Statistical Analysis Plan: I8B-MC-ITSL(a) A Mixed Meal Tolerance Test Study to Evaluate the Pharmacokinetics and Pharmacodynamics of LY900014 Compared to Humalog Following a Single Dose in Adults with Type 1 Diabetes

NCT03449433

Approved: 8-Mar-2018

STATISTICAL ANALYSIS PLAN

A Mixed Meal Tolerance Test Study to Evaluate the Pharmacokinetics and Pharmacodynamics of LY900014 Compared to Humalog Following a Single Dose in Adults with Type 1 Diabetes

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 06-March-2018

Study Drug: LY900014

Sponsor Reference: I8B-MC-ITSL
Covance CRU Study: 1001215-8380290

Clinical Phase I

Approval Date: 08-Mar-2018 GMT

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 - 30min)	AUC from time 0 to 30 minutes
AUC(0 - 1h)	AUC from time 0 to 1 hour
AUC(0 – 2 h)	AUC from time 0 to 2 hours
AUC(0 - 7h)	AUC from time 0 to 7 hours
AUC(0 - ∞)	AUC from time 0 to infinity
AUC(3 – 7 h)	AUC from time 3 hours to time 7 hours
BMI	Body mass index
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
ΔAUC(0-1h)	Area under the baseline subtracted glucose concentration versus time curve from time 0 to 1 hour
ΔAUC(0-2h)	Area under the baseline subtracted glucose concentration versus time curve from time 0 to 2 hours
ΔAUC(0-5h)	Area under the baseline subtracted glucose concentration versus time curve from time 0 to 5 hours
Early 50% t_{max}	Time to early half-maximal drug concentration
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)

ICH	International Council on Harmonisation
Late 50% t_{max}	Time to late half-maximal drug concentration
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed meal tolerance test
MR_{AUC}	Metabolic ratio based on AUC(0-∞)
MRE	Magnetic resonance elastography
NA	Not applicable
PD	Pharmacodynamic
PG	Plasma glucose
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOP	Standard Operating Procedure
T1DM	Type 1 diabetes mellitus
TBL	Total bilirubin
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
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 12 December 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 evaluate the differences in PK between LY900014 and Humalog following a single dose in patients with type 1 diabetes mellitus (T1DM).

4.2 Secondary Objectives

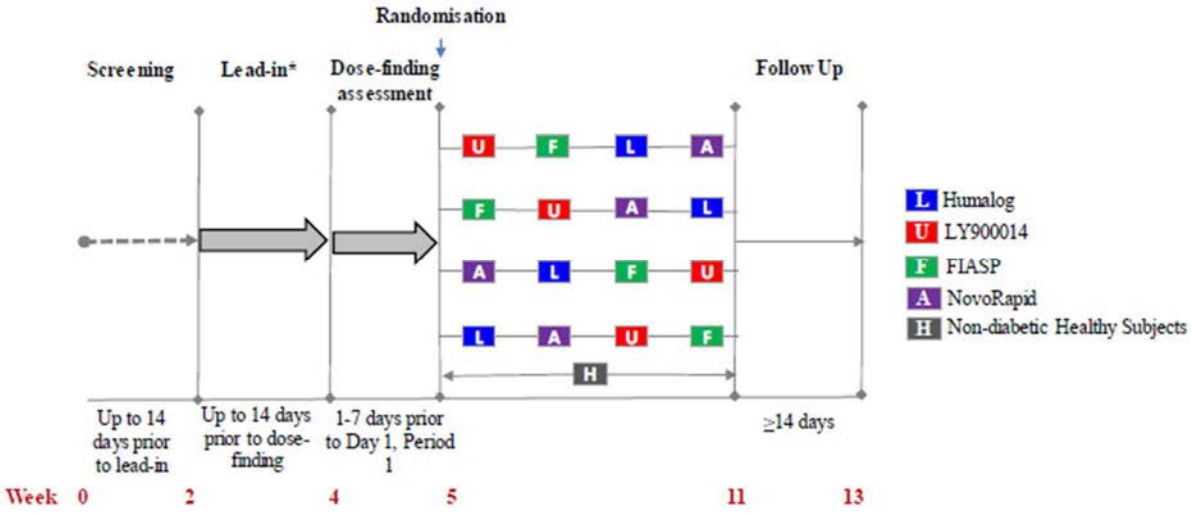
- To characterise the PK profiles of LY900014, Humalog, NovoRapid and FIASP following a single dose in patients with T1DM.
- To evaluate the differences in PD between LY900014 and Humalog following a single dose in patients with T1DM
- To characterise the PD response to LY900014, Humalog, NovoRapid and FIASP, as assessed by the mixed meal tolerance test (MMTT), in patients with T1DM.

4.3 Tertiary/Exploratory Objectives

- To characterise "normal" insulin secretory and glucose response to the MMTT in non-diabetic healthy subjects
- To evaluate the tolerability of subcutaneous (SC) doses of LY900014 in patients with T1DM.

5. STUDY DESIGN

Study I8B-MC-ITSL (ITSL) is a clinical pharmacology, patient- and investigator-blind, randomised, 4-treatment, 4-period crossover study in patients with T1DM to compare insulin lispro PK and PD profiles of the postprandial blood glucose during a standardised MMTT following LY900014 in comparison to Humalog in patients with T1DM following single SC injections administered just before a standardised MMTT. This study will also characterise the PK and PD of insulin aspart analogues NovoRapid and FIASP in patients with T1DM under identical study conditions. A non-diabetic healthy subject cohort, which approximately matches to the cohort of patients with T1DM with regard to the mean body mass index (BMI) and age, is included with the intention of characterising the insulin secretory response to a standardised MMTT within normal physiology. These subjects will undergo a single in-house MMTT and will not receive any of the study drugs. Study ITSL may be conducted at 1 or more clinical research units (CRUs). Figure 1 illustrates the study design.



Abbreviation: MMTT = mixed meal tolerance test.
*Lead-in period up to 14 days prior to dose-finding assessment to enable transition to insulin glargine; patients continue use of insulin glargine and usual prandial insulin analogues throughout the study during lead-in and between MMTT assessments.
Dose-finding MMTT with Humalog is performed between 1 and 7 days prior to MMTT in Period 1.
4-period crossover: the 4 MMTT assessments may occur on successive days, but all should be completed within 6 weeks.
Intravenous glucose insulin infusion is provided from 7 hours to 30 minutes prior to MMTT to achieve a stable baseline glucose target in the patients with type 1 diabetes mellitus.
Single MMTT is performed in non-diabetic healthy subject cohort; no lead-in period is required.

Figure 1 Illustration of 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
LY900014	1
Humalog	2
FIASP	3
NovoRapid	4

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

Population Name	Population order in TFL
Patients with T1DM	1
Healthy subjects	2

7. SAMPLE SIZE JUSTIFICATION

An initial 74 patients with T1DM may be enrolled so that approximately 64 patients complete the study. Sixty-four completing patients will provide at least 95% power to demonstrate a 2-fold increase in the serum insulin lispro AUC from time 0 to 30 minutes (AUC[0-30min]) between LY900014 and the Humalog. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The sample size will also provide greater than 95% power to demonstrate a 35% reduction of early 50% t_{max} between LY900014 and Humalog. The estimated standard deviation of within-subject difference on the log scale is 0.35 for AUC(0-30min) and 0.3 for early 50% t_{max}, according to an analysis of internal Lilly data (Study I8B-FW-ITRG) for LY900014 and Humalog administered in a repeat-dose study.

With this sample size, there is more than 95% power to detect a 40% reduction in postprandial glucose incremental area under the baseline subtracted glucose concentration versus time curve from time 0 to 1 hour (ΔAUC[0-1h]) between LY900014 and Humalog. With similar assumptions, the study is also adequately powered for the comparison between LY900014 and NovoRapid.

With 64 completing patients, there is more than 95% power to detect a 20% reduction of early 50% t_{max} between LY900014 and FIASP. In addition, there is approximately 80% power to demonstrate a 25% reduction in postprandial glucose incremental AUC from time 0 to 1 hour between LY900014 and FIASP. The power calculation is based on published results of FIASP studies and internal Lilly data.

Patients who are randomised but drop out before completing assigned treatment may be replaced to ensure that approximately 64 patients complete the study.

For the healthy cohort, 12 non-diabetic healthy subjects will be evaluated for their glucose and insulin secretory response to the MMTT. No treatment will be provided for this cohort. The sample size for the healthy cohort was chosen to provide sufficient data in order to evaluate the objectives of the study, and is not intended to achieve any a priori statistical requirements.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Safety” population will consist of all enrolled subjects who receive at least 1 dose of study drug. Healthy volunteers will also be included in the safety population.

Primary statistical analyses of PK and PD parameters for the cohort of patients with T1DM will be conducted on the set of patients who complete all treatment periods with identical prandial

insulin doses for the MMTTs during the study, as the PK parameters and PD response is dependent on the insulin dose which is individualised for each patient. Supportive analyses may be done on the key parameters for the patients who complete at least 2 treatment periods.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations.

9. STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, min, max and N; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using [redacted].

Where applicable, data from the T1DM population will be reported separately to the healthy volunteers data.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, screening HbA1c, screening fasting blood glucose, screening fasting C-peptide, duration of T1DM, site ID, body weight, height, and body mass index will be summarized and listed.

In addition, the following dosing data will be listed and summarized:

- Insulin dose at screening (stored in the concomitant dataset) for basal, bolus, and total.
- Dose finding dose for the MMTT (the dose administered for the dose finding and the dose selected after the dose finding on Day 1, Period 1 which will be used for all MMTT, and is the dose selected on the exposure dose finding page).

9.3 Pharmacokinetic Analyses

9.3.1 Pharmacokinetic Parameter Estimation

Patients who complete at least 1 MMTT and have measurable insulin concentrations will be included in the analysis dataset for the PK analyses. Pharmacokinetic analyses will be conducted using standard noncompartmental methods of analysis (Phoenix® version 6.3 or above) on a computer that meets or exceeds the minimum system requirements for these programs. It is possible that other validated equivalent PK software programs may be utilised if appropriate, warranted and approved by global PK management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

Serum insulin lispro and plasma or serum insulin aspart concentrations will be used to calculate several PK parameters, including time to early half-maximal drug concentration (early 50% t_{max}), time to late half-maximal drug concentration (late 50% t_{max}), maximum observed drug concentration (C_{max}), time to maximum observed drug concentration (t_{max}), AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), AUC(0-30min), AUC from time 0 to 1 hour (AUC[0-1h]), AUC from time 0 to 7 hours (AUC[0-7h]) and AUC from time zero to infinity (AUC[0-∞]). Additional partial AUCs may be computed as necessary, such as AUC from time 0 to 2 hours (AUC[0-2h]),AUC from time 3 to 7 hours (AUC[3-7h]), and onset of appearance of serum lispro/aspart in the blood.

In addition, a graphical comparison of the "normal" insulin secretory response using the endogenous insulin levels following the MMTT from healthy subjects to the insulin lispro/aspart profile following these insulin analogues (LY900014, Humalog, FIASP or NovoRapid) in patients with T1DM will be performed. Additional analysis may be performed, if needed.

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

Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

9.3.2 Pharmacokinetic Statistical Inference

Patients who did not keep identical prandial insulin doses for the MMTTs across all periods will be excluded from the statistical analysis of the PK parameters.

The PK time parameters (early 50% t_{max}, late 50% t_{max} and t_{max}) in the original scale will be analysed by the mixed-effect model that includes treatment (LY900014, Humalog, FIASP, NovoRapid), treatment sequence and period as fixed effects and patient within sequence as a random effect. Least-squares means (LSmeans), treatment differences in LSmeans and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance.

The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow and Liu 2009[3]).

Example SAS code:

```
proc mixed data=pk;
class patient period treatment;
model logpk = treatment period / ddfm=kr alpha=0.05;
random patient;
lsmeans treatment;
run;
```

Log-transformed AUCs, C_{max} for insulin lispro/aspart may be evaluated to estimate geometric means, ratios of geometric means and their corresponding 95% CIs using the same mixed-effect model as PK time parameters.

Statistical significance will be achieved when the p-value for a test is less than 0.05. The primary comparison will be of LY900014 to Humalog. The following comparison will also be performed. No multiplicity test adjustment will be made for these comparisons.

- LY900014 versus FIASP
- LY900014 versus NovoRapid
- Humalog versus NovoRapid

9.4 Pharmacodynamic Analyses

9.4.1 Pharmacodynamic Parameter Estimation

Patients who receive at least 1 dose of study drug and have evaluable PD data will be included in the analysis set for the PD analyses.

Data will be analysed for the patients during each MMTT. The change from baseline values (the average of -30, -15 and 0 minutes represented as the 0-hour time point following the start of the MMTT) for each patient will be calculated. The ΔAUC[0-1h], area under the baseline subtracted glucose concentration versus time curve from time 0 to 2 hours post-meal (ΔAUC[0-2h] and area under the baseline subtracted glucose concentration versus time curve from time 0 to 5 hours post-meal (ΔAUC[0-5h]) will be calculated. In addition, the change from baseline maximum glucose observed during the 5 hours post-meal and change from baseline 1 hour glucose and 2 hour glucose after the start of the meal will be calculated. Other partial ΔAUCs may be calculated, as deemed appropriate.

For those patients patients which received treatment (insulin or glucose) for hypoglycemic or hyperglycemic events, the postprandial glucose collected post intervention during the MMTT following will not be included in the glucodynamic assessment. These glucose parameters will be analyzed in 2 different ways:

1) the glucose values collected prior to any treatment intervention due to hypoglycemic or hyperglycemic event. Glucose values collected after intervention were treated as missing in the datafile;
2) last observation carried forward (LOCF): the last observed glucose values prior to treatment intervention due to hypoglycemic or hyperglycemic event were carried forward to the end of the MMTT timing.

In addition, a graphical comparison of the "normal" glucose response following the MMTT from healthy subjects to the glucose response following administration of these insulin analogues (LY900014, Humalog, FIASP or NovoRapid) in patients with T1DM will be presented.

Parameters will be individually calculated for each patient and presented by summary statistics.

9.4.2 Pharmacodynamic Statistical Inference

Patients who did not complete the entire meal or had significant changes in nutrient consumption of the standardised test meal or dose changes during the MMTTs will be excluded from all the statistical analysis of the PD parameters.

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum and maximum) will be presented by treatment. All PD parameters (including ΔAUCs, glucose changes from baseline and time parameters) on the original scale (not log transformed) will be analysed using a statistical model that includes treatment, sequence and period as fixed effects and patient within sequence as a random effect. The p-value on the difference between LSmeans will be used to determine statistical significance and the corresponding 95% CIs for the LSmean ratios from Fieller's theorem will be presented.

Statistical significance will be achieved when the p-value for a test is less than 0.05. The primary comparison will be of LY900014 to Humalog. The following comparisons will also be performed.

- LY900014 versus FIASP
- LY900014 versus NovoRapid
- Humalog versus NovoRapid

No multiplicity adjustment will be done for the above pair comparisons.

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 20.1system 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 September 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 listed for individual subjects.

9.5.5 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.

9.5.6 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 during study and during MMTT.

Hypoglycemia is defined as follows:

- **Documented Glucose Alert Level (Level 1)**, Plasma Glucose (PG) ≤70 mg/dL (3.9 mmol/L):
    - **Symptomatic hypoglycemia**: an event during which typical symptoms of hypoglycemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
    - **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
- **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 requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the patient has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. PG measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤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)

Other Hypoglycemia:

- **Nocturnal hypoglycemia**: any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycaemia) that occurs between bedtime and waking
- **Relative hypoglycemia**: an event during which typical symptoms of hypoglycemia, which do not require the assistance of another person, are accompanied by PG

>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 all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is counted only once in this category

- **Probable symptomatic hypoglycemia**: An event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

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.

3. Chow SC, Liu JP. Design and analysis of bioavailability and bioequivalence studies. 3rd ed. Florida: Taylor and Francis Group, LLC; 2009:88-90

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.”