Statistical Analysis Plan I4L-MC-ABEF(V2)

Relative Bioavailability of LY2963016 to LANTUS® After Single-Dose Subcutaneous Administration in Healthy Chinese Subjects

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STATISTICAL ANALYSIS PLAN

Relative Bioavailability of LY2963016 to LANTUS® after Single-Dose Subcutaneous Administration in Healthy Chinese Subjects

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Study Drug: LY2963016

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Clinical Phase I

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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
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(0-24)	Area under the serum study drug concentration-time curve from zero to 24 hours
AUC(0-∞)	Area under the serum study drug concentration curve from time zero to infinity
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
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
G_{tot}	Total amount of glucose infused
ICH	International Council on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
R_{max}	Maximum glucose infusion rate
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure

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
tR_{max}	Time of maximum glucose infusion rate
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 15 April 2013) and Protocol Amendment (a) (final version dated 24 May 2017).

The SAP is being updated from Version 1 to Version 2 due to errors in the protocol and include updates to Section 7, Section 9.3.2.and Section 9.4.2.

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 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 LY2963016 compared to LANTUS following subcutaneous (SC) single-dose administrations (0.5 U/kg) in healthy Chinese subjects.

4.2 Secondary Objectives

- To evaluate the safety and tolerability of LY2963016 when administered to healthy Chinese subjects.
- To compare other PK parameters of LY2963016 with those of LANTUS after 0.5-U/kg SC administration.
- To compare the PD responses of LY2963016 with those of LANTUS after 0.5-U/kg SC administration.

5. STUDY DESIGN

This is a randomised, open-label, single-dose (0.5 U/kg), 2-treatment, 2-period, crossover, single-site, euglycaemic clamp study to evaluate the relative bioavailability of LY2963016 to LANTUS in healthy subjects. The study will have 2 treatment periods, with subjects randomly assigned in a 1:1 fashion to a treatment sequence of either LY2963016 (Period 1) followed by LANTUS (Period 2), or LANTUS (Period 1) followed by LY2963016 (Period 2) (Figure 1). Study drug will be administered once per period as an SC dose. Up to 60 healthy men and women will be enrolled in order to ensure that 40 subjects complete the study.

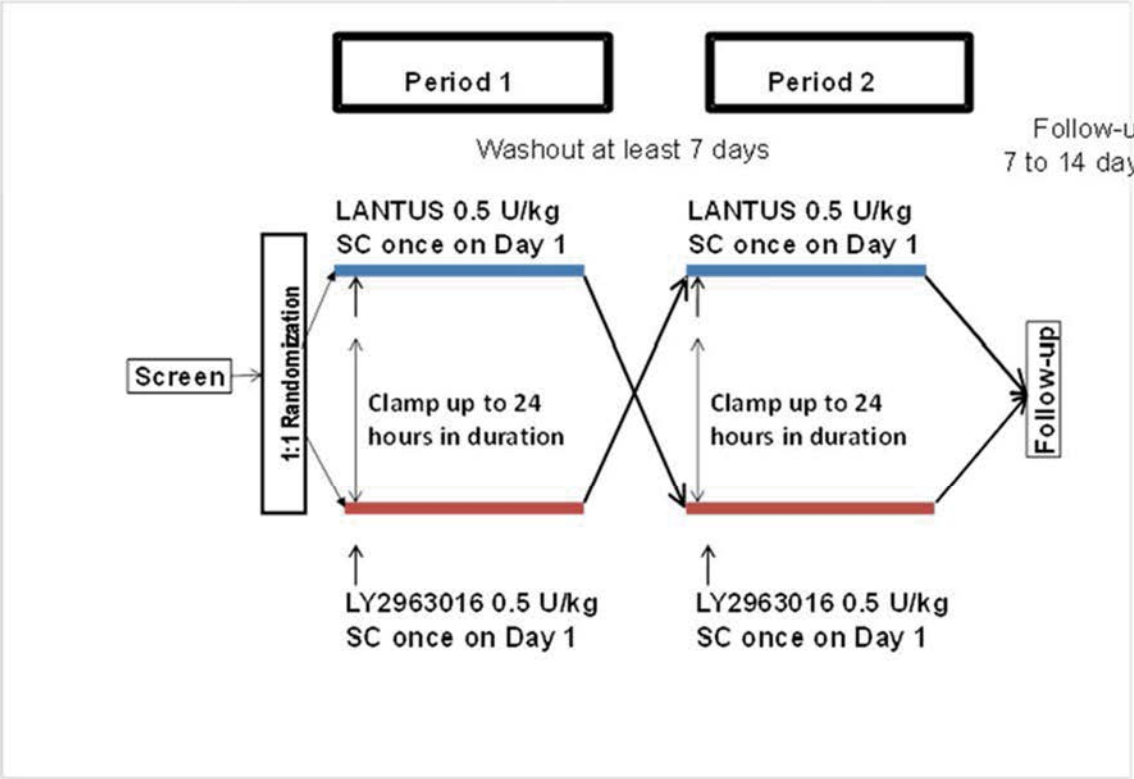

Figure 1. Study design

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL

LY2963016 0.5 U/kg SC	1
LANTUS 0.5 U/kg SC	2

7. SAMPLE SIZE JUSTIFICATION

Up to 60 healthy subjects may be enrolled to ensure that at least 52 subjects complete the study. Assuming the ratio of AUC between test and reference product is 1, with 52 subjects completing, there is 80% coverage probability that the half-width of the 90% confidence interval (CI) of the difference of means for the area under the concentration time curve (AUC) will be within 0.223 in the log scale, which corresponds to approximately 20% in the ratio scale. This precision estimate was based on the intrasubject variability for AUC of 39.26% observed in completed studies in healthy subjects. Drop-outs may be replaced and the replacement subject would assume the withdrawn subject's treatment sequence (receiving both allocated treatments).

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of study drug and have evaluable PK data.

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

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 the maximum drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

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, site ID, body weight, height and body mass index will be summarized and listed.

9.3 Pharmacokinetic Analyses

PK analyses will be conducted on the Pharmacokinetic population.

9.3.1 Pharmacokinetic Parameter Estimation

PK parameter estimates for LY2963016 and LANTUS will be calculated by standard noncompartmental methods of analysis using WinNonlin Phoenix software. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

The analyses will be performed according to the Lilly Global Pharmacokinetics, Pharmacodynamics, and Pharmacometrics Divisional Standards. For each profile, concentration values that are below the quantifiable limit of the assay will be imputed as ½ LLOQ. Actual sampling times in individual subjects will be used in the analysis. The serum concentration of immunoreactive LY2963016 and LANTUS will be corrected for endogenous insulin using the C-peptide data. The primary parameters for PK analysis will be: AUC from time zero to 24 hours [AUC(0-24)] and C_{max}. Other PK parameters that will be reported include: AUC from time zero to last measured concentration value [AUC(0-t_{last})], AUC from time zero to infinity [AUC(0-∞)], t_{max}, apparent clearance (CL/F), $t_{1/2}$, and the apparent volume of distribution (Vz/F). The AUC values will be calculated by the linear/log trapezoidal method, where the linear trapezoidal method will be employed up to t_{max}, and the log trapezoidal rule will be used for concentrations beyond t_{max}.

9.3.2 Pharmacokinetic Statistical Inference

The primary PK parameters, AUC(0-24) and C_{max}, will be log-transformed prior to analysis. A linear mixed effects model will be fitted to the data. The model will include subject as a random effect, with period, sequence, and treatment as fixed effects. For each PK parameter, the difference in least-square treatment means (LY2963016 – Lantus) along with the 90% confidence intervals (CIs) will be back-transformed to produce the ratio of geometric means and the CIs comparing LY2963016 to Lantus. Within subject coefficient of variation (CV) for each insulin may be reported if estimable. A similar statistical analysis will be performed for the log-transformed secondary PK parameters AUC(0-∞) and AUC(0-t_{last}).
Example SAS code:

```
proc mixed data=pk;
class subject period sequence treatment;
model log_pk = period sequence treatment /solution ddfm=kr residual;
random subject;
lsmeans treatment / pdiff alpha=0.1;
ods output lsmeans=lsm;
ods output diffs=diff;
```

```
run;
```

Exploratory analyses may be performed for other PK parameters as deemed appropriate. Descriptive statistics may be reported for other PK parameters as deemed appropriate (e.g, CL/F, Vz/F, $t_{1/2}$). Median t_{max} will be calculated per treatment and a nonparametric approach will be taken to evaluate the difference in median t_{max}, using the Wilcoxon signed-rank test. The difference in median t_{max} between treatments and the 95% CIs for the difference will be reported.

9.4 Pharmacodynamic Analyses

PD analyses will be conducted on Pharmacodynamic population.

9.4.1 Pharmacodynamic Parameter Estimation

The GIRs and blood glucose values will be recorded on Day 1. A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and/or period using S-PLUS® software (v8.2). Glucose infusion rates will be used to calculate several PD parameters, including maximum glucose infusion rate (R_{max}), time of R_{max} (tR_{max}), and total amount of glucose infused (G_{tot}). Other parameters namely, the time of first change of GIR postdose (tRonset), the time of last measurable GIR (tRlast), and the last measurable GIR (GIRlast) may be calculated as appropriate.

9.4.2 Pharmacodynamic Statistical Inference

The PD parameters (R_{max} and G_{tot}) will be log-transformed prior to analysis. A linear mixed effects model will be fitted to the data. The model will include subject as a random effect, with period, sequence, and treatment as fixed effects. From the models, the difference in least-squares mean estimates between the 2 treatments and the corresponding 90% CIs for the difference will be estimated and back-transformed from the log scale to provide estimates of the ratios of geometric means and 90% CI for the ratio of these means. The SAS code will be similar to the SAS code used in the PK analysis. Within subject CV for each insulin may be reported if estimable.

Exploratory analyses of other PD parameters may be performed as deemed appropriate, for example, time to R_{max} (tR_{max}), time to first change of GIR postdose (tRonset), the time of last measurable GIR (tRlast), and the last measurable GIR (GIRlast) .

9.5 Safety and Tolerability Assessments

Safety Analyses will be conducted on Safety population.

9.5.1 Adverse events

Adverse events (AEs) will be coded based upon the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). 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 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 subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, 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; this listing will include the reason the event was categorized as serious as well as relatedness.

9.5.2 Concomitant medication

Concomitant medication will be coded using the latest version of WHO drug dictionary. Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

All clinical chemistry, hematology and urinalysis data will be listed.

Additionally clinical chemistry, hematology and urinalysis data outside the local 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.

9.5.4 Vital signs

Vital signs will be listed for individual subjects.

9.5.5 Electrocardiogram (ECG)

The ECG data will be listed for individual subjects.

9.5.6 Glucose Monitoring and Hypoglycaemia 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 10.3.2.1 of the Protocol) will be listed and summarized by treatment.

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

9.5.7 Other assessments

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

9.5.8 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

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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