

Protocol: I8B-MC-ITRQ(a)

Bioequivalence Study Comparing the Pharmacokinetics and Glucodynamics of LY900014
U-200 Formulation with LY900014 U-100 Formulation in Healthy Subjects

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and Glucodynamics of LY900014 U-200 Formulation with
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LY900014

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1. Protocol Synopsis

Title of Study:

Bioequivalence study comparing the pharmacokinetics and glucodynamics of LY900014 U-200 formulation with LY900014 U-100 formulation in healthy subjects

Rationale:

The aim of the current study is to demonstrate the bioequivalence of a new concentrated form (U-200) of LY900014 relative to LY900014 U-100 after subcutaneous (SC) administration of a 15 U insulin lispro dose to healthy subjects; in addition, the study will evaluate the glucodynamics (GD) of these formulations. The concentrated form of LY900014 (U-200) is being developed as an option for patients with diabetes who require a higher daily mealtime insulin dose. An increased strength formulation would allow for a greater number of units to be included in each injection device.

Objectives/Endpoints:

Objectives	Endpoints
Primary To demonstrate the bioequivalence of pharmacokinetic (PK) parameters for the LY900014 U-200 versus LY900014 U-100 formulations after SC administration to healthy subjects.	Area under the concentration versus time curve (AUC) from time zero to time t, where t is the last time point with a measurable concentration, AUC[0-tlast], AUC from time zero to infinity (AUC[0-∞]), and maximum observed drug concentration (Cmax)
Secondary To compare the GD responses to LY900014 U-200 versus LY900014 U-100 formulations after SC administration. To assess the safety and tolerability of the LY900014 U-200 and LY900014 U-100 formulations.	Total amount of glucose infused (Gtot) and maximum glucose infusion rate (Rmax) Adverse events

Summary of Study Design:

Study I8B-MC-ITRQ is a Phase 1, single-center, subject- and investigator-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 formulation after SC administration of a 15 U insulin lispro dose.

Treatment Arms and Planned Duration for an Individual Subject:

Subjects will be randomly assigned to 1 of 4 dosing sequences; each sequence will have 4 periods. Subjects will be administered single doses of LY900014 U-200 formulation (on 2 occasions) and LY900014 U-100 formulation (on 2 occasions).

The study will include a 28-day screening period, followed by 4 study periods. There will be a wash-out period of at least 3 days between each study period. The follow-up visit will take place at least 14 days after the last dose.

Number of Subjects:

Up to 60 healthy men and women may be enrolled so that approximately 44 subjects complete the study.

Statistical Analysis:

Safety: Safety analyses will be conducted for all enrolled subjects who receive at least 1 dose of the study drug, whether or not they completed all protocol requirements. Safety assessments including, but not limited to vital signs, safety laboratory parameters, and adverse events will be captured and summarized using descriptive statistical methodologies.

Pharmacokinetics: Pharmacokinetic analyses will be conducted on data from all subjects receiving at least 1 dose of study drug and have evaluable PK data. Pharmacokinetic analyses will be conducted using standard noncompartmental method of analysis. Pharmacokinetic parameters will be assessed using free serum insulin lispro.

To compare PK parameters between LY900014 U-200 relative to LY900014 U-100, log-transformed AUC(0-tlast), AUC(0-∞), and Cmax 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 least-squares means (LSmeans) and the corresponding 2-sided 90% confidence intervals (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).

The same model without log transformation will be used for the analysis of the PK time parameters (time to early half-maximal drug concentration [early 50% tmax] and time to Cmax [tmax]). LSmeans, treatment differences in LSmeans, and the corresponding 90% CIs for the treatment differences will be estimated from the model. The treatment ratios and 90% CIs for the ratios will be calculated using Fieller's theorem. Other PK time parameters may be analyzed in a similar manner.

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.

Glucodynamics: Glucodynamic 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. Glucodynamic analyses will be conducted on those subjects who complete at least 1 clamp procedure. A locally weighted scatterplot smoothing function will be applied to all individual GIR versus time profiles in each treatment group and/or period.

To address the secondary objective of comparing GD parameters (Gtot and Rmax) between the LY900014 U-200 and LY900014 U-100 formulations, log-transformed Gtot and Rmax 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. Other GD parameters may be analyzed in a similar manner.

The same model without log transformation will be used for the analysis of the GD time parameters (time to half-maximal GIR before tRmax [early 50% tRmax], and time to maximal GIR [tRmax]). Least-squares means, 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.

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.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITRQ

	Screening	Periods 1, 2, 3, 4			FU/EDa	Comments
Procedure	Up to Day -28	Day -1	Day 1	Day 2		
Informed consent	X					
Subject admission to CRU		X				
Enrollment		X				Applicable to Period 1 only.
Fasting	X	X				Subjects are expected to fast for approximately 8 hours before screening and at least 8 hours before each study drug dose (starting from the night of Day -1) until the end of the glucose clamp procedure (Day 1).
Physical examination	X				X	Physical examination at screening. Thereafter, targeted examination, as appropriate.
Medical assessment	X		Predose	X	X	Medical history at screening. Thereafter, medical assessments per Section 9.4.4.1.
Height	X					
Weight	X	X*			X	*Applicable to Period 1 only
Waist and hip circumference		X*				*Applicable to Period 1 only
Vital signs (supine)	X		Predose and 10 hours postdose (at the end of clamp procedure)		X	Vital signs: Body temperature, blood pressure, and pulse rate. Body temperature will be measured only at screening.
12-lead ECG	X	X			X	Single ECGs will be collected for safety.
Clinical laboratory tests	X		Predose of Period 1		X	See Appendix 2 , Clinical Laboratory Tests, for details.

	Screening	Periods 1, 2, 3, 4			FU/EDa	Comments
Procedure	Up to Day -28	Day -1	Day 1	Day 2		
Pregnancy test	X	X			X	For females of childbearing potential only. A serum pregnancy test will be performed at screening. Urine pregnancy tests at all other time points.
Study drug administration			0 hour			Time of study drug administration = 0 hour. Study drug will be administered at approximately the same times on Day 1 of each study period.
Injection-site assessments			0, 1, 4, and 10 hours postdose (at the end of clamp procedures)			Assessments of injection-site reaction at time '0' will occur immediately following injection of study drug.
Visual Analog Scale (VAS)			0, 20, and 60 min postdose			VAS assessment at time '0' will occur immediately following injection of study drug.
Insulin lispro PK sampling			0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300, 360, 420, 480, 540, and 600 minutes			Sampling times are relative to the time of study treatment administration (time 0). Time 0 sample is to be collected immediately prior to injection.
C-peptide samples			0, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540, and 600 minutes			Sampling times are relative to the time of study drug administration (time 0). Time 0 sample is to be collected immediately prior to injection.
Blood glucose sampling for euglycemic clamp			Approximately every 10 min for approximately 30 min before the start of dosing (for baseline measurement). During clamp, sampling occurs every 2.5 minutes for the first 30 minutes; every 5 minutes for 30 to 120 minutes; every 10 minutes for 120 to 480 minutes and every 20 minutes for 480 to 600 minutes.			Sampling times are relative to study drug administration (time 0). Failure to obtain samples due to clinical issues, such as problems with venous access, will not be considered a protocol violation. Repeat samples for counter-checking of apparent spurious results may be taken where indicated.

	Screening	Periods 1, 2, 3, 4			FU/ED ^a	Comments
Procedure	Up to Day -28	Day -1	Day 1	Day 2		
Pharmacogenetics sample			Predose for Period 1 only			Refer to sample collection instructions provided by the sponsor.
Immunogenicity sample			Predose Period 1, Period 2, and Period 3 only		X	
Discharge from CRU				X		

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; min = minutes; PK = pharmacokinetics.

Note: In cases when several study procedures have the same scheduled time point, the collection of PK samples should be scheduled to occur at the exact time, whilst other procedures may be scheduled to occur earlier or later, as deemed appropriate by the investigator. If the investigator decides based on clinical judgment not to dose a subject on a given day (eg, because of low blood glucose), the subject's visit may be rescheduled; any procedures performed in that period may be repeated.

^a At least 14 days after last dose or early discontinuation.

3. Introduction

3.1. Study Rationale

LY900014 is an ultra-rapid-acting insulin lispro formulation that has shown an increased early absorption compared to commercially available insulin lispro (Humalog®; Eli Lilly and Company). LY900014 U-200 represents a new formulation strength of LY900014. The insulin lispro pharmacokinetics (PK) and glucodynamics (GD) of a 19 unit (U) subcutaneous (SC) dose administration of LY900014 U-193 and LY900014 U-95 have been compared in a previously completed pilot study (CCI [REDACTED]).

The aim of the current study is to demonstrate the bioequivalence of a new concentrated form (U-200) of LY900014 relative to LY900014 U-100 after SC administration of a 15 U insulin lispro dose to healthy subjects; in addition, the study will evaluate the GD of these formulations. The concentrated form of LY900014 (U-200) is being developed as an option for patients with diabetes who require a higher daily mealtime insulin dose. An increased strength formulation would allow for a greater number of units to be included in each injection device.

3.2. Background

The insulin analog, insulin lispro (Humalog), has been shown to be absorbed more quickly than regular human insulin (Humalog package insert, 2015). In healthy volunteers given SC doses of insulin lispro ranging from 0.1 to 0.4 U/kg, peak serum levels were seen 30 to 90 minutes after dosing (Humalog package insert, 2015). However, the general consensus is that rapid-acting insulin, administered either through pumps or syringes/pen injectors, is still not rapid enough to match carbohydrate absorption profiles, which limits efficacy and dosing flexibility. An ultra-rapid-acting prandial insulin would shift the PK and GD profiles so that they have an even faster onset to better match carbohydrate absorption.

LY900014 is an ultra-rapid-acting insulin lispro formulation with treprostinil (CCI [REDACTED]) and other ingredients. LY900014 has an increased early absorption of insulin lispro compared to commercially available insulin lispro (Humalog). CCI [REDACTED]

[REDACTED]

Treprostinil is a prostacyclin analog, administered either through inhalation (CCI [REDACTED]), as an intravenous (IV) infusion, or as a continuous SC administration for the treatment of symptomatic pulmonary arterial hypertension (PAH) and has been approved in the US since 2002 (CCI [REDACTED]). Sodium citrate, an excipient that speeds insulin absorption (likely in part by enhancing vascular permeability), is also included in the formulation to further enhance the absorption of insulin lispro. Each of the other excipients (such as magnesium chloride) in the LY900014 formulation is listed in the US Food and Drug Administration (FDA)'s Generally Recognized as Safe Food Additives database and in the FDA's Inactive Ingredients in Approved Drugs database. Furthermore, the excipient concentration in LY900014 is within the limits

identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

Safety and tolerability of LY900014 at approximately U-100 concentration have been demonstrated in healthy subjects in 4 previous clinical studies, in approximately 103 healthy subjects across a dose range of 7.5 to 30 U. All 4 studies were Phase 1, randomized, subject-blind studies in which the PK and GD of LY900014 and Humalog were evaluated during a euglycemic glucose clamp following SC administration. The total insulin lispro exposure and GD effect were similar for LY900014 and Humalog; however, LY900014 demonstrated a faster and earlier insulin lispro absorption and insulin action compared to Humalog.

In addition, data from two Phase 1b studies showed LY900014 U-95 was well tolerated in patients with type 1 diabetes mellitus (T1DM; 30 patients) and type 2 diabetes mellitus (T2DM; 30 patients) using multiple daily injections (MDIs). There were no serious adverse events (SAEs) related to study treatment or discontinuations from the studies because of a drug-related adverse event (AE). Small numbers of treatment-emergent adverse events (TEAEs) were reported, and there were no notable increases in these events in relation to any of the LY900014 formulations compared to those in relation to Humalog.

A recent pilot study compared the insulin lispro PK and GD of a concentrated formulation of LY900014 (U-193 LY900014) with U-95 LY900014 administered as single 19 U doses to healthy subjects. Both formulations were well tolerated with no clinically relevant differences between formulations. No deaths or SAEs occurred during this study, and no subjects discontinued the study due to an AE. The most common AEs were events related to the glucose clamp procedure. The PK of the 2 formulations was found to be bioequivalent with 90% confidence intervals (CIs) for the ratios of area under the concentration versus time curve (AUC) from time zero to 8 hours, AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-tlast]), AUC from time zero to infinity (AUC[0-∞]), and maximum observed drug concentration (Cmax) falling within (0.80, 1.25). The GD profiles were largely consistent across the 2 formulations.

More information can be found in the Investigator's Brochure (IB) of LY900014.

3.3. Benefit/Risk Assessment

Study I8B-MC-ITRQ (ITRQ) will not offer any direct benefits to the healthy subjects participating in the study. The data from previous studies in healthy subjects and data from studies in patients with T1DM and T2DM have shown that LY900014 was well tolerated and the adverse drug reactions are in keeping with those reported for Humalog.

Potential risks associated with LY900014, derived from the known risks of insulin lispro (Humalog), are hypoglycemia, hypersensitivity reactions (localized allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral edema (Humalog package insert, 2015). Consistent with the risks stated above, in previous Phase 1 studies with LY900014, there were no events of severe hypoglycemia reported and most events of injection-site reactions were of mild severity.

Notably, across all doses in the Lilly clinical studies with healthy subjects and patients with diabetes that have evaluated treprostinil as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those AEs associated with systemic absorption of treprostinil, as described in the CCI [REDACTED]. Moreover, data from Lilly Phase 1b patient studies showed that 1 out of 472 plasma samples had detectable treprostinil levels taken from a total of 30 patients with T1DM (doses up to CCI [REDACTED] per SC bolus injection) and 30 patients with T2DM (doses up to CCI [REDACTED] per SC bolus injection) following MDI administration of LY900014. The exposure levels of treprostinil from the doses of LY900014 planned in this study are expected to be undetectable and substantially lower (at least CCI [REDACTED]) than those observed in the treatment of PAH. In preclinical safety pharmacology and toxicity studies or clinical pharmacology studies involving LY900014 or treprostinil alone, other than known risks associated with Humalog and CCI [REDACTED] no additional risks were identified. No known potential risks are associated with the use of small amounts of treprostinil (CCI [REDACTED]) in the LY900014 formulation. Additionally, local and systemic toxicity profiles of Humalog and CCI [REDACTED] do not suggest the potential for additive or synergistic toxicity.

Following administration of the study insulin, subjects will receive IV glucose infusion at a variable rate to maintain euglycemia up to 10 hours after insulin lispro administration. The aim of the clamp procedure is to maintain blood glucose within the normal glycemic range. In addition, the clamp is performed while the subject is inpatient and under the investigator's supervision. These considerations should minimize the risk of hypoglycemia in subjects participating in Study ITRQ.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY900014 is to be found in the IB.

4. Objectives and Endpoints

Table ITRQ.1 shows the objectives and endpoints of the study.

Table ITRQ.1. Objectives and Endpoints

Objectives	Endpoints
<u>Primary</u> To demonstrate the bioequivalence of PK parameters for the LY900014 U-200 versus LY900014 U-100 formulations after SC administration to healthy subjects.	AUC(0-t _{last}), AUC(0-∞), and C _{max}
<u>Secondary</u> <ol style="list-style-type: none"> To compare the GD responses to LY900014 U-200 versus LY900014 U-100 formulations after SC administration. To assess the safety and tolerability of the LY900014 U-200 and LY900014 U-100 formulations. 	<ol style="list-style-type: none"> G_{tot} and R_{max} Adverse events
<u>Tertiary/Exploratory Objectives</u> <ol style="list-style-type: none"> 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. 	<ol style="list-style-type: none"> t_{max}, early 50% t_{max} tR_{max} and early 50% tR_{max} Anti-insulin lispro antibodies C-peptide concentration

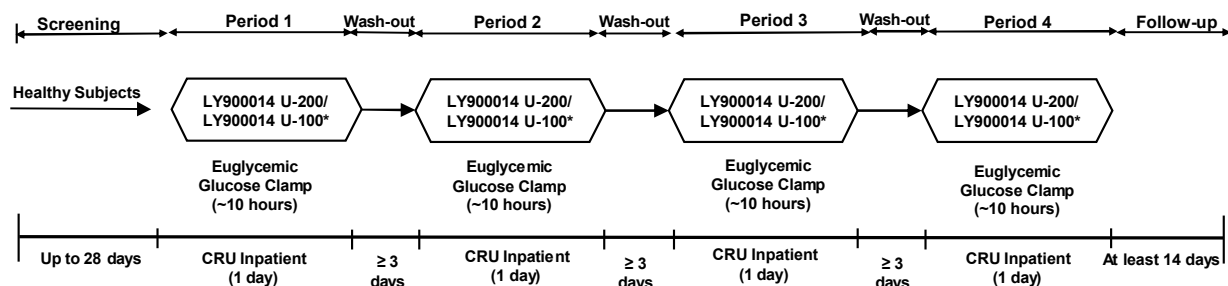
Abbreviations: AUC(0-t_{last}) = area under the concentration versus time curve from time zero to t_{last} where t_{last} is the last time point with a measurable concentration; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; C_{max} = maximum observed drug concentration; early 50% t_{max} = time to early half-maximal drug concentration; early 50% tR_{max} = time to half-maximal glucose infusion rate before tR_{max}; GD = glucodynamic(s); G_{tot} = total amount of glucose infused; PK = pharmacokinetic(s); R_{max} = maximum glucose infusion rate; SC = subcutaneous; t_{max} = time of maximum observed drug concentration; tR_{max} = time to R_{max}.

5. Study Design

5.1. Overall 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 ITRQ.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 ITRQ.1. Illustration of study design for Protocol I8B-MC-ITRQ.

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 ITRQ.2).

Table ITRQ.2. 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 AEs, clinical laboratory tests, electrocardiograms (ECGs), vital signs measurement and through medical assessments.

Study governance considerations are described in detail in [Appendix 3](#).

5.2. Number of Participants

Up to 60 subjects may be enrolled so that at least 44 subjects complete the study. For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been completed.

If a subject discontinues from the study before completion of all 4 dosing periods, replacement subjects may be enrolled up to 60 subjects following agreement between the investigator and the sponsor.

The replacement subject will be assigned the treatment sequence of the discontinued subject and complete that sequence in its entirety.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

A population of healthy subjects is selected based on the likelihood of less physiologic variability in the absence of disease states that may affect multiple organ systems and absence of other confounding factors such as concomitant medications.

The use of a crossover design allows each subject to serve as his or her own control, thereby reducing variability. The replicate crossover design, which was also the design in the pilot study, allows for a decreased sample size and is a commonly used design in bioequivalence studies. The study is subject- and investigator-blind to minimize potential bias related to the clamp procedure.

A euglycemic clamp technique, the gold standard methodology for assessing insulin action, will be used in this study to provide data on the GD activity of each study insulin lispro formulation (see Section 9.6 for a detailed description of the clamp methodology).

Based on the PK properties of treprostinil (half-life associated with the terminal rate constant in noncompartmental analysis [$t_{1/2}$] = CCI) and Humalog ($t_{1/2}$ = approximately CCI), a minimum duration of 3 days for the washout period between clamp visits and at least 14-day duration between the last dose of study drug and the follow-up visit are considered appropriate.

5.5. Justification for Dose

Based on previous studies of both insulin lispro (Humalog) and LY900014 (approximately U-100 concentration), the 15 U dose is within the clinical dose range and should provide measurable PK and GD profiles for insulin lispro. The insulin lispro concentrations in the body resulting from administration of this dose to healthy subjects are anticipated to be measurable over the sampling period. Additionally, it is anticipated that this dose will provide an adequate glucose infusion rate (GIR) for assessment of GD.

The safety, PK, and pharmacology of LY900014 (approximately U-100 concentration) at similar doses and with the similar formulation composition have been assessed in clinical studies in healthy subjects, in patients with T1DM using MDI or insulin pump treatment and T2DM using MDI. In addition, the components of LY900014 have been tested in 3 clinical studies that included the evaluation of the safety, PK, and pharmacology of SC bolus doses of treprostinil (CCI).

All tested doses of treprostinil (up to CCI), insulin lispro (up to CCI), and LY900014 (up to CCI) were well tolerated in healthy subjects, patients with T1DM, and patients with T2DM. There were no SAEs related to study treatment in any of the studies. No subject discontinued from the studies because of drug-related AEs. There were small numbers of TEAEs and injection-site AEs, but there was no clinically significant increase in these or other events compared to placebo or to Humalog and no clinically significant increase in frequency with higher doses of treprostinil. Notably, at the higher doses of treprostinil, there was no clinically significant increase in those AEs associated with systemic absorption as described in the CCI (ie, headache, diarrhea, nausea, jaw pain, vasodilatation, rash, edema, and hypotension). Trial participants in these studies were monitored for changes in vital signs; there were no significant systemic hemodynamic effects of treprostinil at the doses administered based on blood pressure and heart rate. Visual analog scale (VAS) pain scores showed that the SC injections of insulin lispro plus treprostinil co-formulations and treprostinil alone were well tolerated.

The PK of treprostinil in LY900014 following SC administration of 15 U of LY900014 (approximately U-100) in healthy subjects was assessed in previous studies. In these studies, treprostinil exposure was not detectable (CCI ng/mL) for the 15 U dose of LY900014. In addition, the concentration of treprostinil in LY900014 U-200 CCI than in LY900014 U-100 CCI ; therefore the exposure to treprostinil in the U-200 formulation is expected to be negligible.

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to enrollment. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening:

[1] are overtly healthy males or females, as determined by medical history and physical examination.

[1a] No male contraception required except in compliance with specific local government requirements.

[1b] females:

For females of childbearing potential (defined as not surgically sterilized and between menarche and 1 year postmenopause):

- test negative for pregnancy at the time of screening
- are not lactating
- intend not to become pregnant during the study
- are sexually inactive or have practiced a reliable method of birth control (eg, use of oral contraceptives or levonorgestrel, diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, intrauterine devices, partner with vasectomy, or abstinence) for at least 6 weeks prior to screening
- agree to continue to use a reliable method of birth control (as determined by the investigator) until the end of the study

Females not of childbearing potential due to surgical sterilization (at least 6 weeks after surgical bilateral oophorectomy with or without hysterectomy or at least 6 weeks after tubal ligation) confirmed by medical history or due to menopause.

- Menopausal women include women with either

- 1) spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications during the amenorrhea that induced the amenorrhea (eg, oral contraceptives, hormones, gonadotropin-releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy)
 - or
 - 2) spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone level consistent with menopausal state
- [2] are between 21 and 70 years of age, inclusive, at the time of screening.
 - [3] have a body weight of ≥ 45 kg, and body mass index (BMI) of 18 to 30 kg/m², inclusive.
 - [4] have clinical laboratory test results within normal reference range for the population or CRU, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
 - [5] have venous access sufficient to allow for blood sampling, IV glucose administration, and clamp procedure as per the protocol.
 - [6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
 - [7] are able and willing to give signed informed consent.
 - [8] have a hemoglobin level of ≥ 12.5 g/dL at screening.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

- [9] are CRU personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
- [10] are Lilly employees.
- [11] are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
- [12] have participated, within the past 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.
- [13] have previously completed or withdrawn from this study.
- [14] have known allergies to insulin lispro or treprostinil-related compounds or any components of the formulation, or a history of significant atopy.

- [15] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study.
- [16] have a clinically relevant abnormal blood pressure and/or pulse rate as determined by the investigator.
- [17] have a history or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data.
- [18] have known or ongoing psychiatric disorders as deemed clinically significant by the investigator.
- [19] regularly use known drugs of abuse.
- [20] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
- [21] show evidence of hepatitis C and/or positive hepatitis C antibody.
- [22] show evidence of hepatitis B and/or positive hepatitis B surface antigen.
- [23] use over-the-counter or prescription medication within 7 or 14 days, respectively, prior to dosing (apart from vitamin/mineral supplements, occasional paracetamol, thyroid replacement medication, or birth control methods) and throughout the study period. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the investigator and sponsor.
- [24] have used nicotine-containing products (eg, cigarettes, cigars, pipes, smokeless tobacco or nicotine replacement therapy) within 2 months of study entry or intend to use for the duration of the study
- [25] have donated blood of more than 450 mL or have participated in a clinical study that required similar blood volume drawn for the past 3 months.
- [26] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption from 24 hours prior to each dosing and until discharge from the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
- [27] are unwilling to comply with the dietary requirements/restrictions during the study: (i) comply with the fasting requirements of the study, (ii) consume only the meals/snacks provided during the inpatient visits.
- [28] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

For all treatment periods, subjects will fast for at least 8 hours prior to dosing and until the glucose clamp procedure is completed, after which subjects will receive a meal. There is no restriction on water during the fasting periods of the study.

When not resident at the CRU, subjects will be encouraged to follow their normal diets.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed at least 24 hours before each dose and for the duration of each CRU visit. Between the study periods, subjects' alcohol consumption should not exceed 2 units per day.

Subjects should refrain from caffeine-containing food/beverages (eg, cola, chocolate, Milo, tea, and coffee) for at least 12 hours before each dose and throughout the duration of each CRU visit.

Smoking (cigars, cigarettes, or pipes), nicotine replacements, and the use of smokeless tobacco will not be permitted during the study.

6.3.3. Activity

Subjects are encouraged to maintain their regular exercise habits; however, they should not undertake vigorous or prolonged exercise within 48 hours prior to dosing. These subjects will be excluded from this study, as judged by the investigator to prevent interference with study results. After dosing, subjects should remain recumbent or sitting in the CRU until the end of the glucose clamp.

Movement will be restricted to retain the integrity of connections to the infusion(s) and the study procedures.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

7. Treatment

7.1. Treatment Administered

The study will compare formulations of LY900014 containing 200 U/mL of insulin lispro (LY900014 U-200) and 100 U/mL of insulin lispro (LY900014 U-100). [Table ITRQ.3](#) shows the treatments to be administered.

Table ITRQ.3. Treatments Administered

Treatment Name	LY900014 U-200	LY900014 U-100
Insulin lispro dosage formulation	200 U/mL	100 U/mL
Insulin lispro dosage level	15 U	15 U
Treprostinil concentration (treprostinil dose)	CCI	CCI
Route of administration	SC injection	SC injection
Injection volume administered	CCI	CCI

Abbreviation: SC = subcutaneous.

The investigator or designee is responsible for

- explaining the correct use of the investigational product(s) to the CRU personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensation and collection
- returning all unused medications to Lilly or its designee at the end of the study (if required) or destroying the materials (if the site has appropriate facilities/service provider and written procedures to dispose of clinical materials) following authorization by the study sponsor.

Qualified CRU personnel will be instructed on proper preparation and administration techniques for all study drugs used in this study. To maintain the blind, all insulin injections will be given by only a few appropriately qualified members of the CRU staff who are independent of the clamp team and who will not provide assessment of AEs. In addition, where possible, the same personnel should give the injections to reduce variability of the injection technique.

Injection sites selected should be about 5 cm from the umbilicus and the treatment administered SC with the needle applied at about 90° without pinching the skinfold. Injections will be rotated among different injection sites on the anterior abdominal wall during the 4 study periods (ie, left and right lower quadrants). All subjects will receive study drugs as a single SC injection in each period.

7.1.1. Packaging and Labeling

Clinical study materials will be labeled according to the country's regulatory requirements. The study insulins will be supplied by Lilly or its representative in accordance with current good manufacturing practices and will be supplied with lot numbers.

The study insulins (LY900014 U-200 and LY900014 U-100) will be provided to the CRU unblinded. Each formulation will be supplied in 3 mL glass cartridges for use with disposable pens.

7.2. Method of Treatment Assignment

The study insulin to be injected in a given treatment period will be determined according to a randomization schedule.

7.2.1. Selection and Timing of Doses

The actual date and time of all dose preparations will be documented, and the actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF). For each subject, the doses will be administered at approximately the same time on Day 1 of each study period.

7.3. Blinding

Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

The study is subject- and investigator-blind with reference to the identity of the study drug administered. The CRU pharmacy staff (involved in preparation of study drug for administration) and dosing nurses will be unblinded to the identity of the study drug administered due to the difference in the appearance of the pens. Appropriate measures at the CRU are to be taken to maintain the blind to subjects and blind the CRU staff.

The Lilly clinical pharmacologist (CP)/Lilly study team will be unblinded.

Emergency codes will be available to the investigator. A code that reveals the treatment group for a specific study subject may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

Dose adjustments are not allowed in this study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all study drugs received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive the study drugs, and only authorized CRU personnel may supply or administer the investigational product. All investigational products should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized CRU personnel.

The study drugs must be stored at the CRU under refrigerated conditions (between 2°C and 8°C) in a locked and secure place. Insulin must not be frozen.

The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

The study drug will be administered at the CRU, and documentation of treatment administration will occur at the CRU.

7.7. Concomitant Therapy

Subjects should not use over-the-counter or prescription medications as described in exclusion criterion 23 throughout the study period. If a subject does use these medications, inclusion of the subject may be at the discretion of the investigator and sponsor.

If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly CP or clinical research physician (CRP). Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Subjects discontinuing the study drug and/or study prematurely for any reason should complete follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product due to abnormal liver tests **should be considered** by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- alanine aminotransferase (ALT), aspartate aminotransferase (AST) >5X upper limit of normal (ULN) for healthy subjects
- ALT or AST >3X ULN for healthy subjects sustained for more than 2 weeks or
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5 or
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP/CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP/CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
 - the investigator decides that the subject should be discontinued from the study
- Subject Decision
 - the subject, or legal representative, requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the CRU personnel. The CRU personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the CRU personnel.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the subject to discontinue the investigational product before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form (ICF) is signed, the CRU personnel will record, via electronic data entry, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

Additionally, CRU personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the investigational product, and/or study procedure and the AE.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above.

The CRU personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

Additionally, CRU personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the electronic data entry after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving study drug, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

Pregnancy (maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of the study drugs is considered any dose higher than the dose assigned through randomization.

Excess insulin administration, including LY900014, may cause hypoglycemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/SC glucagon or concentrated IV glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

Refer to the IB for further information.

9.4. Safety

9.4.1. Laboratory Tests

For each subject, laboratory tests detailed in [Appendix 2](#) should be conducted according to the Schedule of Activities (Section [2](#)).

With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the study.

9.4.2. Vital Signs

For each subject, vital signs measurement should be conducted according to the Schedule of Activities (Section [2](#)) and as clinically indicated.

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

9.4.3. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section [2](#)).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational product should be reported to Lilly, or its designee, as an AE via electronic data entry.

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section [2](#)). Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be

obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the CRU as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT interval from baseline) after enrollment, the investigator will determine if the subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in subject management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Other Tests

9.4.4.1. Physical Examinations

Physical examinations and routine medical assessments (including review of AEs, concomitant medications, inquiry of subjects' health status and performing targeted examinations, as deemed appropriate by the investigator) will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.4.2. Body Weight and Height

Body weight and height will be recorded as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.4.3. Hip and Waist Circumference

Hip and waist circumference will be recorded as specified in the Schedule of Activities (Section 2). The average of triplicate measurements of waist (narrowest circumference between lowest aspect of the ribs and anterior superior iliac crests) and the hip (widest circumference between the anterior superior iliac crests and the greater trochanters) circumference will be measured.

9.4.5. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review all safety data including laboratory analytes and AEs.

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the Unblinding/Blinding Plan.

9.4.5.1. Glucose Monitoring

Hypoglycemia will be described using the following definitions:

- **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 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.

The goal of the euglycemic clamp is to maintain glucose concentrations at normoglycemic levels close to a predefined target. Therefore, the equivalence of plasma glucose concentrations below 70 mg/dL will not routinely be recorded as hypoglycemic events during the glucose clamp procedure. However, at the discretion of the investigator, decrease in glucose concentrations may be recorded as a hypoglycemic event based on clinical concern or related to technical issues resulting in hypoglycemia.

9.4.5.1.1. Severe Hypoglycemia

The determination of a hypoglycemic event as an episode of severe hypoglycemia as defined above will be made by the investigator based on the medical need of the subject to have required assistance and is not predicated on the report of a subject simply having received assistance.

Episodes of severe hypoglycemia as determined by the investigator must be reported as SAEs.

9.4.5.2. Hepatic Safety

If a study subject experiences elevated ALT $\geq 3X$ ULN, ALP $\geq 2X$ ULN, or elevated TBL $\geq 2X$ ULN, liver tests ([Appendix 4](#)) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to $\geq 5X$ ULN on 2 or more consecutive blood tests
- elevation of serum TBL to $\geq 2X$ ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to $\geq 2X$ ULN on 2 or more consecutive blood tests
- patient/subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.4.6. Injection-Site Assessments (Local Tolerability)

Injection-site assessments for local tolerability will be conducted as specified in the Schedule of Activities and more frequently if deemed necessary by the investigator (Section 2).

Digital pictures of the injection site will be taken, if possible, at the time of identification of local intolerance and thereafter as often as judged necessary by the investigator. The pictures should include subject number, visit number, time after dosing, and a ruler for scaling.

Local tolerability at the injection site will be evaluated by means of assessments within the following categories: pain on palpation, itching, erythema, edema, and induration/infiltration.

9.4.6.1. Pain Measurements Using the Visual Analog Scale

Pain measurements will be assessed using a 100-mm validated VAS for pain. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection-site pain. The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually “no pain” and “worst imaginable pain.” The subject will be asked to mark the 100-mm line to indicate pain intensity at time points according to the Schedule of Activities (Section 2) and as clinically indicated. A staff member will use a caliper to measure the distance from 0 to the mark that the subject placed on the VAS and record the measurement in the source document.

As injection-site pain is an expected AE, injection-site pain (especially transient episodes of pain) will generally not be considered a clinically significant event unless the duration or intensity of the pain interferes with normal activities of daily living or constitutes a risk to the well-being of the subject. Analgesia can be prescribed in response to pain and must be documented in the concomitant medication section of the eCRF.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 1 mL each will be collected to determine serum concentrations of insulin lispro. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. Failure to obtain blood samples due to clinical reasons, such as problems with venous access, will not be considered protocol violations. However, the CRU personnel will still be required to notify the sponsor in writing to account for missing samples for data reconciliation purpose.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of insulin lispro in serum following LY900014 U-200 and LY900014 U-100 administration will be assayed using a validated enzyme-linked immunosorbent assay.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study.

9.6. Glucodynamics (Euglycemic Glucose Clamp)

The aim of the euglycemic glucose clamp is to maintain target glucose levels through infusion of a 20% d-glucose (dextrose) solution after the administration of a dose of insulin. During the glucose clamp, the GIR will be adjusted to maintain a predetermined target blood glucose concentration for the individual subject. Thus, blood glucose concentrations are kept constant while the GIR varies. The varying GIR will then reflect the GD activity of insulin.

All glucose clamp procedures will be performed after an overnight fast of at least 8 hours. On the morning of each study period, a small catheter will be placed into a forearm vein, ideally at the elbow, for infusion of glucose. Another catheter will be placed at the wrist or hand or, in the case of difficult venous access, in the forearm as close to the wrist as possible for blood sampling. This area will be heated with a warming device to approximately 55°C to 60°C for sampling arterialized venous blood. Blood samples will be obtained at the bedside for immediate determination of whole blood glucose concentrations using an automated glucose oxidase technique or other appropriate analytical method. These glucose measurements shall be used for subject safety management as well as for GD evaluations.

The time of administration of LY900014 will be defined as time zero. Following completion of dosing, in conjunction with frequent blood sampling for measurement of blood glucose, 20% dextrose will be infused IV at a variable rate in order to maintain euglycemia up to 10 hours after LY900014 administration.

The clamp procedure will continue for up to 10 hours after dose or until after blood glucose concentrations return to baseline without any glucose being administered for at least 30 minutes, whichever is earlier.

Sampling for blood glucose should occur as described in the Schedule of Activities (Section 2). Repeat samples for counter-checking of apparent spurious results may be taken where indicated. Three or 4 predose glucose values will be used for calculation of mean predose fasting blood glucose concentration.

The target value for blood glucose concentrations is defined as 5 mg/dL below the mean of predose fasting blood glucose concentration measured on the day of the glucose clamp. Subjects will not be clamped to a glucose target of lower than 63 mg/dL (whole blood). Therefore, subjects with a mean predose fasting blood glucose less than 68 mg/dL (equivalent to a fasting plasma glucose of 76 mg/dL [4.21 mmol/L]) will not undergo the clamp procedure but may be deferred to a later period. In addition, any study procedures conducted up to that time may be repeated in that later period.

The GIRs required to maintain target glucose levels and blood glucose concentrations will be documented throughout the procedure. Subjects will be medically assessed before discharge from the CRU (see Schedule of Activities [Section 2]).

9.6.1. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro as described in the Schedule of Activities (Section 2). Additional samples may be collected if there is a possibility that an AE is immunologically mediated.

Immunogenicity will be assessed using a validated assay designed to detect antidrug antibodies in the presence of insulin lispro.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and ethical review boards (ERBs) allow, at a facility selected by the

sponsor. The duration allows the sponsor to respond to future regulatory requests related to the study drugs. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to study drugs and to investigate genetic variants thought to play a role in diabetes mellitus. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY900014 or after LY900014 is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Exploratory Biomarkers

9.8.1. C-Peptide

Blood samples (2.5 mL) will be collected to determine serum concentrations of C-peptide as described in the Schedule of Activities (Section 2) using a validated method at a central laboratory. These samples and any remaining serum after C-peptide analyses will be discarded. Instructions for the collection and handling of these samples will be provided by the sponsor.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

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% CIs of the ratios of geometric least-squares means (LSmeans) for AUC(0-∞), AUC(0-tlast) 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 \sqrt{CC} 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 Cmax between the 2 formulations also within 0.80 to 1.25. This calculation assumes a log-scale standard deviation for within-subject difference of \sqrt{CCI} and a 10% difference in geometric LSmean ratio for Cmax 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 (Gtot) and maximum GIR (Rmax) are within 0.80 to 1.25. This calculation assumes a log-scale standard deviation for within-subject difference of \sqrt{CCC} for Gtot and \sqrt{CCI} for Rmax 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.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of subject disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

The subject's age, sex, weight, BMI, height, race/subrace, smoking habits, or other demographic characteristics will be recorded.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Pharmacokinetic/pharmacodynamic analyses will be conducted on data from all subjects who receive at least 1 dose of the study drug and have evaluable PK.

Primary statistical analyses will be conducted on the set of subjects who complete at least the first period of treatment. Supportive analyses may be done on the key parameters for the subjects who complete all treatment periods. Safety analyses will be conducted for all enrolled

subjects who receive at least 1 dose of the study drug whether or not they completed all protocol requirements.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the study results.

Additional exploratory analyses of the data will be conducted as deemed appropriate. 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.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All study drugs and protocol-procedure AEs will be listed; if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with study drug as perceived by the investigator. Symptoms reported to occur prior to study entry/enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of study drug-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.1.3. Statistical Evaluation of the Intensity of Injection-Site Pain

Pain intensity will be assessed at each injection site immediately after the injection as reported by the subject and measured according to the 0- to 100-mm VAS.

A mixed-effect model will be used to analyze the time 0 (immediately after dosing) data using the statistical model that includes treatment, sequence, and period as fixed effects; and subject within sequence as a random effect. The distribution of the score data will be explored prior to analysis to determine whether data transformation is required. It is possible that VAS scores will be 0; hence if the distribution of the data implies that a log transformation is required, then the score may be updated to log (VAS+1) to allow for the inclusion of the 0 values in the analysis.

Visual analog scale data will also be summarized based on the following categories of score: 0, 1 to 10, 11 to 20, 21 to 30, 31 to 40, etc., up to the maximum category by treatment and time point.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

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

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

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

10.3.2.2. 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).

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}). Least-squares means, 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. Other PK time parameters may be analyzed in a similar manner.

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.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

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

A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and/or period using CCI. The fitted data for each subject will be used to calculate the following GD parameters: time to onset of insulin action (tonset), time to maximal GIR (Rmax), time to Rmax (tRmax), time to half-maximal GIR before tRmax (early 50% tRmax), time to half-maximal GIR after tRmax (late 50% tRmax), total amount of glucose infused (Gtot), Gtot over 30 minutes (Gtot_{0-30min}), and Gtot over 1 hour (Gtot_{0-1h}). Additional partial glucose AUCs, such as Gtot over 2 hours, and Gtot from 3 hours to 10 hours 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.

10.3.3.2. Pharmacodynamic Statistical Inference

To address the secondary objective of comparing GD parameters (Gtot and Rmax) between the LY900014 U-200 and LY900014 U-100 formulations, log-transformed Gtot and Rmax 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% CI for the difference will be estimated and back-transformed from the log scale to provide estimates of the ratios of geometric LSmeans and 90% CI for the ratio of the LSmeans.

In addition, the same model without log transformation will be used for the analysis of the GD time parameters (tRmax and early 50% tRmax). Least-squares means, 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.

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.

10.3.4. Evaluation of 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.

10.3.5. C-Peptide

Mean and individual C-peptide concentration versus time plots with both treatments will be presented. In addition, individual plots overlaying the C-peptide concentration versus time with the insulin lispro serum concentration versus time will be presented. Other plots that may be explored include the C-peptide concentrations relative to the GIR, and/or blood glucose concentrations during the euglycemic clamp.

10.3.6. Data Review During the Study

This section is not applicable for this study.

10.3.7. Interim Analyses

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

11. References

Humalog [package insert]. Indianapolis, IN 46285: Lilly USA, LLC; 2015.

CCI

Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales.
J Clin Nurs. 2005;14(7):798-804.

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-tlast)	AUC from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	AUC from time zero to infinity
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock.
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CP	clinical pharmacologist
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
early 50% t_{max}	time to early half-maximal drug concentration
early 50% tR_{max}	time to half-maximal glucose infusion rate before tR _{max}
ECG	electrocardiogram
eCRF	electronic case report form
ERB	ethical review board
FDA	Food and Drug Administration
GCP	good clinical practice
GD	glucodynamic(s)
GIR	glucose infusion rate
G_{tot}	total amount of glucose infused

HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous
LOESS	locally weighted scatterplot smoothing
LSmeans	least-squares means
MDI	multiple daily injection
PAH	pulmonary arterial hypertension
PK	pharmacokinetic(s)
randomize	The process of assigning subjects to an experimental group on a random basis.
Rmax	maximum glucose infusion rate
SAE	serious adverse event
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSAR	suspected unexpected serious adverse reaction
t_{1/2}	half-life associated with the terminal rate constant in noncompartmental analysis
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment

t_{max}	time of maximum observed drug concentration
tR_{max}	time to R _{max}
U	units
ULN	upper limit of normal
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests^a

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphate
Leukocytes (WBC)	Glucose
Absolute counts of:	Blood urea
Neutrophils	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Triglycerides
Eosinophils	Total protein
Basophils	Albumin
Platelets	Total bilirubin
Urinalysis	Alkaline phosphatase (ALP)
Specific gravity	Aspartate aminotransferase (AST)
pH	Alanine aminotransferase (ALT)
Protein	Creatinine
Glucose	Serology^b
Ketones	Hepatitis B surface antigen
Bilirubin	Hepatitis C antibody
Urobilinogen	HIV
Blood	Pregnancy test^c
Nitrite	Beta human chorionic gonadotropin (HCG)
Leukocytes	FSH ^d
Microscopy ^e	

Abbreviations: ED = early discontinuation; FSH = follicle-stimulating hormone; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

^a Fasting at screening and at predose of Day 1 in Period 1.

^b Only at screening.

^c Pregnancy test is applicable to women only. A blood test for pregnancy will be done at screening (HCG, rapid), and a urine pregnancy test (HCG, urine) will be done during the study and at follow-up/ED as indicated in the Schedule of Activities (Section 2).

^d Only at screening in women for assessment of menopause status if necessary.

^e If clinically indicated, per investigator's discretion.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the CRU. Lilly or its representatives must approve the ICF before it is used at the CRU. All ICFs must be compliant with the ICH guideline on GCP.

The CRU's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with the protocol and with

- 1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- 2) applicable ICH GCP Guidelines
- 3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate eCRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The CRU must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject/patient personal information collected will be provided in a written document to the subject/patient by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

Clinical research unit participation may be discontinued if Lilly, the investigator, or the ERB of the CRU judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Lilly or its designee CRP.

Hepatic Monitoring Tests

Hepatic Hematology^a	Haptoglobin^a
Hemoglobin	
Hematocrit	Hepatic Coagulation^a
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	Hepatic Serologies^{a,b}
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry^a	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	Anti-nuclear Antibody
AST	Alkaline Phosphatase Isoenzymes^a
GGT	Anti-smooth Muscle Antibody (or Anti-actin
CPK	Antibody)^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

^a Assayed by Lilly-designated or local laboratory.

^b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol I8B-MC-ITRQ Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests ^{a,b}	17	1	17
Clinical laboratory tests ^{a,b}	11 (fasting)	1	11
	9 (non-fasting)	1	9
Pharmacokinetic samples serum insulin lispro	1	25 samples × 4 periods = 100	100
Blood for glucose	0.2	76 samples × 4 periods = 304	60.8
Blood discard for cannula patency	0.25	76 samples × 4 periods = 304	76
C-peptide samples	2.5	12 samples × 4 periods = 48	120
Immunogenicity	5	4	20
Pharmacogenetics	10	1	10
Total			423.8
Total for clinical purposes (rounded up to nearest 10 mL)			430

^a Additional samples may be drawn if needed for safety purposes.

^b Fasting clinical laboratory tests at screening and Predose Day 1 Period 1.

**Appendix 6. Protocol Amendment I8B-MC-ITRQ(a)
Summary
Bioequivalence Study Comparing the Pharmacokinetics
and Glucodynamics of LY900014 U-200 Formulation with
LY900014 U-100 Formulation in Healthy Subjects**

Overview

Protocol I8B-MC-ITRQ [Bioequivalence Study Comparing the Pharmacokinetics and Glucodynamics of LY900014 U-200 Formulation with LY900014 U-100 Formulation in Healthy Subjects] has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Subjects who had participated in a study requiring similar blood sampling as the current study within 3 months of screening will be excluded as per the ethics committee's suggestion
- The hypoglycemia criteria was clarified further
- The number of blood samples to be obtained for immunogenicity testing was corrected in the blood sampling summary
- Other minor edits, such as typographical corrections that do not affect the content of this protocol, were made. These changes may not be reflected in the Revised Protocol Sections.

Revised Protocol Sections

Note: All deletions have been identified by ~~strikethroughs~~.
All additions have been identified by the use of underscores.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

6.2. Exclusion Criteria

[25] have donated blood of more than 450 mL or have participated in a clinical study that required similar blood volume drawn for the past 3 months ~~within the previous 3 months of study screening~~.

9.4.5.1 Glucose Monitoring

- **Documented Glucose Alert Level (Level 1), Plasma Glucose (PG) ≤ 70 mg/dL (3.9 mmol/L) hypoglycemia:**
- **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.
 - ~~an event during which plasma glucose is < 54 mg/dL (3.0 mmol/L), where it is considered sufficiently low to indicate serious, clinically important hypoglycemia.~~
- **Severe hypoglycemia (Level 3):**
 - **Severe hypoglycemia requiring medical attention:** a severe hypoglycemic event when patients require therapy by HCPs (EMTs, emergency room personnel, etc.).

Appendix 5 Blood Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests ^{a,b}	17	1	17
Clinical laboratory tests ^{a,b}	11 (fasting)	1	11
	9 (non-fasting)	1	9
Pharmacokinetic samples serum insulin lispro	1	25 samples × 4 periods = 100	100
Blood for glucose	0.2	76 samples × 4 periods = 304	60.8
Blood discard for cannula patency	0.25	76 samples × 4 periods = 304	76
C-peptide samples	2.5	12 samples × 4 periods = 48	120
Immunogenicity	5	34	1520
Pharmacogenetics	10	1	10
Total			418423.8
Total for clinical purposes (rounded up to nearest 10 mL)			420430