Statistical Analysis Plan B5K-EW-IBHG

Comparative Pharmacokinetics and Pharmacodynamics of Human Regular U-500 Insulin Administered Subcutaneously as a Bolus via Syringe versus Continuous Subcutaneous Insulin Infusion and Characterization of TID and BID Dosing at Steady State in High-Dose Insulin-Treated Subjects with Type 2 Diabetes Mellitus

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STATISTICAL ANALYSIS PLAN

Comparative Pharmacokinetics and Pharmacodynamics of Human Regular U-500 Insulin Administered Subcutaneously as a Bolus via Syringe versus Continuous Subcutaneous Insulin Infusion and Characterization of TID and BID Dosing at Steady State in High-Dose Insulin-Treated, Obese Subjects with Type 2 Diabetes Mellitus

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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
BID	Twice daily
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
CSR	Clinical Study Report
CSII	Continuous subcutaneous insulin infusion
CRU	Clinical Research Unit
CV	Coefficient of variation
Early tR_{max50}	Time of 50% of maximum GIR before R_{max}
ECB	Early clinical biometrics
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
GIR	Glucose infusion rate
ICH	International Conference on Harmonisation
Late tR_{max50}	Time of 50% of maximum GIR after R_{max}
LLOQ	Lower limit of quantitation
LS	Least square
MDI	Multiple daily injections
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PD	Pharmacodynamic

PK	Pharmacokinetic
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
R_{max}	Maximum glucose infusion rate
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SMPG	Self-monitored plasma glucose
TDD	Total daily dose
T2DM	Type 2 diabetes mellitus
TID	Thrice daily
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 29 April 2015 and amendment (a) dated 24 August 2015).

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 between Eli Lilly and Company and Covance Early Clinical Biometrics (ECB). 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 ECB 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

Primary Objectives

Part A: to compare the t_{max} of a 100-U bolus of U-500R (500 U/mL) administered via single subcutaneous (SC) injection versus a 100-U bolus of U-500R administered via continuous subcutaneous insulin infusion (CSII) in high-dose insulin-treated, obese subjects with type 2 diabetes mellitus (T2DM).

Part B: to evaluate the area under the concentration versus time curve (AUC) from time zero to 24 hours postdose (AUC[0-24]), maximum drug concentration (C_{max}), and maximum glucose infusion rate (R_{max}) of U-500R at steady state following thrice daily (TID) or twice daily (BID) SC dosing in the study population.

Secondary Objectives

Part A: to compare the time of maximum glucose infusion rate (GIR) (tR_{max}) and exposure (AUC from time zero to time t, where t is the last time point with a measurable concentration [$AUC(0\text{-}t_{last})$]) of a 100-U bolus of U-500R administered via single SC injection versus CSII in the study population.

Part B: to evaluate the time of C_{max} (t_{max}), total amount of glucose infused (G_{tot}) and tR_{max} of U-500R at steady state following TID or BID SC dosing in the study population.

Exploratory Objectives

Other PK and PD parameters may be evaluated including but not limited to:

Part A: half-life associated with the terminal rate constant in no ncompartmental analysis ($t_{1/2}$), apparent total body clearance of drug calculated after extra -vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra -vascular administration (V_z/F), time of last GIR measurement (tR_{last}), the time of first change of GIR postdose (tR_{onset}), the time of 50% of maximum GIR before R_{max} (early tR_{max50}), and the time of 50% of maximum GIR after R_{max} (late tR_{max50}) in the study population.

Part B: AUC of U-500R over each dosing interval and over each meal at steady state following TID or BID SC dosing in the study population.

5. STUDY DESIGN

This is a 2-part, Phase 1 (postmarketing), single-center, 3-period, 4-sequence, randomized, open-label, crossover euglycemic clamp study in high-dose insulin-treated, obese subjects with T2DM. Part A (Periods 1 and 2) will compare the PK and PD of a 100-U bolus of U-500R administered via single SC injection versus a 100-U bolus of U-500R administered via CSII. Subjects completing Part A will transition to Part B (Period 3), which will evaluate the PK and PD characteristics of U-500R administered by TID and BID multiple daily injections (MDIs) under steady-state conditions.

Up to 32 subjects may be enrolled to achieve a target of approximately 24 completing all 3 periods of the study.

Subjects will be randomly assigned to 1 of 4 dosing sequences (Table 1.). Each subject will be administered 100 U of U-500R by single SC injection, and 100 U of U-500R by CSII in Part A and either TID U-500R or BID U-500R in Part B.

Table 1. Dosing Schedule

	Part A		Part B
Sequence	Period 1	Period 2	Period 3
1	SC	CSII	TID
2	CSII	SC	BID
3	SC	CSII	BID
4	CSII	SC	TID

Abbreviations: BID=twice-daily administration of U-500R; CSII=100 U U-500R administered via continuous subcutaneous insulin infusion; SC=100 U U-500R administered via single subcutaneous injection; TID=thrice-daily administration of U-500R

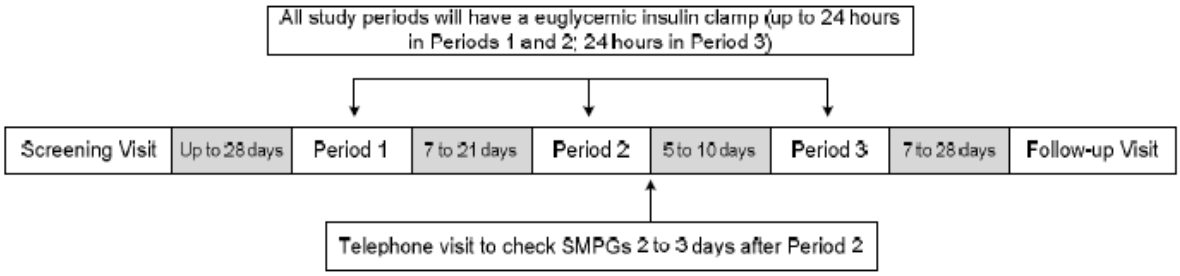

Figure 1. Study Design

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
100-U bolus U-500R (SC)	1
100-U bolus U-500R (CSII)	2
U-500R (BID)	3
U-500R (TID)	4

7. SAMPLE SIZE JUSTIFICATION

The primary objective of Part A of the study is to compare the t_{max} of U-500R administered by single SC injection or CSII. Up to 32 subjects may be enrolled to ensure that approximately 24 subjects complete the study.

The sample size is based on a calculation of precision of the t_{max}. Intra-subject variability for t_{max} has not been assessed previously. Based on an assumption of an intra-subject variability estimate of 20% for t_{max}, a sample size of 24 completed subjects in Part A will provide approximately 90% coverage probability that the half-width of the 90% confidence interval (CI) for the ratio of

geometric means for t_{max} will be within 0.116 in the log scale, which corresponds to approximately 12% of the geometric mean ratio estimate in the natural scale.

If any subjects discontinue the study prior to completion of the 3 periods, the replacement subjects who are enrolled will assume the discontinued subjects' randomization schedule and will complete all 3 periods.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of study drug, and have at least one postdose safety assessment.

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

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.

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.

The TFLs will be programmed using SAS® Version 9.3 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrollment, site ID, body weight, height and body mass index will be summarized and listed.

Screening HbA1c, HbA1c >8.0%, HbA1c ≤8.0% , fasting blood glucose, duration of T2DM and prestudy insulin treatment will be summarized and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

For the primary analysis, serum immunoreactive concentrations of insulin will be corrected using C-peptide data. Specifically, drug insulin concentrations will be calculated as the difference between total insulin and endogenous insulin, which in turn will be estimated with the C-peptide concentration data using Owens method (Owens 1986) with the following equation:

Drug insulin = Total insulin – F*C-peptide

where F is the average of the ratios of insulin to C-peptide at baselines (-0.5, and 0 hour) and will be calculated for the subject per the following rule:

1. If there is BQL values for insulin or C-peptide, set them to ½ LLOQ.

2. Take the mean of the ratios of insulin to C-peptide at the two pre-dose time points (-0.5h, and 0h) during the single SC injection period as the F for the subject.

Pharmacokinetic parameter estimates will be calculated using non-compartmental methods of analysis in validated software (Phoenix WinNonlin Version 6.3, Pharsight Corporation, USA or later). The analyses will be performed according to the Lilly Global Pharmacokinetics, Pharmacodynamics, and Pharmacometrics Divisional Standard Operating Procedures. The actual validated software version used when actual analyses are conducted will be specified in the clinical study report. C-peptide may be used to correct serum immunoreactive insulin concentrations for endogenous insulin.

The primary parameter for analysis in Part A will be t_{max}. Other noncompartmental parameters such as C_{max}, AUC from time zero to infinity (AUC[0-∞]), AUC(0-t_{last}), half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$), the last time point with a measurable concentration (t_{last}), apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra-vascular administration (V_z/F) may be reported, as appropriate.

In the treatment of CSII, the PK profile of insulin via SC injection can be corrected by subtracting baseline concentration, given steady-state of infused basal insulin via CSII will be reached after 12hrs.

The primary PK parameters for Part B will be AUC(0-24) and C_{max}; other PK parameters such as t_{max} and AUC of U-500R over each dosing interval and over each assumed meal time period at steady state may also be reported, as appropriate.

Parameters will be individually calculated by Eli Lilly and Company and sent to Covance for statistical analysis.

9.3.2 Pharmacokinetic Statistical Methodology

For Part A, the primary parameter for statistical analysis will be t_{max}. The values for t_{max} will be log-transformed and evaluated in a linear mixed-effects model with fixed effects for administration method, period and sequence order (order 1 is derived based on sequences 1 and 3, and order 2 is derived based on sequences 2 and 4), and a random effect for subject. The difference in least squares (LS) means along with the 90% CI will be back-transformed to present the ratios of geometric means and the 90% CI for the comparison of the administration methods (single SC injection [test] and CSII [reference]). This same analysis will be repeated for AUC(0-t_{last}), AUC(0-∞), and C_{max}.

Example SAS code:

```
proc mixed data= ;
   class seqorder period method subject;
   model l_pk = seqorder period method / outpred=resids ddfm=kr;
   random subject;
   lsmeans method / pdiff alpha=0.1;
   ods output lsmeans=lsm;
   ods output diffs=diff;
run; quit;
```

The values of t_{max} will also be analyzed non-parametrically using a Wilcoxon signed-rank test using the SAS procedure PROC UNIVARIATE. Median differences and approximate 90% CIs for the difference will be calculated for the comparisons of the administration methods (single SC injection and CSII).

No formal statistical analysis will be conducted for Part B.

PK parameters will be listed and summarized for both parts of the study.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

The PD measurements will be derived from the euglycemic clamp procedure, where the glucose infusion rate (GIR) over time is used as a measure of insulin effect. The analyses will be performed according to the Lilly Global PK, PD, and Pharmacometrics Divisional Standard Operating Procedures.

A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group using S Plus® software (Version 8.2 or higher, TIBCO, USA). The fitted data for each subject will be used to calculate the PD parameters: the maximum GIR (R_{max}), the total amount of glucose infused (G_{tot}) over the duration of the clamp procedure, the time of maximum GIR (tR_{max}). Raw (that is, observed) GIR values from each clamp procedure will be used to calculate other PD parameters, such as the time of first change of GIR postdose (tR_{onset}), the time of last measurable GIR (tR_{last}). Other parameters, such as early tR_{max50}, and late tR_{max50}, may also be reported. Parameters will be individually calculated by Eli Lilly and Company and sent to Covance for statistical analysis.

9.4.2 Pharmacodynamic Statistical Methodology

For Part A, the values of tR_{max} will be analyzed non-parametrically using a Wilcoxon signed-rank test using the SAS procedure PROC UNIVARIATE. Median differences and approximate 90% CIs for the difference will be calculated for the comparisons of the administration methods (single SC injection [test] and CSII [reference]).

The PD parameters (R_{max} and G_{tot}) will be log-transformed prior to analysis and a linear mixed-effects model fitted to the data, with administration method, period, and sequence order (order 1 is derived based on sequences 1 and 3, and order 2 is derived based on sequences 2 and 4), as fixed effects and subject as a random effect. For each parameter, the difference in LS means along with the 90% CI will be back-transformed to present the ratios of geometric means and the CI for comparison of the administration methods.

See the PK statistical methodology for example SAS code.

Other time parameters (tR_{last}, tR_{onset}, early tR_{max50}, and late tR_{max50}) will be analyzed non-parametrically if reported.

No formal statistical analysis will be conducted for Part B.

PD parameters will be listed and summarized for both parts of the study.

Mean daily 4-point self-monitored plasma glucose (SMPG) data will be listed and also summarised for the 5 days prior to period 1, 2 and 3. Figures of mean SMPG prior to periods 1, 2 and 3 will be produced. Profiles prior to meals, bedtime and at 3am will also be produced as appropriate.

Exploratory analyses may be performed for other PD parameters as 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 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 adverse events, the number of subjects experiencing an adverse event and the percentage of subjects experiencing an adverse event) of treatment-emergent adverse events will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 system organ class and preferred

term. The summary and frequency adverse event tables will be presented for all causalities and those considered related to the study drug. Any serious adverse events will be tabulated.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2015). Concomitant medication and anti-hyperglycemic 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 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 data will be summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose of the relevant period. Figures of mean vital signs and change from baseline profiles will be presented. Furthermore, values for individual subjects will be listed.

9.5.5 Blood Glucose Monitoring and Hypoglycemia

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.

Hypoglycemic events will be listed, and summarised if appropriate. Severe hypoglycemic events will be reported as SAEs.

9.5.6 Other assessments

Body weight will be listed. Change in weight and BMI from period 1 to period 2, and from period 2 to period 3 will be listed and summarized.

Change in total daily dose (Units and Units/kg) from pre-Period 3 U-100 to Period 3 U-500R will be listed.

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

9.5.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

An interim analysis will be conducted after approximately 12 subjects have completed both periods of Part A of the study. An interim analysis of safety, PK and PD will be carried out and will be used to inform ongoing analysis of a Phase 3b trial, as appropriate.

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. DR Owens, ed. Human Insulin: Clinical pharmacological studies in normal man. Lancaster, UK: MTP Press; 1986.

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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