H9X-MC-GBGM Statistical Analysis Plan

Relative Bioavailability of an Investigational Single Dose of Dulaglutide after Subcutaneous Administration by a Single Dose Pen Compared to a Prefilled Syringe in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

Relative Bioavailability of an Investigational Single Dose of Dulaglutide after Subcutaneous Administration by a Single Dose Pen Compared to a Prefilled Syringe in Healthy Subjects

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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]).

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
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
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-168h)	Area under the concentration versus time curve from time zero to 168 hours post dose
AUC(0-336h)	Area under the concentration versus time curve from time zero to 336 hours post dose
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
%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CRU	Clinical research unit
CSR	Clinical Study Report
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantitation
LS	Least square

MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
NA	Not applicable
PK	Pharmacokinetic
PFS	Prefilled syringe
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SDP	Single dose pen
SOP	Standard Operating Procedure
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
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 24 September 2017).

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 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 Council 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 relative bioavailability of a single dose of dulaglutide administered subcutaneously (SC) to healthy subjects as a single injection by single dose pen (SDP; test) compared to 3 injections by prefilled syringe (PFS; reference).

4.2 Secondary Objective

- To assess the tolerability of a single dose of dulaglutide administered SC to healthy subjects as a single injection by SDP compared to 3 injections by PFS.

5. STUDY DESIGN

This study is a Phase 1, single-center, open-label, randomized, 2-period, crossover study in healthy subjects to evaluate the relative bioavailability of 4.5 mg of a new formulation of

dulaglutide administered SC as a single injection by SDP (test) compared to 3 injections by PFS (reference).

Each subject will provide informed consent for study participation and will undergo a screening examination within 27 days prior to enrollment.

In each treatment period, subjects will be admitted to the clinical research unit (CRU) on Day -1. On Day 1 of each period, subjects will receive a single dose of 4.5 mg dulaglutide administered SC as a single SDP injection or as 3 injections by PFS according to the randomization schedule. Blood samples will be collected predose and up to 336 hours postdose to measure dulaglutide concentrations. At a minimum, subjects will remain at the CRU until collection of the 168-hour (Day 8) PK sample in each period.

There will be a washout period of at least 28 days between doses in Periods 1 and 2. Each subject will be required to return to the CRU for a follow-up visit 28 ±3 days after the last dulaglutide dose. The total duration for each subject (from screening through the follow-up visit) is approximately 84 days. The treatment sequences are detailed below:

Treatment Sequence	**Period 1**	**Period 2**
1	Prefilled Syringe	Single Dose Pen
2	Single Dose Pen	Prefilled Syringe

Safety and tolerability will be assessed throughout the study by means of vital sign measurement, physical examination, clinical laboratory tests, electrocardiograms (ECGs), and AE recording.

6. TREATMENTS

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

Study Treatment Name	**Abbreviation**	**Treatment order in TFL**
4.5 mg Dulaglutide (Prefilled Syringe)	Dulaglutide (PFS)	1
4.5 mg Dulaglutide (Single Dose Pen)	Dulaglutide (SDP)	2

7. SAMPLE SIZE JUSTIFICATION

Approximately 24 subjects may be enrolled in order that at least 18 subjects complete the study. The sample size was based on a within-subject variability (coefficient of variation) of 21% for the area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}) of dulaglutide from previous studies. Eighteen subjects will provide a 90%

probability that the half-width of the 90% confidence interval (CI) of the ratio of the geometric means for AUC and C_{max} is no larger than 14%.

Subjects who are randomized may be replaced to ensure that at least 18 subjects may complete the study.

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 at least one dose of dulaglutide 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: 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 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, body weight, height and body mass index will be summarized and listed. Tobacco/nicotine habits will be listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Pharmacokinetic parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 6.4 or later).

Plasma concentrations of dulaglutide 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(0-168h)	ng.h/mL	area under the concentration versus time curve from time zero to 168 hours post dose
AUC(0-336h)	ng.h/mL	area under the concentration versus time curve from time zero to 336 hours post dose
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(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
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 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}.
- 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.
- 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 observed 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 pharmacokinetic 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 pharmacokinetic 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

The PK parameters will be summarized using descriptive statistics by treatment and also presented graphically. Mean (with and without SD bars) and individual profiles over time will be presented for PK concentrations.

The PK parameter estimates will be evaluated to determine the relative bioavailability of dulaglutide administered SC by SDP (test) compared to dulaglutide administered by PFS (reference).

Log-transformed C_{max} and AUC(0-∞) (primary parameters) and AUC(0-168h) and AUC(0-336h) (secondary parameters) will be evaluated in a linear mixed-effects analysis of variance model with fixed effects for treatment (SDP or PFS), period, and sequence and a random effect for subject within sequence. The ratios of least squares geometric means of SDP compared to PFS, as well as the corresponding 90% CIs, will be estimated and reported. Example SAS code is given below:

```
proc mixed data=pk;
class subject treatment period sequence;
model log(pk) = treatment period sequence / ddfm=kr;
lsmeans treatment / pdiff alpha=0.1;
random intercept / subject=subject(sequence);
run;
```

The t_{max} will be analyzed nonparametrically using the Wilcoxon signed rank test. Estimates of the median difference and the corresponding 90% CIs will be calculated.

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 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 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 the first dose. 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 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) version 20.0 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2017). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry (including amylase and lipase), hematology and urinalysis data will be listed. Additionally clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

9.4.4 Vital signs

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose from each relevant period. Furthermore, values for individual subjects will be listed.

9.4.5 Hepatic Monitoring

If a patient 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.

If a patient has a liver abnormality then they will be included in the listings and summaries detailed below.

The patients' 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 in a frequency table by treatment and will also be 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 patient data listings.

9.4.6 Injection Site Reaction Assessment

Local tolerability at the injection site will be evaluated for erythema, induration, pain, pruritus, rash, and edema. If one or more symptom(s) of an injection site reaction (ISR) is reported during the assessment, a single AE for ISR will be recorded as an AE. Data will be summarized in a frequency table and listed for individual subjects.

9.4.7 Immunogenicity

The frequency and percentage of subjects with pre-existing ADA and with treatment-emergent ADA to dulaglutide will be tabulated. Treatment-emergent ADA are defined as a change from negative at baseline to positive at endpoint with antibody titer greater or equal to 1:4 or a positive at baseline to a positive at endpoint with greater or equal to 4-fold increases. That is, if a positive antibody titer changes from 1:2 at baseline to 1:8 at endpoint, it is considered treatment emergent. For subjects with treatment-emergent ADA, a listing of maximum titers will be produced. If a neutralization assay is performed, the frequency of neutralizing antibodies will be tabulated in subjects with treatment-emergent ADA.

The relationship between the presence (or absence) of antibodies and safety and PK parameters may be assessed.

9.4.8 Other assessments

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

9.4.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

An interim PK analysis (including C_{max} and AUC[0-168h]) will be conducted 1 week after the start of Period 1. The purpose of this analysis is to provide preliminary data to further support Phase 3 development. The PK samples collected predose through 168-hour time point will be analyzed.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

The protocol specified that t_{max} will be analyzed nonparametrically using the Wilcoxon ranked sum test however this has been amended to the Wilcoxon signed rank test as it is a crossover study.

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.

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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