Statisitcal Analysis Plan I8B-MC-ITSC

A Study to Assess the Pharmacokinetics, Glucodynamics, Safety, and Tolerability of LY900014 in Patients with Type 1 Diabetes Mellitus on Continuous Subcutaneous Insulin Infusion Therapy

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STATISTICAL ANALYSIS PLAN

A Study to Assess the Pharmacokinetics, Glucodynamics, Safety, and Tolerability of LY900014 in Patients with Type 1 Diabetes Mellitus on Continuous Subcutaneous Insulin Infusion Therapy

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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[0-15 min]	Area under the concentration versus time curve from time zero to 15 minutes
AUC[0-30 min]	Area under the concentration versus time curve from time zero to 30 minutes
AUC[0-1 h]	Area under the concentration versus time curve from time zero to 1 hour
AUC[2-5 h]	Area under the concentration versus time curve from time 2 to 5 hours
AUC[0-5 h]	Area under the concentration versus time curve from time zero to 5 hours
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
BGRI	Sum of the LBGI and HBGI
CGM	Continuous glucose monitoring
CI	Confidence interval
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CRP	Clinical research physician
CSII	Continuous subcutaneous insulin infusion
CV	Coefficient of variation
Early 50% T_{max}	Time to early half-maximal concentration
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
GD	Glucodynamic

HbA1c	Hemoglobin A1c
HBGI	High blood glucose index
ICH	International Council on Harmonization
Late 50% T_{max}	Time to early half-maximal concentration
LBGI	Low blood glucose index
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed meal tolerance test
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
T1DM	Type 1 diabetes mellitus
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
VAS	Visual analog scale
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 19 November 2016 and amendment (a), dated 6 February 2017).

This SAP describes the planned analysis of the safety, tolerability, 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 [redacted]. 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 patient 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 CCI [redacted] 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 Harmonization (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 difference in insulin lispro PK when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with type 1 diabetes mellitus (T1DM) during a breakfast meal test.

4.2 Secondary Objectives

- To evaluate the sustainability of any difference in insulin lispro PK of LY900014 and Humalog over 3 days when administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test.

- To evaluate the difference in GD response when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test.

- To compare the durability of GD response over 3 days when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a breakfast meal test.

4.3 Exploratory Objectives

- To evaluate the safety and tolerability of LY900014 administered with an insulin pump.
- To compare the GD response using continuous glucose monitoring (CGM) when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a standardized lunch meal.
- To compare the GD response using CGM when LY900014 and Humalog are administered as different test bolus doses with an insulin pump to patients with T1DM during a standardized dinner meal.
- To evaluate the intrapatient and interpatient insulin lispro PK variability of LY900014 compared with Humalog after 3 days of continuous subcutaneous insulin infusion (CSII).
- To determine catheter occlusion rates with LY900014 and Humalog after 3 days of CSII.
- To perform an exploratory comparison of glucose fluctuations with time in patients with euglycemic, hypoglycemia, and hyperglycemia receiving LY900014 and Humalog.

5. STUDY DESIGN

This is a single-site, 4-period, patient- and investigator-blind, randomized, crossover study in patients with T1DM to evaluate the insulin lispro PK and GD characteristics of LY900014 (Test) over 3 days with CSII compared with that of Humalog (Reference) using a CCI [redacted]

Each patient will be randomized to 1 of 4 treatment sequences comprising CSII of LY900014 or Humalog, with different combinations of the modes of administration of the bolus doses relative to the breakfast, lunch, and dinner meals using an insulin pump (refer to Figure 1 and Table 1). The modes of administration are as follows:

- Mode 1: bolus dose is administered as a standard dual-wave bolus (50% immediate bolus delivery [speed = 1.5 U/minute] and 50% as a square-wave over 3 hours)
- Mode 2: bolus dose is administered as a standard single-wave bolus (speed = 1.5 U/minute)
- Mode 3: bolus dose is administered as a rapid single-wave bolus (speed = 15 U/minute)
- Mode 4: bolus dose is administered as a rapid dual-wave bolus (50% immediate bolus delivery [speed = 15 U/minute] and 50% as a square wave over 3 hours)

The compositions of the meals are described in Section 6.3.1 of the protocol.

A mixed-meal tolerance test (MMTT) will be administered at breakfast as an individually standardized solid test meal on Day 1 and Day 3 and as a high-glycemic index test meal on Day 2. The assigned treatment will be administered as a bolus dose at time 0 relative to the start of each breakfast test meal via 3 different modes: Modes 1, 2, and 3.

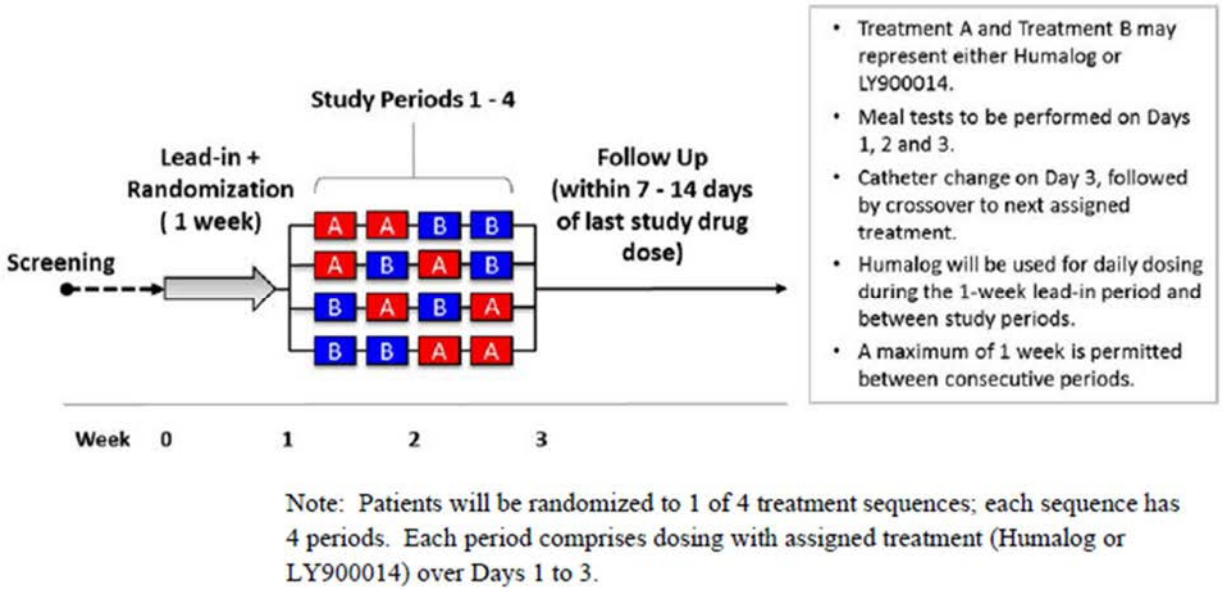
An individually standardized solid lunch will be administered on Days 1, 2, and 3. The assigned treatment will be administered as standard (Mode 1) or rapid (Mode 4) dual-wave bolus doses at time 0 relative to the start of each lunch meal.

An individually standardized dinner will be administered on Days 1 and 2. The assigned treatment will be administered as standard (Mode 2) or rapid (Mode 3) single-wave bolus doses at time 0 relative to the start of each dinner meal.

The study design is shown in Figure 1 and planned treatment sequences are shown in Table 1. Details of the inpatient and outpatient procedures are described in Section 5.1.1 and Section 5.1.2 of the protocol, respectively.

Patients who are eligible to participate in the study based on the results of the screening procedures will proceed to a 1-week lead-in period. During the lead-in period, patients will (if not receiving Humalog) switch from their short-acting insulin used before the start of the study to Humalog, which will be administered using their own personal pump. Patients will also be provided with a general diabetes training including, but not limited to, dose calculation for short-acting insulins; correct self-monitoring of plasma glucose; and interpretation of results, symptoms, and treatment of hypoglycemia. A patient diary will also be provided for documentation of dosing, meals, and glucose monitoring outcomes.

Patients will be randomly assigned to a treatment sequence according to the actual randomization schedule provided to the site at the beginning of or during the lead-in period. The Medtronic CCI [redacted] will be used for all study treatment administrations, while maintaining the catheter needle at the same catheter insertion-site location for the 3-day duration of each study period. Before each MMTT on Day 1 and Day 3, a run-in period to stabilize plasma glucose levels will occur. Details of run-in activities are described in Section 5.1.1.2 and Section 2 of the protocol. Before the breakfast meal test on Day 2, the patients will have their plasma glucose monitored approximately every hour during the night to ensure that the targeted plasma glucose range is met before the start of the Day 2 meal test.



Note: Patients will be randomized to 1 of 4 treatment sequences; each sequence has 4 periods. Each period comprises dosing with assigned treatment (Humalog or LY900014) over Days 1 to 3.

Figure 1. Study design

Patients will be required to attend the clinical research unit (CRU) on at least 8 occasions:

- a visit for informed consent
- a screening visit (may occur up to 21 days before the lead-in period)
- an initial CRU visit at the start of the 1-week lead-in period in which all patients will receive Humalog as their CSII
- 4 inpatient stays from Day –1 to Day 3 (one in each study period)
- a follow-up visit (within 7 to 14 days after the last dose or early discontinuation)

Treatment Sequence	Meal	Period 1			Period 2			Period 3			Period 4		
		Days			Days			Days			Days		
		1	2	3	1	2	3	1	2	3	1	2	3
1		Treatment A			Treatment A			Treatment B			Treatment B		
	Breakfast	SD	RS	SD	SS	SS	SS	SD	RS	SD	SS	SS	SS
	Lunch	RD	RD	RD	SD	SD	SD	RD	RD	RD	SD	SD	SD
	Dinner	SS	SS		RS	RS		SS	SS		RS	RS	
2		Treatment A			Treatment B			Treatment A			Treatment B		
	Breakfast	SS	SS	SS	SS	SS	SS	SD	RS	SD	SD	RS	SD
	Lunch	SD	SD	SD	SD	SD	SD	RD	RD	RD	RD	RD	RD
	Dinner	RS	RS		RS	RS		SS	SS		SS	SS	
3		Treatment B			Treatment A			Treatment B			Treatment A		
	Breakfast	SD	RS	SD	SD	RS	SD	SS	SS	SS	SS	SS	SS
	Lunch	RD	RD	RD	RD	RD	RD	SD	SD	SD	SD	SD	SD
	Dinner	SS	SS		SS	SS		RS	RS		RS	RS	
4		Treatment B			Treatment B			Treatment A			Treatment A		
	Breakfast	SS	SS	SS	SD	RS	SD	SS	SS	SS	SD	RS	SD
	Lunch	SD	SD	SD	RD	RD	RD	SD	SD	SD	RD	RD	RD
	Dinner	RS	RS		SS	SS		RS	RS		SS	SS	

Note: Patients will be randomized to 1 of 4 treatment sequences, each comprising different administration modes for the prandial bolus dose for the breakfast, lunch, and dinner meals on Days 1 through 3 in each of the 4 periods.

"Treatment A" and "Treatment B" may represent either Humalog or LY900014. Patients will be assigned a treatment sequence according to the actual randomization schedule provided to the site.

Bolus dose administration modes: RD = rapid dual-wave; RS = rapid single-wave; SD = standard dual-wave; SS = standard single-wave.

Table 1. Planned Treatment Sequences by Period

Patients will be discharged from the CRU on Day 3 (at least 5 hours after the st art of the lunch meal) or later, if deemed necessary for safety monitoring as determined by the investigator. Study treatments may be administered on consecuti ve days from one period to the next, and a maximum time of 1 week is permitted between consecutive periods.

Patients will continue their individual CSII basal rate using the insulin pump during the entire study including the meal test days unless safety issues arise; in this case, the investigator will discuss a change of the basal rate with the sponsor clinical research physician (CRP) and implement this change, if necessary, to prevent any medical problems. However, during the MMTT (approximately 6:00 AM to 2:00 PM on Days 1 and 3) and the high-glycemic index breakfast meal test (approximately 6:00 AM to 2:00 PM on Day 2), the basal rate will be changed to a single hourly rate based on the patient's mean basal needs during the meal test period. For all lunch and dinner meals during the inpatient periods, the patients' individual CSII basal rate will be continued unchanged.

Assessment of local tolerability at all catheter insertion sites will be performed as specified in the Study Schedule (Section 2) of the protocol, including visual analog scale (VAS) scores for pain and inspection of the catheter insertion site for signs such as edema, erythema, and rash.

For each meal test day (Days 1, 2, and 3), serial blood samples will be collected over approximately 300 minutes to assess the PK and GD responses following start of the breakfast meal test, as specified in the Study Schedule (Section 2) of the protocol. For each standardized lunch and dinner meal on Days 1 through 3, the GD response will be assessed using CGM following start of the meals.

6. TREATMENTS

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

For Safety outputs

Study Treatment Name	**Treatment order in TFLs**
Humalog	1
LY900014	2
Bolus Dose Administration Method	**Method order in TFLs**
Standard dual-wave	1
Standard single-wave	2
Rapid single-wave	3
Rapid dual-wave	4

Statistical analysis treatment names

Study Treatment Name	**Treatment order in TFL**
Humalog standard dual-wave	1
Humalog standard single-wave	2
Humalog rapid dual-wave	3
Humalog rapid single-wave	4
LY900014 standard dual-wave	5
LY900014 standard single-wave	6

LY900014 rapid dual-wave	7
LY900014 rapid single-wave	8

7. SAMPLE SIZE JUSTIFICATION

An initial 24 patients may be randomized in order that approximately 20 patients complete the study. Twenty completing patients will provide approximately 80% power to demonstrate a 25% decrease in the time to early half-maximal concentration (early 50% Tmax) between LY900014 and Humalog. Testing will be done at an α-level of 0.1 with a 2-sided confidence interval (CI). The variability was estimated by analyzing internal Lilly data (CCI) for LY900014 and Humalog administered on CSII therapy, resulting in approximately 35.9% coefficient of variation of within-patient variability for early 50% Tmax. Patients who are randomized but drop out before completing assigned treatment may be replaced to ensure that approximately 20 patients complete the study (refer to Section 5.1).

8. DEFINITION OF ANALYSIS POPULATIONS

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

The "PK" population for the statistical inference will consist of all patients who complete the study according to the sequence/treatment to which they are randomized. In addition, a sensitivity analysis will be performed on the population consisting of all patients who complete at least 1 MMTT and have measurable insulin lispro concentrations.

The "GD" population for the statistical inference will consist of all patients who complete the study according to the sequence/treatment to which they are randomized. In addition, a sensitivity analysis will be performed on the population consisting of all patients who complete at least 1 MMTT and have measurable GD concentrations.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients 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, 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 patients up to the point of withdrawal, with any patients excluded from the relevant population

highlighted. Summary statistics and statistical analyses will generally only be performed for patients 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 patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient's change from baseline values will be used to calculate the mean change from baseline using a CCI [redacted].

Unless otherwise specified, testing for significance is all done at an α-level of 0.1 with 2-sided confidence intervals (CIs). Statistical significance will be claimed if the p-value of a test is less than 0.1.

Data analysis will be performed using [redacted].

9.2 Demographics and Patient Disposition

Patient disposition will be listed. The demographic variables age, sex, race/subrace, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. In addition, screening HbA1c, fasting blood glucose, total daily insulin dose at screening, bolus dose at randomization, basal dose at randomization, fasting C-peptide and duration of T1DM will be summarized and listed.

Alcohol consumption will be reported in the SDTMs in units of alcohol and will be converted to grams for the TFLs, where 1 unit is equal to 8 grams of pure alcohol.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Parameter Estimation

Patients who complete at least 1 MMTT and have measurable insulin lispro concentrations will be included in the analysis dataset for the PK analyses. Patients who did not keep identical insulin lispro doses for the MMTTs (Days 1 and 3) will be excluded from the PK analysis on the MMTT days. In addition, patients who did not keep identical insulin lispro doses for the high-glycemic index meal tests (Day 2) will be excluded from the PK analysis on the Day 2 meal test days.

PK analyses will be conducted using standard noncompartmental methods of analysis 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 used 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 concentrations will be used to calculate several PK parameters, including time to maximum concentration (T_{max}), early 50% T_{max}, time to late half-maximal concentration (late 50% T_{max}), C_{max}, area under the plasma concentration versus time curve (AUC) from time 0

to 15 minutes postdose (AUC[0-15min]), AUC from time 0 to 30 minutes postdose (AUC[0-30min]), AUC from time 0 to 1 hour postdose (AUC[0-1h]), AUC from time 0 to the last recorded time (AUC[0-t_{last}]), AUC from time 0 to 5 hours postdose (AUC[0-5h]), change from baseline PK parameters such as change from baseline AUC (CFBLAUC[0-5], and CFBL AUC[0-∞]). These will be the key parameters for analysis; other parameters (that is, partial AUCs and CL/F) may be calculated as deemed appropriate.

Although attempts will be made to adhere to the scheduled collection times (Section 2) detailed in the protocol, it is recognized 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.

9.3.2 Pharmacokinetic Statistical Inference

The "PK" population for the statistical inference is defined in Section 8.

Log-transformed insulin lispro T_{max}, early 50% T_{max}, late 50% T_{max}, C_{max}, $t_{1/2}$, and AUC estimates will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within LY900014 to Humalog by day and bolus administration mode, and the corresponding 90% CIs of the ratios.

The statistical model for the Day 1 and Day 3 breakfast meal tests will include treatment (4 combinations of treatment and bolus administration mode: LY900014 dual-wave, Humalog dual-wave, LY900014 single-wave, or Humalog single-wave), period, day (Day 1 or Day 3), and treatment-by-day interaction as fixed effects and patient as a random effect.

Example SAS code:

```
proc mixed data=pk;
  class patient treatment period day ;
  model logpk = treatment period day treatment*day / ddfm=kr;
  lsmeans trt*day;
  random patient / grp= treatment;
  repeated / grp= treatment;
run;
```

A separate analysis model will be used for the Day 2 breakfast meal test, including treatment (4 combinations of treatment and bolus administration mode: LY900014 rapid, LY900014 standard, Humalog rapid, or Humalog standard, all given as a single-wave bolus) and period as fixed effects and patient as a random effect.

Example SAS code:

```
proc mixed data=pk;
  class patient treatment period;
  model logpk = treatment period / ddfm=kr;
  random patient / grp= treatment;
  repeated / grp= treatment;
run;
```

For the primary inference, insulin lispro administered from LY900014 will be concluded to have a significantly decreased early 50% T_{max} relative to Humalog if the upper confidence bound of the 2-sided 90% CI of the ratio of geometric means of the early 50% T_{max} is <1.

If possible, the above models will also be used to calculate the intra-patient and inter-patient variability of LY900014, however if convergence issues occur, then the model will be appropriately updated to account for these issues.

As a sensitivity analysis, early 50% T_{max} will be analyzed by day using the Wilcoxon signed-rank test. The difference in median early 50% T_{max} between LY900014 and Humalog and the 90% CIs for the difference will be presented.

An exploratory analysis of Early 50% $T_{max,}$ from breakfast on Days 1, 2 and 3 based on the standard single-wave data only will also be performed. The model will include sequence, treatment and day within period and treatment by day as fixed effects, and patient as a random effect.

9.4 Glucodynamic Assessment

9.4.1 Glucodynamic Parameter Estimation

The "GD" population for the statistical inference is defined in Section 8.

Also, for Days 1 and 3 and Day 2, separately, patients who did not complete the entire test meal or had significant changes in nutrient consumption (greater than 10%) of the test meal or dose changes during the breakfast test meal will be excluded from all the GD analyses.

Data will be analyzed 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) for each patient will be calculated. Incremental change from baseline glucose AUC values will be calculated during a 5-hour meal test. Partial AUCs may be calculated as deemed appropriate. Parameters will be calculated and provided to Covance by Lilly. Parameters will include:

- BGAUC(0-30 min)
- BGAUC(0-1 h)
- BGAUC(0-2 h)
- BGAUC(0-3 h)
- BGAUC(0-4 h)
- BGAUC(0-5 h)
- BGAUC(2.5-5 h)
- Maximum change from baseline (BG_{max})
- Maximum change from baseline up to 1 h (BG_{1h})
- Maximum change from baseline up to 2 h (BG_{2h})

9.4.2 Glucodynamic Statistical Inference

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum, and maximum) will be presented by treatment and by bolus dose administration mode (all 4 combinations of treatment) for Days 1 and 3 (and combined) and Day 2, separately. The same statistical model and comparisons used to analyze the PK parameters will be used to analyze the GD parameters on the original scale (not log-transformed) using Fieller's theorem (Chow and Liu 2009[3]). A macro provided by Lilly will be used to complete the Fieller's theorem analysis.

The analysis will be repeated for the completers population.

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 patient 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 the first dose and becomes more severe postdose. Any AE that occurs during the outpatient period will be associated with open-label Humalog (and not treatment).

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, bolus administration mode, meal, severity and relationship to the study drug. The frequency (the number of adverse events, the number of patients experiencing an adverse event and the percentage of patients experiencing an adverse event) of treatment-emergent adverse events will be summarized by treatment, bolus administration mode, meal, Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 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 September 2016). Concomitant medication will be listed.

9.5.3 Clinical laboratory parameters

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 patient data listings.

9.5.4 Vital signs

Vital signs data will be summarized by treatment and bolus administration mode, together with changes from baseline, where baseline is defined as predose of Day 1. Furthermore, values for individual patients will be listed.

9.5.5 Dosing information

Daily bolus dosing and basal dosing information will be listed.

9.5.6 Immunogenicity

Immunogenicity data will be listed. The number of patients who have detected anti-insulin lispro antibodies at predose and follow-up, and number of patients who have anti-insulin lispro antibodies that become cross-reactive with human insulin at follow-up will be summarized by overall population.

9.5.7 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, and the time of occurrence relative to the patient's last meal. Each category of hypoglycemic events (defined below) will be listed and summarized for the outpatient, inpatient before the MMTT, inpatient during the MMTT, or inpatient after the MMTT periods and overall. Severe hypoglycemic events will be reported as SAEs. "During MMTT" refers to 0-300 minutes postdose. Events will be summarized by treatment, bolus dose administration method and meal.

Hypoglycemia is defined as follows:

- Documented Hypoglycemia:
    - 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 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 plasma glucose determination (but that was presumably caused by PG ≤70 mg/dL [≤3.9 mmol/L]).
- 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

- Relative hypoglycemia: an event during which typical symptoms of hypoglycemi a, 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

- Total hypoglycemia: an optional category that combines all cases of hypoglycemia. If an event which hypoglycemia falls into multiple subcategories, the event is only counted once in this category

- Overall hypoglycemia: This category combines all cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). If an event of hypoglycemia falls into multiple subcategories, then the event is only counted once in this category.

- Serious and clinical important hypoglycemia: A hypoglycemia that is accompanied by a measured plasma glucose <54 mg/dl (<3.0 mmol/L).

9.5.8 Catheter Injection-site assessment

Injection-site assessment data will be listed and summarized in frequency tables by treatment, bolus administration mode and day.

9.5.9 Pain Measurements using the Visual Analog Scale (VAS)

Pain measurements during bolus application will be assessed using the electronic version of the 100-mm validated VAS (or electronic VAS [eVAS]) for pain. Data will be listed and summarized by treatment and bolus administration mode.

VAS data will also be summarized based on the following categories of score: 0 mm, 1-10 mm, 11-20 mm, 21-30 mm, 31-40 mm, 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.

9.5.10 Exploratory Continuous Glucose Monitoring Analyses

The CGM outcome variables will be derived based on the raw data collected from the individualized standardized lunch meals on Days 1, 2, and 3 and from the individualized standardized dinner meals on Days 1 and 2.

The following incremental glucose AUCs will be calculated:

- AUC(0-1 h)
- AUC(0-2 h)
- AUC(0-5 h)

- AUC(2.5-5 h)

The incremental glucoseAUCs will be calculated using the linear trapezoidal method (with negative areas included in the calculation of the trapezoidal areas). For the calculation of the incremental glucose AUC parameters, baseline is defined as the average of all CGM values recorded in the 19 minutes prior to each meal.

For the CGM data, time in range parameters will be derived from the raw data collected through the 3 days of CGM device use by patient, treatment, bolus dose administration method and meal. The following ranges will be calculated:

- Normal range (>70 mg/dL and <=180 mg/dL) for each day, normalized to 5 hours (duration and % of 5 hours)
- Strict normal range (>70 mg/dL and <=140 mg/dL) for each day, normalized to 5 hours (duration and % of 5 hours)
- Hyperglycemia (>180 mg/dL) during the treatment period, normalized to 5 hours (duration and also as % of 5 hours)
- Hypoglycemia (≤70 mg/dL) during the treatment period, normalized to 5 hours (duration and % of 5 hours)
- Severe hypoglycemia (≤55 mg/dL) during the treatment period, normalized to 5 hours (duration and % of 5 hours)

For the calculation of the incremental glucose AUCs and range parameters, the following rules will be used to define a valid CGM session prior to parameter calculation:

- Minimum number of measures for each parameter must be greater than 70% of the total measures obtained. For example, for iAUC(0-2 h), there will be 24 measurements during this period so a patient must have at least 17 valid measurements to be able to calculate the parameter. Similarly, for the time in range parameters calculated over 5 hours, there will be 60 measurements so must be at least 42 valid measurements to be able to calculate these parameters
- The maximum allowable continuous missing interval will be 10 minutes for incremental glucose AUC(0-1 h), 20 minutes for incremental glucose AUC(0-2 h) and incremental glucose AUC(2.5-5 h), and 25 minutes for incremental glucose AUC(0-5 h), Low blood glucose index (LBGI), high blood glucose index (HBGI), combined blood glucose risk index (BGRI, sum of the LBGI and HBGI), and the time in range parameters

The incremental glucose AUCs and time in range parameters will also be analyzed statistically with separate analyses based on the parameters at lunch times on Days 1, 2 and 3 only, and based on the parameters at Dinner times on Days 1 and 2 only. The model will include treatment (combination of treatment and bolus administration mode), period and day within period and treatment- by-day within period as fixed effects, and patient as a random effect. The model will be used to estimate least squares means, differences of least squares means of insulin lispro within LY900014 to Humalog by bolus administration mode, and the corresponding 90% CIs of the ratios.

In addition to the above parameters, within-day and between-day CGM variability parameters will be calculated. The within-day parameters (derived by day and meal) will include the standard deviation, CV% and Mean amplitude of glycemic excursions (MAGE). The between-day parameters will be based on the lunch data on Day 1-3 and dinner data on Days 1-2 separately, and will include the standard deviation, CV% and mean of daily differences (MODD).

The LBGI, HBGI and BGRI will also be derived. The LBGI has been developed to quantitate both frequency and severity of hypoglycemia. The LBGI has been validated as a predictor of severe hypoglycemia, which is a serious adverse event and could result in coma or death if unrecognized and untreated. The HBGI quantifies both frequency and severity of hyperglycemia and has been related to HbA1c and risk for hyperglycemia (Kovatchev et al. 2005). Additionally, both the LBGI and HBGI have a high sensitivity to changes in glycemic profiles and control (Kovatchev et al. 2005). LBGI is a non-negative number that increases as the number of low readings increases. HBGI is a non-negative number that increases as the number of high readings increases.

The LBGI, HBGI, and BGRI will be derived in the following steps:

Step 1: For each blood glucose (BG [mg/dL]) at the i^{th} time point, compute the following:

$f(BG_i)=1.509\times[(\ln(BG_i))^{1.084}-5.381]$

Transform the BG data using a nonlinear transformation that maps the BG range of 20 to 600 mg/dL to a symmetric interval of $\left(-\sqrt{10},\sqrt{10}\right)$

The center of the BG scale is 112.5 mg/dL and is mapped to 0

Step 2: Compute BG risk for each reading

$rl(BG_i)=10\times f(BG_i)^2$ if f(BG) < 0; otherwise rl(BGi) = 0

$rh(BG_i)=10\times f(BG_i)^2$ if f(BG) > 0; otherwise rh(BGi) = 0

Assign the risk of each BG value by applying the above quadratic risk function

Range from 0 (achieved when BG = 112.5, the center) to 100

Left side of the parabola is risk of hypoglycemia, where the right side is risk of hyperglycemia

Step 3: Compute LBGI and HBGI

$$LBGI = \frac{1}{n}\sum_{i=1}^{n} rl(BG_i), \text{ where n is the number of measurements}$$

$$HBGI = \frac{1}{n}\sum_{i=1}^{n} rh(BG_i), \text{ where n is the number of measurements}$$

Step 4: Compute BGRI

$$BGRI_m = LBGI + HBGI$$

The calculated parameters will be summarized and listed by treatment, bolus dose administration mode, day and meal. In addition, the average across the three days for lunch and two days of dinner will be calculated separately.

9.5.11 Acceptability of Insulin Delivery Experience

Acceptability of patient overall experience with the study insulin delivery will be summarized (yes/no) by treatment.

9.5.12 Other assessments

To determine catheter occlusion rates with LY900014 and Humalog after 3 days of CSII, the frequency of "occlusions observed on macroscopic examination of the catheter and catheter tubing" from the CRF will be.

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

10. INTERIM ANALYSES

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

The Lilly clinical pharmacologist/CRP/Lilly study team is unblinded. Data may be accessed and analyzed while the trial is ongoing, but no changes to the study design are planned. The results may help Lilly expedite final delivery and enable planning of future studies. Information that may unblind the study during the analyses will not be reported to the study site until the study has been unblinded. An assessment committee will not be formed.

11. 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.

4. Kovatchev BP, Clarke WL, Breton M, Brayman K, McCall A. Quantifying temporal glucose variability in diabetes via continuous glucose monitoring: mathematical methods and clinical application. Diabetes Technol Ther. 2005 Dec;7(6):849-62.

12. DATA PRESENTATION

12.1 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.

12.2 Missing Data

Missing data will not be displayed in listings.

12.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

13. BLINDING AND UNBLINDING PLAN

Levels of unblinding are indicated in the table below. This table provides general guidance as to who will be allowed access to blinding information (including data or documents that can potentially unblind such as randomization codes, treatment assignments, and unblinded data) at various steps of the trial. For Interim Analysis (IA), appropriate IA team members, including the statistician, programmer and data manager will be identified and agreed upon between Lilly and any relevant Third Party Organizations (TPO).

Blinding information is kept strictly confidential and is accessible only by authorized personnel until unblinding of the trial as described below. All measures possible must be taken to maintain the blind; which means that access to the blinding information must be restricted to authorized personnel as described in the protocol and summarized in the table below.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient’s treatment assignment is warranted for medical management of the event. In such cases, the unblinding is to be conducted according to the protocol.

In the event of unplanned intentional unblinding, the detailed process, including information of the unblinded team, creating restricted access electronic folders, and measures taken to guard against inappropriate dissemination of treatment codes, will be described in a blinding plan revision or another appropriate document and review sought from the study team statistician.

	Study Timelines				
Study Team Member	**Screening**	**Randomisation**	**Treatment Phase**	**Follow-Up**	**Database Entry Lock**
General					
Clinical Supply Coordinator	NA	U	U	U	U
Randomization Statisticians	NA	U	U	U	U
ECG Reader	NA	U	U	U	U
Central Laboratory	NA	U	U	U	U
Local Laboratory	NA	NA	NA	NA	NA
Bio and Sample Analysis Lab	NA	U	U	U	U
Clinical Site					
Pharmacist	NA	U	U	U	U
Study/Dosing Nurse	NA	B	B	B	U
Technicians/Data entry staff	NA	B	B	B	U
Patient/Subject	NA	B	B	B	U
Investigator(s)	NA	B	B	B	U
Study Monitor (Covance)	NA	U	U	U	U
Covance Biometrics					
Project Integration	NA	U	U	U	U
Data Management	NA	U	U	U	U
Programming	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical Writing	NA	U	U	U	U
PK Scientist/Associate	NA	U	U	U	U
Lilly					
CP/CRP/CRS/Biologist	NA	U	U	U	U
Consultant CPM	NA	U	U	U	U
CPA / Study Manager	NA	U	U	U	U
DSA	NA	U	U	U	U
SDTM Core Team	NA	U	U	U	U
Statistician	NA	U	U	U	U
Statistical Analyst	NA	U	U	U	U
Medical Writing	NA	U	U	U	U
PK Scientist/Associate	NA	U	U	U	U
PK Analyst	NA	U	U	U	U
PK Data Delivery	NA	U	U	U	U
CLO Representative	NA	U	U	U	U

Abbreviations: B = blinded; CLO = clinical laboratory operations; CP = clinical pharmacologist; CPA = clinical pharmacology associate; CPM = clinical project manager; CRP = clinical research physician; CRS = clinical research scientist; DBL = database lock; DSA = data solutions associate; ECG = electrocardiogram; FPET = first patient enters treatment; LPET = last patient enters treatment; N/A = not applicable; PK = Pharmacokinetic; SDTM = study data tabulation model; TPO = third party organization; U = unblinded.