Statistical Analysis Plan: I8B-MC-ITRQ Bioequivalence Study Comparing the Pharmacokinetics and Glucodynamics of LY900014 U-200 Formulation with LY900014 U-100 Formulation in Healthy Subjects
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STATISTICAL ANALYSIS PLAN

Bioequivalence Study Comparing the Pharmacokinetics and Glucodynamics of LY900014 U-200 Formulation with LY900014 U-100 Formulation 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-∞)	Area under the concentration versus time curve from time zero to infinity
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
C_{max}	Maximum observed drug concentration
CI	Confidence interval
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 tRmax
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
G_{tot}(0-30min)	Amount of glucose infused from time zero to 30 minutes
G_{tot}(0-1h)	Amount of glucose infused from time zero to 1 hour
ICH	International Council on Harmonisation
late 50% t_{max}	Time to late half-maximal drug concentration
late 50% tR_{max}	Time to half-maximal GIR after tRmax
LSmeans	Least square means
LOESS	Locally weighted scatterplot smoothing

MedDRA	Medical Dictionary for Regulatory Activities
MRE	Magnetic resonance elastography
PD	Pharmacodynamic
PG	Plasma glucose
PK	Pharmacokinetic
R_{max}	Maximum glucose infusion rate
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
tR_{max}	Time to maximum glucose infusion rate
ULN	Upper limit of normal
VAS	Visual analog scale

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 21 August 2017) and the version 1 SAP (dated 12 October 2017).

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 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

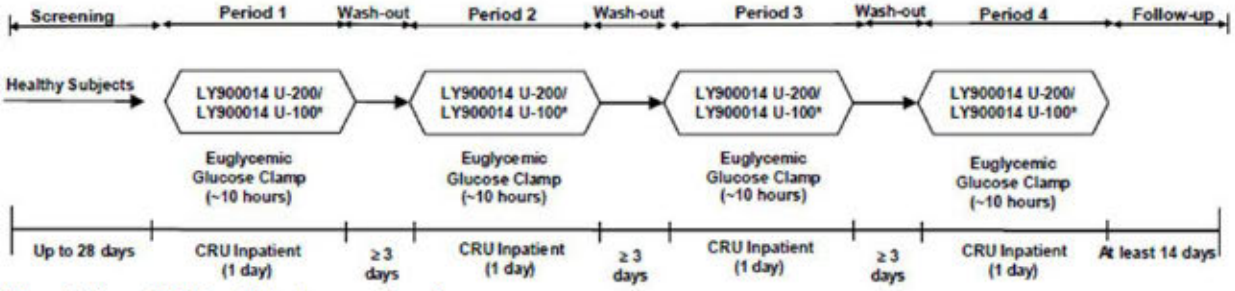
- To compare the glucodynamic (GD) responses to LY900014 U-200 versus LY900014 U-100 formulations after SC administration.
- To assess the safety and tolerability of the LY900014 U-200 and LY900014 U-100 formulations.

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 anti-drug 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, 4-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.



Abbreviation: CRU = clinical research unit
*Single dose of LY900014 U-200 or LY900014 U-100 administered subcutaneously to the abdomen

Figure 1. Illustration of study design

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 4 dosing sequences (Table 1).

Table 1. Treatment Sequence Example for I8B-MC-ITRQ

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
3	LY900014 U-200	LY900014 U-100	LY900014 U-100	LY900014 U-200
4	LY900014 U-100	LY900014 U-200	LY900014 U-200	LY900014 U-100

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 an 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 signs measurement and through medical assessments. Study governance considerations are described in detail in Appendix 3 of the protocol.

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 SC	1
15 U LY900014 U-200 SC	2

7. SAMPLE SIZE JUSTIFICATION

Up to 60 subjects may be enrolled so that approximately 44 subjects complete the study. Forty-four 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 area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) and 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-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 CCI and up to a 5% difference in geometric LSmean ratio. There is also at least 95% power to show the 2-sided 90% CI of the ratio of the geometric means for maximum observed drug concentration (C_{max}) between the 2 formulations also within 0.80 to 1.25. This calculation assumes a log-scale standard deviation (SD) for within-subject difference of CCI and a 10% 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 at least 85% 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 (R_{max}) are within 0.80 to 1.25. This calculation assumes a log-scale SD for within-subject difference of CCI for G_{tot} and CCI for R_{max} and up to a 10% difference in the LSmean ratios.

Subjects who are randomized but not administered treatment may be replaced to ensure that approximately 44 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, whether or not they completed all protocol requirements.

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.

Primary statistical analyses will be conducted on the set of subjects who complete at least the first period of treatment.

Supportive analyses will be done on the key parameters for the subjects who complete all treatment periods.

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 SD, median, min, max and N; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [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 CCI procedure such as CCI.

Data analysis will be performed using C C or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, 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. PK 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 maximum observed drug concentration (t_{max}), time to early half-maximal drug concentration (early 50% t_{max}), time to late half-maximal drug concentration (late 50% t_{max}), and AUC([0-t_{last}), area under the concentration versus time curve from time zero to 10 hours (AUC[0-10h]), and AUC(0-∞), 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-t_{last}], AUC[0-∞]) and C_{max} will be analyzed using the mixed-effects model that includes treatment, sequence, and period as fixed effects and subject within sequence as a random effect. From the model, the difference in LSmeans and the corresponding 2-sided 90% CIs for the 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).

Example CCI code:

```
proc mixed data=pk;
class patient period treatment sequence ;
model logpk = treatment period sequence / ddfm=kr alpha=0.1;
random patient(sequence);
lsmeans treatment;
run;
```

In addition, the same model without log transformation will be used for the analysis of the PK time parameters (early 50% t_{max}, and t_{max}). 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. As a sensitivity analysis, the PK time parameters will be analyzed nonparametrically using Wilcoxon signed rank test.

In addition, the analyses described above will also be performed on the population of subjects who completed and had evaluable PK data in all study periods.

9.4 Pharmacodynamic Analyses

9.4.1 Pharmacodynamic Parameter Estimation

GD assessments will be determined from the glucose clamp procedure, where the glucose infusion rate (GIR) over time will be used as a measure of insulin effect. GD 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 S-PLUS software (version 8.2). The fitted data for each subject will be used to calculate the following GD parameters: time to onset of insulin action (tonset), time to maximal GIR (R_{max}), time to R_{max} (tR_{max}), time to half-maximal GIR before tR_{max} (early 50% tR_{max}), and total amount of glucose infused (G_{tot}),. Additional partial glucose AUCs, 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 the mixed-effects model that includes treatment, sequence, and period as fixed effects and subject within sequence as a random effect. From the model, the difference in LSmean estimates and the corresponding 90% for the difference will be estimated and back-transformed from the log scale to provide estimates of the ratios of geometric LSmeans and 90% for the ratio of the LSmeans. For GD parameters that have at least 1 patient with a value equal to zero, an analysis of original scale data (not log-transformed) will be performed as described below for the GD time parameters.

In addition, the same model without log transformation will be used for the analysis of the GD time parameters (tR_{max} and early 50% tR_{max}). LSmeans, treatment differences in LSmeans, and the corresponding 90% CIs for the treatment differences will be estimated from the model. The p-value for the difference between LSmeans will be used to determine statistical significance. 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. As a sensitivity analysis, the GD time parameters will be analyzed nonparametrically using Wilcoxon signed rank test.

In addition, the analyses described above will also be performed on the population of subjects who completed and had evaluable GD data in all study periods.

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 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 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.

9.5.2 Concomitant medication

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

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

Hypoglycemia is defined as follows:

- **Documented Glucose Alert Level (Level 1), Plasma Glucose (PG) ≤70mg/dL (3.9 mmol/L):**
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by plasma glucose ≤70 mg/dL (3.9 mmol/L)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with plasma glucose ≤70 mg/dL (3.9 mmol/L)
  - **Unspecified hypoglycemia:** an event during which plasma glucose ≤70 mg/dL (3.9 mmol/L) but with no available information related to symptoms of hypoglycemia
- **Probable symptomatic hypoglycemia:** an event during which symptoms indicative of hypoglycemia are observed but not accompanied by a plasma glucose determination (but that was presumably caused by plasma glucose ≤70 mg/dL [3.9 mmol/L])
- **Documented Clinically significant hypoglycemia (Level 2) PG <54 mg/dL (3.0 mmol/L):**
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG ≤54 mg/dL (3.0 mmol/L)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG ≤54 mg/dL (3.0 mmol/L)
  - **Unspecified hypoglycemia:** an event during which PG ≤54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded.

- **Severe hypoglycemia (Level 3):** an event during which patients had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (≤70 mg/dL [3.9 mmol/L]).
  - **Severe hypoglycemia requiring medical attention**: a severe hypoglycemic event when patients require therapy by HCPs (EMTs, emergency room personnel, etc.).

- **Nocturnal hypoglycemia:** any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking
- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, that do not require the assistance of another person, are accompanied by plasma glucose >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold

Overall (or total) hypoglycemia: This optional category combines most cases of hypoglycemia except relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should be counted only once in this category of overall (or total) hypoglycemia

9.5.6 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.

9.5.7 Injection Site Local Tolerability Assessment Data

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

9.5.8 Pain Measurements using the Visual Analog Scale (VAS)

Intensity of pain data at the injection site as soon as practicably possible after the injection, and at multiple postdose timepoints, as reported by the patient and measured according to the 0- to 100-mm VAS will be listed and summarized by treatment.

The time 0 (immediately after dosing) data will be analyzed,using the Wilcoxon signed-rank test. The difference in medians between LY900014 U-200 and LY900014 U-100 and the 90% CIs for the difference will be presented.

VAS data will also be summarized based on the following categories of score: 0, 1-10, 11-20, 21-30, 31-40, etc up to the maximum category by treatment and timepoint and also the categories <=10 mm, <=20 mm and <=45 mm. The table will show number and percent of patients with observations in each category.

9.5.9 Immunogenicity

The frequency of antibody formation to insulin lispro will be determined. The relationship between the presence (or absence) of antibodies and AEs will be assessed. Likewise, the

relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may be assessed.

9.5.10 C-peptide

C-peptide data will be summarized by treatment. Figures of mean and individual C-peptide concentrations versus time will be presented by dose level for both treatments. In addition, individual plots overlaying the C-peptide concentration versus time with the insulin lispro serum concentration versus time will be presented.

Senstivity analysis removing subject(s) who could have potential confounding on the PD parameters will be performed as described in Section 9.4.2. Potential C-peptide confounding is defined as a lack of C-peptide suppression from baseline after the start of the euglycemic clamp, or a signficiant rise in C-peptide over baseline while the euglycemic clamp procedures are ongoing.

9.5.11 Other assessments

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

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

The VAS statistical analysis was updated to a non-parametric analysis due to issues observed in ITSC.

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."