Statistical Analysis Plan I8B-MC-ITSS v2

Bioequivalence Study Comparing 2 Formulations of LY900014 in Healthy Subjects

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STATISTICAL ANALYSIS PLAN

Bioequivalence Study Comparing 2 Formulations of LY900014 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
AUC	Area under the concentration versus time curve
AUC_τ	Area under the concentration versus time curve during one dosing interval
$AUC(0-t_{last})$	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
$AUC(0-10\ h)$	Area under the concentration versus time curve from time zero to time 10 h
$AUC(0-\infty)$	Area under the concentration versus time 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
Early 50% t_{max}	Time to early half-maximal drug concentration
Early 50% tR_{max}	Time to half-maximal glucose infusion rate before tR_{max}
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
GD	Glucodynamic
GIR	Glucose infusion rate
G_{tot}	Total amount of glucose infused
ICH	International Council on Harmonisation
Late 50% t_{max}	Time to late half-maximal drug concentration
LOESS	Locally weighted scatterplot smoothing

LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PK	Pharmacokinetic
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 to R_{max}
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 14 June 2018 and amendment (a) dated 20 July 2018).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) and glucodynamic (GD) 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 CCI . 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 demonstrate the bioequivalence of PK parameters for the LY900014 U-200 versus LY900014 U-100 formulations after subcutaneous (SC) administration to healthy subjects.

4.2   Secondary Objectives

- To compare the GD responses to LY900014 U-200 versus LY900014 U-100 formulations after SC administration.
- To assess the safety and tolerability of the LY900014 U-200 and LY900014 U-100 formulations.

4.3 Tertiary/Exploratory Objectives

- To compare other PK and GD parameters for LY900014 U-200 versus LY900014 U-100 after SC administration.
- Explore the formation of antidrug antibodies to insulin lispro.
- To assess C-peptide levels following administration of LY900014.

5. STUDY DESIGN

This is a Phase 1, single-center, investigator- and subject-blind, 2-sequence, 4-period, randomized, replicated-crossover, 10-hour euglycemic clamp study in healthy subjects to compare the PK and GD of insulin lispro in LY900014 U-200 formulation versus insulin lispro in LY900014 U-100 after SC administration of 15 U insulin lispro dose. The treatments will be replicated such that each formulation is administered twice on different occasions to healthy subjects over 4 study periods. Figure 1 illustrates the study design.

Figure 1. Illustration of study design
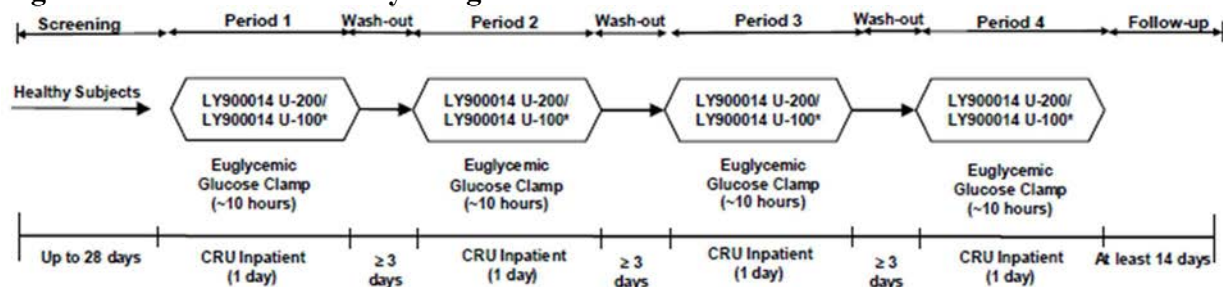
Abbreviation: CRU = clinical research unit;

*Single dose of LY900014 U-200 or LY900014 U-100 administered subcutaneously to the abdomen

Each subject will be administered LY900014 U-200 formulation (on 2 occasions) and LY900014 U-100 formulation (on 2 occasions). Subjects will be randomly assigned to 1 of the 2 dosing sequences (Table 1).

Table 1. Treatment Sequences Example for I8B-MC-ITSS

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
1	LY900014 U-200	LY900014 U-100	LY900014 U-200	LY900014 U-100
2	LY900014 U-100	LY900014 U-200	LY900014 U-100	LY900014 U-200

Note: This is only an example table for illustration purpose; subjects will be assigned a treatment sequence according to the actual treatment randomization schedule provided to the unblinded site pharmacist.

Subjects will be required to attend the clinical research unit (CRU) on at least 6 occasions:

- 1 screening visit (may occur up to 28 days prior to randomization)

- 4 inpatient treatment visits for the clamp procedure (Periods 1 to 4) with a wash-out period of ≥3 days between discharge and the next admission to the CRU

- 1 follow-up visit (at least 14 days after the last dose).

Subjects will be admitted to the CRU on the evening before each dosing day and will remain in the CRU for the duration of the clamp period and until discharge by the investigator. Subjects are expected to fast for at least 8 hours before each dose. Following dose administration, each subject will undergo a euglycemic clamp procedure of up to 10 hours. Upon completion of the clamp procedures, the subjects will be provided a meal and observed overnight. Subjects will be discharged from the CRU the next day after medical assessments. Subjects may remain in the CRU if deemed necessary for safety monitoring, as determined by the investigator.

Safety will be assessed throughout the study by monitoring adverse events (AEs), clinical laboratory tests, electrocardiograms (ECGs), vital sign measurement, and through medical assessments.

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
15 U LY900014 U-100	1
15 U LY900014 U-200	2

7. SAMPLE SIZE JUSTIFICATION

Up to 72 subjects may be enrolled so that approximately 58 subjects complete the study. Fifty-eight completing subjects in a replicated design will provide at least 95% power to show the 2-sided 90% confidence intervals (CIs) of the ratios of geometric least-squares means (LSmeans) for AUC(0-∞), AUC(0-t_{last}) between LY900014 U-200 and LY900014 U-100 to be within limits of 0.80 to 1.25. This calculation assumes a log-scale standard deviation for within-subject difference of 0.28 and up to a 5% difference in geometric LSmean ratio. There is also at least 80% power to show the 2-sided 90% CI of the ratio of the geometric means for C_{max} between the 2 formulations also within 0.80 to 1.25. This calculation assumes a log-scale standard deviation for within-subject difference of 0.59 and an 8% difference in geometric LSmean ratio for C_{max} with LY900014 U-200 compared to LY900014 U-100.

In addition, the study is adequately powered to evaluate the GD parameters. There is approximately 90% power to show the 2-sided 90% CI of the ratio of the geometric means between the 2 formulations for total amount of glucose infused (G_{tot}) and maximum glucose infusion rate (GIR) (R_{max}) are within 0.80 to 1.25. This calculation assumes a log-scale standard

deviation for withinsubject difference of 0.57 for G_{tot} and 0.64 for R_{max} and up to a 5% difference in the LSmean ratios.

Subjects who are randomized but not administered treatment may be replaced to ensure that approximately 58 subjects complete the study. The replacement subjects will assume the same treatment sequence as the subjects who dropped out and will complete that treatment sequence in its entirety.

8. DEFINITION OF ANALYSIS POPULATIONS

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

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

The GD population will consist of all subjects who received at least one dose of study drug and have evaluable GD 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.

Data from individual treatment periods may be excluded from the analysis for the following reasons:

- the clamp was terminated early (e.g., due to an AE, technical issues, or subject withdrawal),

- failure to administer full dose (e.g., appearance of liquid on the skin after withdrawing the needle) or

- failure to collect sufficient PK or GD samples in order to define key endpoints (e.g., C_{max}, R_{max}).

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: area under the concentration 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, 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 ▆▆▆▆▆▆▆▆▆▆ or greater.

9.2   Demographics and Subject Disposition

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

9.3   Pharmacokinetic Analyses

9.3.1 Pharmacokinetic Parameter Estimation

Subjects who completed at least 1 period and had evaluable insulin lispro concentrations will be included in the PK analysis dataset. Pharmacokinetic analyses will be conducted using standard noncompartmental methods of analysis using ▆CCI▆ on a computer that meets or exceeds the minimum system requirements for these programs. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by global PK management.

Free serum insulin lispro concentrations will be used to calculate several PK parameters, including C_{max}, time of C_{max} (t_{max}), time to early half-maximal drug concentration (early 50% t_{max}), and AUC(0-t_{last}), AUC from time zero to 10 hours (AUC[0-10h]), and AUC(0-∞). The apparent total body clearance of drug calculated after extravascular administration (CL/F), half-life ($t_{1/2}$), apparent volume of distribution during the terminal phase after extra-vascular administration (Vz/F), time to late half-maximal drug concentration (late 50% t_{max}), may be determined. Other parameters may be calculated as deemed appropriate, such as partial AUCs.

Although attempts will be made to adhere to the scheduled collection times, it is recognized that situations arise that may compromise the scheduled times. Parameters will be individually calculated for each subject based on actual collection times and presented by summary statistics.

9.3.2 Pharmacokinetic Statistical Inference

To compare PK parameters between LY900014 U-200 relative to LY900014 U-100, log-transformed AUC parameter estimates (AUC[0-tlast], AUC[0-∞], AUC[0-15min], AUC[0-30min] and C_{max}) will be analysed using a repeated measures, linear mixed-effects model where treatment, sequence, and period will be considered as fixed effects and subject as a random effect. From the model, the difference in LSmeans and the corresponding 2-sided 90% CIs for the treatment difference will be estimated and back-transformed from the log scale to provide estimates of the ratio of geometric LSmeans and 90% CI for the ratio of the LSmeans. Bioequivalence will be concluded if the 2-sided 90% CI is completely contained within the

interval (0.80, 1.25). This method is consistent with the FDA recommended methodology of analysis and will involve all available data. The within- and between-subject variability of both treatments will also be estimated directly from the model for all AUC parameters and C_{max}.

Example SAS code:

```
PROC MIXED;
CLASS SEQ SUBJ PER TRT;
MODEL Y = SEQ PER TRT / DDFM=SATTERTH;
RANDOM TRT / TYPE=FA0(2) SUB=SUBJ G;
REPEATED / GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1 / CL ALPHA=0.1;
RUN;
```

Should the model produce the SAS warning "Estimated G matrix is not positive definite" then the following code will be used:

```
PROC MIXED;
CLASS SEQ SUBJ PER TRT;
MODEL Y = SEQ PER TRT / DDFM=KR;
RANDOM INTERCEPT / SUB=SUBJ G GROUP=TRT;
REPEATED / GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1 / CL ALPHA=0.1;
RUN;
```

$AUC(0-tl_{ast})$, $AUC(0-\infty)$, and C_{max}) will also be analyzed using a linear fixed-effects model. 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 formulation, 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 and will involve only study completers.

Example SAS code:

```
PROC MIXED;
CLASS SEQ SUBJ PER TRT;
MODEL Y = SEQ PER TRT SUBJ(SEQ) / DDFM=SATTERTH;
ESTIMATE 'T vs. R' TRT 1 -1 / CL ALPHA=0.1;
RUN;
```

The PK time parameters time parameters (early 50% t_{max} and t_{max}) will be analyzed nonparametrically using the Wilcoxon signed rank test.

9.4 Pharmacodynamic Analyses

9.4.1 Pharmacodynamic Parameter Estimation

Glucodynamic assessments will be determined from the glucose clamp procedure, where the GIR over time will be used as a measure of insulin effect. Glucodynamic analyses will be conducted on those subjects who complete at least 1 clamp procedure.

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 CCI. The fitted data for each subject will be used to calculate the following GD parameters: time to onset of insulin action (t_{onset}), maximal GIR (R_{max}), time to R_{max} (tR_{max}), time to half maximal GIR before tR_{max} (early 50% tR_{max}), total glucose infused over the duration of the clamp (G_{tot}). Additional time to half-maximal GIR after tR_{max} (late 50% tR_{max}),and partial glucose AUCs, such as Gtot over 30 minutes (Gtot0-30min), and Gtot over 1 hour (Gtot0-1h) may be computed as necessary. The values of these GD parameters will be summarized by treatment and/or period through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated.

9.4.2 Pharmacodynamic Statistical Inference

To address the secondary objective of comparing GD parameters (G_{tot} and R_{max}) between the LY900014 U-200 and LY900014 U-100 formulations, log-transformed G_{tot} and R_{max} estimates will be analyzed using a repeated measures, linear mixed-effects model where treatment, sequence, and period will be considered as fixed effects and subject as a random effect. From the model, the difference in LSmeans and the corresponding 2-sided 90% CIs for the treatment difference will be estimated and back-transformed from the log scale to provide estimates of the ratio of geometric LSmeans and 90% CI for the ratio of the LSmeans. The SAS code will be the similar to the PK analysis code and is consistent with the FDA recommended methodology of analysis and will involve all available data. The within- and between-subject variability of both treatments will also be estimated directly from the model for G_{tot}, R_{max} and early insulin activity (i.e G_{tot}[0-30min], G_{tot}[0-1h])

The GD parameters (G_{tot} and R_{max}) will also be analyzed using a linear fixed-effects model. 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 formulation, 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. The SAS code will be the similar to the PK analysis code and is consistent with the EMA recommended methodology of analysis and will involve only study completers. In addition, 95% CIs and p-values will also be provided for this analysis in a separate table.

An additional sensitivity analysis will be performed for the GD parameters using the FDA methodology, based on C-peptide confounders. This sensitivity analysis will involve all available data.

The GD time parameters (tR_{max} and early 50% tR_{max}) will be analyzed nonparametrically using the Wilcoxon signed rank test.

Should any of the GD parameters have zero values, a model with fixed effects for sequence, period and treatment, and subject nested within sequence as a random effect, without log transformation will be used for the analysis. The LSmeans, treatment differences in LSmeans, and the corresponding 90% CIs for the treatment differences will be estimated from the model. The treatment ratios and 90% CIs for the ratios will be calculated using Fieller's theorem. Other GD time parameters may be analyzed in a similar manner. In addition,

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 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 21.0 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.

9.5.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2018). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

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

Furthermore, values for individual subjects will be listed.

9.5.5 Electrocardiogram (ECG)

The ECG data will be listed for individual subjects.

9.5.6 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. Each category of hypoglycemic events (defined below) will be listed and summarized by treatment.

Hypoglycemia is defined as follows:

•**Documented Hypoglycemia:**

o Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by plasma glucose (PG) ≤70 mg/dL (≤3.9 mmol/L).

o Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (≤3.9 mmol/L).

• **Unspecified hypoglycemia:** An event during which PG ≤70 mg/dL (≤3.9 mmol/L) but no information relative to symptoms of hypoglycemia was recorded

• **Probable symptomatic hypoglycemia:** An event during which symptoms indicative of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by PG ≤70 mg/dL [≤3.9 mmol/L]).

• **Clinically significant hypoglycemia:** An event during which plasma glucose is <54 mg/dL (3.0 mmol/L), where it is considered sufficiently low to indicate serious, clinically important hypoglycemia.

• **Severe hypoglycemia:** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

• **Nocturnal hypoglycemia:** Any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic or severe hypoglycemia) that occurs between bedtime and waking.

• **Overall hypoglycemia:** This optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category.

9.5.7 Hepatic Monitoring

If a subject 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.

The subjects' 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 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 subject data listings.

9.5.8 Injection Site Local Tolerability Assessment Data

Injection-site assessment data will be listed and summarized in frequency tables by treatment.

9.5.9 Pain Measurements using the Visual Analog Scale

In case of an AE of injection-site reaction, pain will be assessed using a 100-mm validated visual analog scale for pain and will be listed and summarized by treatment.

9.5.10   Immunogenicity

The frequency of antibody formation to insulin lispro will be determined. The number of patients who have not-detected anti-insulin lispro antibody at pre-dose for period 1 and detected anti-insulin lispro antibody at post-dose (measured at pre-dose for period 2, 3, or follow-up) will be summarized for combined treatments. The number of patients who have detected anti-insulin lispro antibody at pre-dose for period 1 and 57% increase from the pre-dose to post-dose (measured at pre-dose for period 2, 3, or follow-up) will also be summarized in a similar way.

The relationship between the presence (or absence) of antibodies and AEs will be assessed and listed.

9.5.11   C-Peptide

Mean and individual C-peptide concentration versus time plots with both treatments will be presented. In addition, individual plots overlaying the C-peptide concentration versus time with the serum insulin lispro concentration versus time will be presented. Other plots that may be explored.

9.5.12   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."