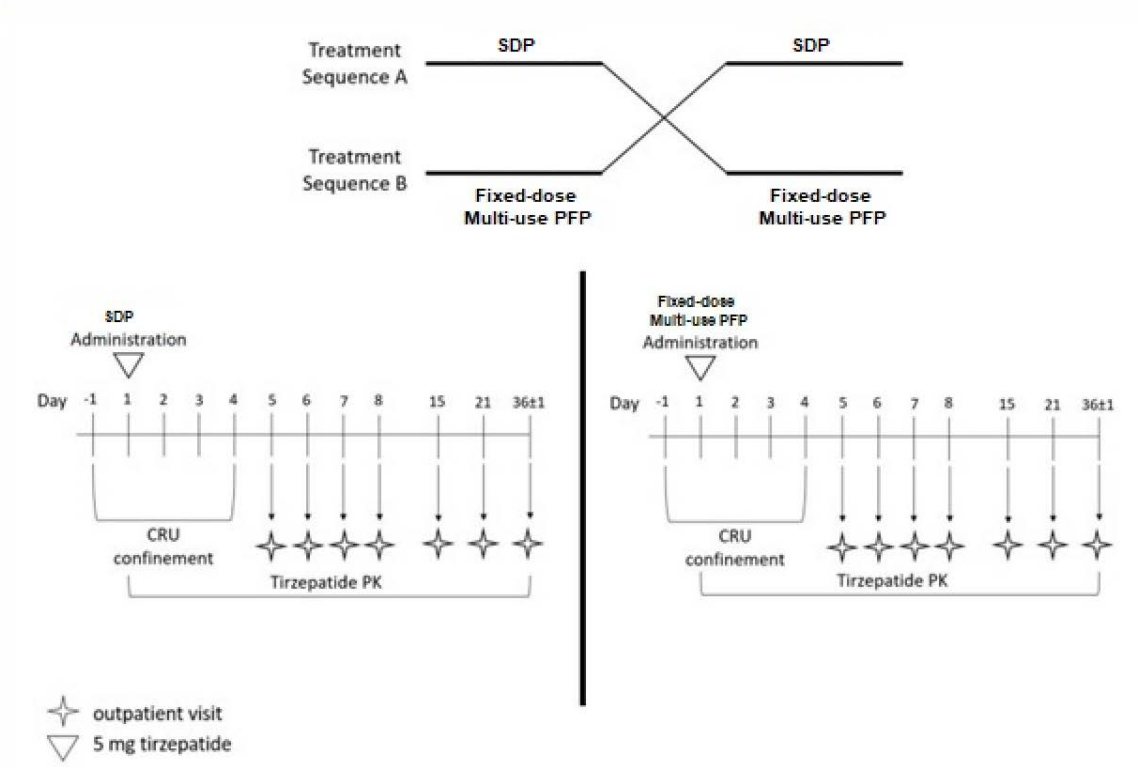
This is a multicenter, open-label, randomized, 2-period, 2-sequence, crossover study conducted in healthy participants.

The study will include 2 treatment arms. Approximately 65 participants may be enrolled so that at least 54 participants complete the study. Participants will be randomly assigned 1:1 to the 2 treatment sequences. It is intended that approximately the same number of participants will be randomly assigned into each treatment sequence. The treatment sequence is:

- a single dose of 5 mg tirzepatide administered SC via MUPFP followed by SDP; or
- a single dose of 5 mg tirzepatide administered SC via SDP followed by MUPFP.

The study duration for individual participants, inclusive of screening, is expected to be approximately 14 weeks.

Following is the study design:



2. Statistical Hypotheses

The primary objective of this study is to evaluate bioequivalence of the MUPFP (test) and the SDP (reference) with a 5-mg dose, as assessed using tirzepatide PK parameters C_{max}, AUC(0-tlast), and AUC(0-∞) in healthy participants.

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3. Analysis Sets

The following analysis sets are defined:

Table 2 Analysis sets

Participant Analysis Set / Population	Description
Enrolled	All randomly assigned participants.
Safety analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All randomly assigned participants who received at least 1 study intervention and have evaluable PK data.
PK completer data set	For each PK primary parameter, only include participants who received all study interventions, and have evaluable PK data for both treatment periods.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

PK analyses will be conducted for the PK analysis set according to the actual tirzepatide formulation received. Safety analyses will be conducted with the safety analysis set.

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 (eg, the PK parameters: area under the concentration versus time curve [AUCs] 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. 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.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety and population PK analysis purposes

4.2. Participant Dispositions

Subject disposition will be listed. Subject ID, date of study discontinuation, reason for discontinuation, adverse events for discontinuation due to AE, and last dose information (treatment, study period, study day) will be listed.

The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

4.3. Primary Analysis

4.3.1. Pharmacokinetic analysis

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

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

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last timepoint with a measurable concentration
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC (0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{½}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration

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 non-bolus pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

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- 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 serum concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on the last observed quantifiable drug concentration (C_{last}) will be reported.

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantification (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 timepoints 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 timepoint 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≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and n ≥ 6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

4.3.2. Main analytical approach

Two one-sided equivalence tests will be applied to the ratios of each of $C_{max,}$ AUC(0-t), and AUC(0-∞) using the MUPFP as the test sample and the SDP as the reference. Test limits of the ratios to establish bioequivalence are 0.8 and 1.25.

PK parameters will be evaluated to estimate the relative bioavailability. Log-transformed $C_{max,}$ AUC(0-t), and AUC(0-∞) will be evaluated in a linear mixed-effects model with fixed effects for treatment, sequence, period, and a random effect for subject within sequence. The treatment differences will be back-transformed to present the ratios of geometric means between MUPFP and SDP treatments and the corresponding 90% CI.

AUC(0-tl_{ast}), AUC(0-∞), and C_{max} will also be analyzed using a linear fixed-effects model. This analysis will be performed using PK completer data set. The parameter estimates will be log-transformed before analysis. The model will include fixed effects for sequence, period, treatment, and subject nested within sequence. The LSmeans for each treatment, the difference in means between treatments, and the 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric LSmeans, the ratio of the geometric LSmeans, and the 90% CIs. This method is consistent with the EMA recommended methodology of analysis.

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4.4. Secondary Endpoint(s)/Estimands(s)] Analysis

The t_{max} will be analyzed through non-parametric methods. The median for each treatment and median of differences between the MUPFP and SDP treatments will be presented, along with the approximate 90% CI for the difference (see Hauschke). The p-value from a Wilcoxon ranked sum test will also be presented.

4.5. Safety Analyses

4.5.1. Extent of Exposure

Exposure data will be listed.

4.5.2. Adverse Events

A treatment-emergent AE is defined as an AE which occurs after the first dose of study intervention of period 1 or which is present prior to dosing and becomes more severe post first dose. All AEs will be listed. Treatment-emergent AEs will be summarized by treatment (MUPFP, SDP, and Overall) and severity. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Serious AEs will be listed.

Discontinuations due to AEs will be listed.

4.5.3. Device Product Complaints (if applicable)

Devices product complaints will be listed.

4.5.4. Hypoglycemic Events

Hypoglycemic events will be appropriately recorded in the CRF. Hypoglycemic events are defined as follows:

Table 3. Hypoglycemic events

Category	Glucose
Level 1 hypoglycemia	<70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
Level 2 hypoglycemia	<54 mg/dL (3.0 mmol/L)
Level 3 (Severe) hypoglycemia	N/A
Nocturnal hypoglycemia	N/A

Severe hypoglycemia is a severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Details can be found in the protocol.

Nocturnal hypoglycemia is a hypoglycemic event (including severe event) that occurred at night and presumably during sleep –between bedtime and waking.

Hypoglycemic events will be listed.

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4.5.5. Vital Signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as the Day 1 Predose assessment.

4.5.6. Electrocardiograms

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.

4.5.7. Injection Site Reactions

Injection-site assessments for local tolerability will be conducted, when reported as:

- an AE from a subject, or
- a clinical observation from an investigator.

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

4.5.8. Clinical Laboratory Parameters

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be listed.

4.6. Interim Analyses

No interim statistical analyses are planned.

4.7. Changes to Protocol-Planned Analyses

There are no changes from the protocol specified statistical analyses.

5. Sample Size Determination

Approximately 65 participants may be enrolled so that approximately 54 evaluable participants complete the study. A sample size of 54 participants will provide at least 95% power that the 90% confidence interval of the geometric mean ratio of C_{max} and AUC between the 2 devices will fall within the equivalence range of 0.8 to 1.25. This assumes a nominal expected mean ratio of 1.05 (test vs reference), a within-subject coefficient of variation of 24%.

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6. Supporting Documentation

Not applicable.

7. References

Hauschke D, Steinijans VW, Diletti E. A distribution-free procedure for the statistical analysis of bioequivalence studies. Int J Clin Pharm Ther Toxicol. 1990;28(2):72–8. PMID 2307548.

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