I8B-MC-ITRY Protocol (a)

A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Following Single Dose Administration in Health Chinese Subjects

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A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Following Single Dose Administration in Healthy Chinese Subjects

LY900014

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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1. Protocol Synopsis

Title of Study:
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Following Single Dose Administration in Healthy Chinese Subjects

The aim of this study is to assess the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) profiles, and safety and tolerability following administration of LY900014 during a euglycemic glucose clamp in healthy Chinese subjects.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To evaluate the PK of insulin lispro following administration of single subcutaneous (SC) doses of 7 and 15 U of LY900014 and 15 U of Humalog in healthy Chinese subjects.	Area under the serum concentration versus time curve (AUC) from time zero to 10 hours (AUC[0-10h]), AUC from zero to infinity (AUC[0-∞]), and maximum observed concentration (C_{max}).
Secondary	
To evaluate the GD of insulin lispro during a euglycemic clamp procedure following SC doses of 7 and 15 U of LY900014 and 15 U of Humalog in healthy Chinese subjects.	Total amount of glucose infused (G_{tot}) and maximum glucose infusion rate (R_{max}).
To evaluate the safety and tolerability of LY900014.	Adverse events (AEs).

Summary of Study Design:

Study I8B-MC-ITRY is a Phase 1, single-center, randomized, subject-blind, 3-period, crossover study to evaluate the PK of insulin lispro for LY900014 in healthy Chinese subjects.

Following satisfactory completion of screening procedures, subjects will receive a dose of LY900014 or Humalog, according to the randomization, on Day 1 of each of 3 dosing periods and the time-concentration and time-action profiles of insulin lispro will be evaluated simultaneously during a euglycemic glucose clamp of approximately 10 hours duration. On completion of the euglycemic clamp, subjects will be provided with a meal and will undergo glucose monitoring prior to discharge. Serial blood samples will be collected during the clamp procedure at prespecified times to assess the PK parameters of insulin lispro. Safety assessments and an evaluation of local tolerability at injection sites will be conducted at prespecified times. Local tolerability assessments will include injection-site assessments for signs of edema and erythema. A physician's medical assessment will be required before subjects are discharged from the clinical research unit (CRU), which will be at the discretion of the investigator.

Dosing Arms and Planned Duration for an Individual Subject:
Subjects will be randomized to 1 of 3 dosing sequences as follows:

Dosing Sequence	Period 1	Period 2	Period 3
1	15 U Humalog	7 U LY900014	15 U LY900014
2	7 U LY900014	15 U Humalog	15 U LY900014
3	7 U LY900014	15 U LY900014	15 U Humalog

Each subject will participate in a screening visit up to 28 days prior to dosing (Day 1 of Period 1) followed by 3 study periods each comprising a minimum of 1 night inpatient stay (Day -1 through Day 1). Dosing in consecutive periods will be separated by at least 3 days and subjects will attend a follow-up ≥14 days after receiving the last dose of study drug.

Number of Subjects:

Up to 15 subjects may be randomized to ensure at least 12 subjects (4 per sequence) complete the study.

Statistical Analysis:

Safety: Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements. Safety parameters that will be assessed include AEs, safety laboratory parameters, vital signs, and electrocardiogram (ECG) parameters. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Pharmacokinetics: Pharmacokinetic analyses will be conducted on data from all subjects receiving at least 1 dose of study drug with evaluable PK. Pharmacokinetic analyses will be conducted using standard noncompartmental method of analysis. Free serum insulin lispro concentrations will be used to calculate C_{max}, AUC(0-10h), and AUC(0-∞). Other additional parameters, such as partial AUCs, may be calculated as deemed appropriate.

The PK parameter estimates for insulin lispro will be summarized using standard descriptive statistics.

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 (LOESS) function will be applied to all individual GIR versus time profiles in each dosing group and/or period. The fitted data for each subject will be used to calculate R_{max} and G_{tot}. Other additional GD parameters 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. The GD parameter estimates for insulin lispro will be summarized using standard descriptive statistics.

2. Schedule of Activities

Study Schedule Protocol I8B-MC-ITRY

	Screening	Euglycemic clamp procedure Periods 1, 2, and 3		Follow-up/Early discontinuation	Instructions/Comments
Procedure	Up to -28 days	Day -1	Day 1[a]	≥14 days after last dose	
Informed consent	X				
Admission to CRU		X			
Overnight fast	X	X		X	Subjects will fast for approximately 8 hours prior to screening and follow-up/early discontinuation and from approximately 8 hours before each dose until the end of the glucose clamp procedure.
Hip and waist circumference		Period 1 only			Measurements taken in triplicate.
Height	X				
Body weight	X	X			
Medical history and physical examination	X				
Medical assessment		X	Predose and before discharge from CRU	X	Medical assessment includes medical review and targeted examination as appropriate.
Vital signs (supine): body temperature, blood pressure and pulse rate	X		Predose and approximately 10 hours postdose (end of the clamp procedure)	X	Single vital signs measurements for safety.
12-lead ECG	X		Predose and approximately 10 hours postdose (end of the clamp procedure)	X	Single ECGs will be collected for safety. Electrocardiograms may be collected at additional times when deemed clinically necessary.

	Screening	Euglycemic clamp procedure Periods 1, 2, and 3		Follow-up/Early discontinuation	Instructions/Comments
Procedure	Up to -28 days	Day -1	Day 1[a]	≥14 days after last dose	
Clinical laboratory tests	X			X	All scheduled clinical laboratory tests will be conducted after at least 8 hours fasting. To monitor subject safety, additional tests may be performed at the discretion of the investigator as needed throughout the study. All testing will be conducted at a local laboratory.
Serology	X				
FSH	X				Female subjects only, when needed to confirm postmenopausal status.
Pregnancy test	X	X		X	Female subjects only. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed on Day -1 of Period 1, at follow-up, and on Day -1 of Periods 2 and 3 if the time since the previous pregnancy test is >2 weeks.
Urine drug screen and alcohol breath test	X				
Study drug administration			X (time = 0)		
Injection-site local tolerability assessments			Immediately postdose, 60, 240, and 600 minutes postdose		
Insulin lispro PK sampling			0 (predose), 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 postdose		

	Screening	Euglycemic clamp procedure Periods 1, 2, and 3		Follow-up/Early discontinuation	Instructions/Comments
Procedure	Up to -28 days	Day -1	Day 1[a]	≥14 days after last dose	
Euglycemic clamp			X 0 to 10 hours postdose		If the GIR falls to zero for at least 30 minutes after the clamp has been underway for at least 8 hours, the clamp will be discontinued. Following completion of the euglycemic clamp, subjects will receive a meal and undergo glucose monitoring as deemed necessary by the investigator prior to discharge.
Blood glucose sampling (euglycemic clamp)			Approximately every 10 minutes for approximately 30 minutes before the start of dosing (for baseline measurement). During clamp, sampling occurs every 2.5 to 3 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.
Immunogenicity sample			Predose	X	
Discharge from CRU			X		Subjects will be discharged after completion of all study procedures on Day 1, at the discretion of the investigator.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; GIR = glucose infusion rate; PK = pharmacokinetics.

Note: The site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, the order of priority will be as follows: PK samples including blood sampling for blood glucose and laboratory samples per protocol nominal times. Electrocardiograms and vital sign measurements should be scheduled before but as close as possible to the PK sampling times.

[a] There will be a minimum of 3 days between dosing in consecutive periods.

3. Introduction

3.1. Study Rationale

A prandial insulin with faster-on and/or faster-off characteristics might reduce glycemic excursions and the incidence of postprandial hypoglycemia compared to currently available fast-acting insulin analogs. LY900014 is an ultra-rapid-acting insulin lispro formulation that has shown an increased early absorption compared to commercially available insulin lispro formulation (Humalog®, Eli Lilly) in studies conducted outside of China. LY900014 aims to closely mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions.

The aim of this study is to evaluate the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) profiles, and safety and tolerability following administration of LY900014 and Humalog during a euglycemic glucose clamp in healthy Chinese subjects.

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 subjects given subcutaneous (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). The effects of race on Humalog PK have not been assessed. Although some prandial insulin analogs are absorbed faster than human insulin, the general consensus is that rapid-acting insulin administered SC either by pumps or syringes/pen injectors is still not rapid enough to match carbohydrate-absorption profiles, limiting efficacy and dosing flexibility. Ultra-rapid-acting prandial insulin would shift the PK/GD of insulin analogs such that they have an even faster onset to better match carbohydrate absorption.

LY900014 is a novel formulation of insulin lispro that contains a prostacyclin analog (treprostinil), sodium citrate, and other excipients. This formulation involves the novel use of a microdose of treprostinil as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an API to elicit a systemic effect.

Treprostinil is the active ingredient in CCI [redacted] which is approved by the FDA as a continuous IV or SC infusion for the treatment of PAH. Treprostinil has been approved in China since 2013. Sodium citrate, an excipient that speeds insulin absorption (by enhancing vascular permeability), is also included in the formulation to further enhance the absorption of insulin lispro. Sodium citrate and other excipients (zinc chloride and magnesium chloride) that have been used in the LY900014 Phase 1 clinical trial formulation are listed in the FDA GRAS food additives database (FDA 2018a) and in the FDA Inactive Ingredients in Approved Drugs database (FDA 2018b). Furthermore, concentrations of these excipients in LY900014 are within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

LY900014 has been evaluated in 16 completed Phase 1 studies for up to 14 days in duration. Of these, 7 studies were conducted using a developmental formulation of LY900014, and 9 studies

were conducted using the final formulation of LY900014. These included studies in healthy subjects (N=236), patients with type 1 diabetes (N=196), and patients with type 2 diabetes (N=103), administered at least 1 dose of LY900014.

More information can be found in Section 5.5 (Justification for Dose), and in the Investigator's Brochure (IB).

3.3. Benefit/Risk Assessment

Study I8B-MC-ITRY (ITRY) will not offer any direct benefits to the subjects participating in the study. Data from studies with healthy subjects and patients with T1DM or T2DM have shown that LY900014 is well tolerated with an adverse drug reaction profile consistent with that of Humalog.

As of 17 September 2018, no new safety issues beyond those already known for insulin lispro have been identified for LY900014. Severe hypoglycemia is an important identified risk. Potential important risks include serious allergic reactions, medication errors, and loss of glycemic control due to antidrug antibodies.

Notably, across all doses in the Lilly clinical studies 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 package insert (2014). Moreover, data from Lilly Phase 1b patient studies showed that only 1 out of 472 plasma samples had detectable treprostinil levels taken from a total of 30 patients with T1DM (doses up to 40 U per SC bolus injection) and 29 patients with T2DM (doses up to 50 U per SC bolus injection) following MDI administration of LY900014. The exposure levels of treprostinil from the doses of LY900014 planned in this study are thus expected to be undetectable and substantially lower than those observed in the treatment of PAH.

No additional potential risks of LY900014 or treprostinil alone were identified in preclinical safety pharmacology and toxicity studies or clinical pharmacology studies. No known potential risks are associated with the use of a microdose of treprostinil (CCI) in the LY900014 formulation.
Additionally, local and systemic toxicity profiles of Humalog and CCI do not suggest the potential for additive or synergistic toxicity.

Following administration of the study insulin (Humalog or LY900014), 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 (BG) within the normal glycemic range. In addition, the clamp is performed while the participant is inpatient and under the investigator's supervision. These considerations should minimize the risk of hypoglycemia in subjects participating in Study ITRY.

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

4. Objectives and Endpoints

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

Table ITRY.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the PK of insulin lispro following administration of single SC doses of 7 and 15 U of LY900014 and 15 U of Humalog in healthy Chinese subjects	AUC(0-10h), AUC(0-∞), and C_{max}
Secondary To evaluate the GD of insulin lispro during a euglycemic clamp procedure following SC doses of 7 and 15 U of LY900014 and 15 U of Humalog in healthy Chinese subjects To evaluate the safety and tolerability of LY900014	G_{tot} and R_{max} Adverse events
Exploratory Explore the formation of antibodies to insulin lispro	Anti-insulin lispro antibodies

Abbreviations: AUC(0-∞) = area under the serum concentration versus time curve from zero to infinity; AUC(0-10h) = area under the serum concentration versus time curve from time zero to 10 hours postdose; C_{max} = maximum observed concentration; GD = glucodynamics; G_{tot} = total amount of glucose infused; PK = pharmacokinetics; R_{max} = maximum glucose infusion rate; SC = subcutaneous.

5. Study Design

5.1. Overall Design

This is a Phase 1, single-center, randomized, subject-blind, 3-period, crossover study to evaluate the PK of insulin lispro for LY900014 in healthy Chinese subjects.

After satisfying the study entry criteria, subjects will be randomized to 1 of 3 dosing sequences (Section 7.2; Table ITRY.2). Subjects will be required to attend the clinical research unit (CRU) on 5 occasions:

- screening visit (up to 28 days prior to dosing [Day 1 of Period 1])
- 3 study periods, each comprising a 1 night inpatient stay from Day -1 to Day 1 for the clamp procedure (subjects may remain for longer in the CRU at the investigator's discretion for safety reasons)
- follow-up visit ≥14 days after the last dose, or early discontinuation

Subjects will be fasted (except for water and barley tea) for at least 8 hours prior to collection of clinical safety laboratory samples and dosing, and during glucose clamp procedures according to the Schedule of Activities (Section 2).

Each subject will participate in 3 inpatient visits; on Day 1 of each period, the time-concentration and time-action profiles of insulin lispro will be evaluated simultaneously during a euglycemic glucose clamp of approximately 10 hours duration. Briefly, the aim of the euglycemic clamp is to maintain euglycemia after the administration of a dose of insulin by means of variable glucose infusion. The variable glucose infusion maintains or "clamps" glucose at a constant euglycemic target; therefore, the glucose infusion rate (GIR) reflects the GD effect of the insulin. More information on the clamp methodology can be found in Section 9.6.

Serial blood samples will be collected during the 10-hour glucose clamp at the times specified in the Study Schedule (Section 2) to assess the PK and GD parameters of LY900014. On completion of the euglycemic clamp, subjects will be provided with a meal and will undergo glucose monitoring to ensure that there is no risk of hypoglycemia. A physician's medical assessment will be required before subjects are discharged from the CRU.

There will be a minimum of 3 days between study doses in consecutive periods.

There are no outpatient visits planned between study periods.

Safety assessments and an evaluation of local tolerability at injection sites will be performed as specified in the Study Schedule (Section 2). Local tolerability assessments will include injection-site assessments for signs of edema and erythema.

Study governance considerations are described in detail in Appendix 3.

Table ITRY.2. Dosing Sequences

Dosing Sequence	Period 1	Period 2	Period 3
1	15 U Humalog	7 U LY900014	15 U LY900014
2	7 U LY900014	15 U Humalog	15 U LY900014
3	7 U LY900014	15 U LY900014	15 U Humalog

5.2. Number of Participants

Up to 15 subjects may be enrolled so that approximately 12 subjects complete the study (4 per sequence). For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities have been finished. Subjects who discontinue prior to study completion may be replaced, with the replacement subject assuming the discontinued subject's dosing sequence and taking part in all 3 study periods.

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 upon 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. Chinese subjects are studied as Chinese patients with T1DM or T2DM are a potential target population for LY900014 and the PK and GD profiles of LY900014 are yet to be studied in this population

The study is subject-blind to minimize potential data bias while the crossover design allows each subject to serve as his or her own control, thus reducing variability. The study design uses LY900014 dose levels selected to support potential future comparison between studies.

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 dose (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 [$t_{1/2}$] = approximately [redacted] hour) and Humalog ($t_{1/2}$= [redacted] hours), the duration of the washout period between clamp visits (a minimum of 3 days) and the duration between the last dose of study drug and the follow-up visit (at least 14 days) are considered appropriate.

5.5. Justification for Dose

LY900014 has been evaluated in 16 completed Phase 1 studies. All tested doses of treprostinil, insulin lispro, or LY900014 were well tolerated in development studies in healthy subjects, and in patients with T1D and T2D. No study-drug related SAEs were reported in the completed Phase 1 studies.

Based on previous studies of both insulin lispro (Humalog) and LY900014, the 7 and 15 U doses planned in this study are within the clinical dose range and should provide measurable PK and GD profiles for both study insulins. The insulin lispro concentrations in the body resulting from administration of these doses to healthy subjects are anticipated to be measurable over the sampling period. Additionally, it is anticipated that this dose will provide an adequate GIR for assessment of GD.

At the highest dose level of 15 U of LY900014, subjects will be expected to receive approximately [redacted] treprostinil in a single SC dose, which is within the range evaluated as safe and tolerated in previous studies.

More information can be found in the LY900014 IB.

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 electrocardiogram (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 dosing (Day 1 of Period 1). 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, are 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 and/or enrollment:

[1] are overtly healthy native Chinese (all 4 grandparents to be of Chinese origin) males or females, as determined by medical history and physical examination.

[1a] male subjects:

i. No male contraception required except in compliance with specific local government requirements.

[1b] female subjects:

i. Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.

ii. Otherwise, women of child-bearing potential participating must use 2 effective methods of contraception for the entirety of the study (until discharge from the final dosing period).

A. Women of child-bearing potential must test negative for pregnancy prior to initiation of dosing as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure in Period 1.

B. Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) will be used.

The patient may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

iii. Women not of child-bearing potential may participate and include those who are:

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

B. post-menopausal – defined as either

i. A woman aged at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

a) cessation of menses for at least 1 year; or

b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or

ii. A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

iii. A woman 55 or older with a diagnosis of menopause prior to starting hormone replacement therapy.

[2] are aged 18 to 65 years old, inclusive

[3] have a body mass index (BMI) of 18 to 28 kg/m^2, inclusive

[4] have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

[5] have venous access sufficient for glucose infusion and to allow for blood sampling 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] are nonsmokers, have not smoked for at least 2 months before entering the study, and agree not to smoke (cigars, cigarettes, or pipes) or to use smokeless tobacco for the duration of the study

[9] have a fasting plasma glucose value ≥71 mg/dL (3.9 mmol/L) and <108 mg/dL (6.0 mmol/L) 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:

[10] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

[11] are Lilly employees

[12] 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

[13] have participated, within the last 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.

[14] have previously completed or withdrawn from this study or any other study investigating LY900014, and have previously received the investigational product

[15] have known allergies to LY900014, treprostinil, related compounds or any components of the formulation, or history of significant atopy

[16] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[17] have an abnormal blood pressure and/or pulse rate deemed to be clinically significant by the investigator

[18] have a significant history of 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

[19] have known or ongoing psychiatric disorders

[20] regularly use known drugs of abuse and/or show positive findings on drug screening

[21] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies

[22] show evidence of hepatitis C and/or positive hepatitis C antibody

[23] show evidence of hepatitis B and/or positive hepatitis B surface antigen

[24] intend to use over-the-counter or prescription medication within 7 and 14 days, respectively, prior to dosing (apart from vitamin/mineral supplements, occasional paracetamol, thyroid replacement therapy, oral contraceptives, or hormone replacement therapy) or during the study. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the investigator, preferably after consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP).

[25] have donated blood of more than 400 mL within the previous 6 months of study screening or donated more than 100 mL within the last 30 days.

[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 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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [10] and [11] prevent conflict of interest in study participants. Criteria [12] through [28] exclude medical conditions, medication intolerance, and concomitant medication use that may constitute a risk for the subject and/or may confound the assessment of study endpoints.

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

Subjects will be fasted (except for water and barley tea) for at least 8 hours prior to collection of clinical safety laboratory samples, prior to dosing, and during glucose clamp procedure according to the Schedule of Activities (Section 2). Water and caffeine-free barley tea may be consumed freely at all times.

While resident in the CRU, subjects may not consume any food or caloric drinks other than that provided by the CRU. When not resident in the CRU, subjects may resume their regular diet.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects should refrain from consuming caffeine-containing food/beverages (e.g., cola, chocolate drinks, tea, coffee, and energy drinks) for at least 12 hours prior to each dose and throughout the duration of each CRU visit.

No alcohol will be allowed from at least 24 hours prior to each dose and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 3 units for males and 2 units for females.

No cigarette smoking will be permitted during the study.

6.3.3. Activity

Subjects will be encouraged to maintain their regular exercise; however, they should not undertake vigorous or prolonged exercise from at least 48 hours prior to each dosing day. Should this occur, these subjects will have their dosing visits deferred or may be excluded from the 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 glucose clamp 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

This study involves administration of LY900014 at 7 and 15 U, once by SC injection. The reference formulation will be Humalog. Table ITRY.3 shows the dosing regimens.

Table ITRY.3. Investigational Products Administered

Investigational Product Name	LY900014	Humalog
Dosage Formulation	100 U/mL	100 U/mL
Dosage Levels	7, 15 U	15 U
Route of Administration	Subcutaneous injection	Subcutaneous injection

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- and returning all unused medication to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled as investigational product as appropriate, and according to the country's regulatory requirements. Study insulins (LY900014 and insulin lispro [Humalog]) will be supplied by Lilly or its representative, in accordance with current good manufacturing practices, and will be supplied with clinical trial lot numbers. Instruction for Use for the prefilled devices will be provided.

The prefilled pens will contain a concentration of 100 U/mL in 3-mL cartridges of either LY900014 or insulin lispro.

7.2. Method of Treatment Assignment

The investigational product to be injected on a given dosing day will be determined according to the dosing sequence (Table ITRY.2) assigned using 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.

The site of administration of each injection will be recorded in the eCRF. Injection sites selected should be about 5 cm from the umbilicus. An appropriately sized insulin syringe and needle will be used in all dosing periods to ensure all injections are delivered to a consistent depth target into the SC space. Injections will be rotated among different injection sites on the anterior abdominal wall during the 3 study periods.

All study doses will be given in the CRU by qualified CRU personnel as designated by the investigator. Study injections should be given by a limited number of individuals for consistency.

7.3. Blinding

The study is subject-blind with reference to the identity of the study drug administered (LY900014 or Humalog). The CRU staff will not be blinded to the dose administered due to the difference in volume of injection in the 2 doses being studied. The Lilly CP/Lilly study team will be unblinded.

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 investigational product received and any discrepancies are reported and resolved before use of the investigational product.

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product 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 site staff.

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of dose administration will occur at the site.

7.7. Concomitant Therapy

Subjects should not use over-the-counter or prescription medication within 7 and 14 days, respectively, before each dosing (apart from vitamin and mineral supplements, occasional paracetamol, thyroid replacement therapy, oral contraceptives, or hormone replacement therapy). If a subject does use these medications, inclusion of the subject may be at the discretion of the investigator.

Subjects should not apply any creams or lotions to the abdominal skin on the morning of the injection or during the inpatient study procedure.

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 CRP. Any additional medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

This section is not applicable for this study.

8. Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason must complete early discontinuation procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product for 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)
- ALT or AST >3X ULN 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 upper-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 or 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 or 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 in 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 study site. Site 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 site.

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, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions. Additionally, site 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 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.

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, 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 one of the other outcomes listed in the definition above.

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

Additionally, study site 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 eCRF 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 investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to investigational product) 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 investigational products 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 or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY900014 or Humalog is considered any dose higher than the dose assigned through randomization.

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia can usually be treated with oral glucose. 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. Hypokalemia must be corrected appropriately.

Refer to the LY900014 IB.

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). Blood and urine samples will be collected to determine whether subjects meet inclusion/exclusion criteria and to monitor subject health (additional tests may be performed at the discretion of the investigator). Clinical laboratory tests will be analyzed by a laboratory selected by Lilly.

9.4.2. Vital Signs

For each subject, vital signs (body temperature and supine blood pressure and pulse rate) measurements should be conducted according to the Schedule of Activities (Section 2).

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. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 2 minutes. If the subject feels unable to stand, only supine vital signs will be recorded.

Additional vital signs may be measured during each study period if warranted.

9.4.3. Electrocardiograms

For each subject, a single12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood

samples. 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 site 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/QT corrected for heart rate [QTc] 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. Physical Examination

Physical examinations and medical assessments will be conducted as specified in the Schedule of Activities and as clinically indicated (Section 2).

9.4.5. Body Weight

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

9.4.6. Hip and Waist Circumference

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

9.4.7. Injection-Site Assessments

Injection-site local tolerability assessments will be conducted as specified in the Schedule of Activities and as clinically indicated (Section 2).

9.4.8. 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 the following data:

- trends in safety data

- laboratory analytes
- AEs

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

9.4.8.1. Glucose Monitoring

Hypoglycaemia will be described using the following definitions:

Documented Glucose Alert Level (Level 1), plasma glucose (PG) ≤70 mg/dL (3.9 mmol/L)

- **Documented symptomatic hypoglycemia:** with typical symptoms of hypoglycemia.
- **Documented asymptomatic hypoglycemia:** without typical symptoms of hypoglycemia.
- **Documented unspecified hypoglycemia**: with no information about symptoms of hypoglycemia available. (This has also been called unclassifiable hypoglycemia.)

Documented Clinically Significant Hypoglycemia (Level 2) with similar criterion as above except for threshold PG <54 mg/dL (3.0 mmol/L)

- **Level 2 Documented symptomatic hypoglycemia**
- **Level 2 Documented asymptomatic hypoglycemia**
- **Level 2 Documented unspecified hypoglycemia**

Severe hypoglycemia (Level 3)

- **Severe hypoglycemia:** Subjects 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 PG concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L]).

Other hypoglycemia:

- **Nocturnal hypoglycemia:** Any documented hypoglycemic event (including severe hypoglycemia) that occurs at night and presumably during sleep. This is captured as hypoglycemia that occurs between bedtime and waking. This definition is more useful than the commonly used ~midnight to ~6 AM definition which does not take subjects' individual sleep times into consideration, and is consistent with the American Diabetes Association (ADA) recommendations of reporting events that occur during sleep (ADA 2005). It is also important to collect the actual time when a hypoglycemic event occurred to allow further characterization of hypoglycemia timing (e.g., to allow analysis of frequency of events occurring across a 24-hr clock). Nocturnal hypoglycemia may occur at severity Levels 1, 2, or 3.
- **Relative hypoglycemia (also referred to as Pseudohypoglycemia [Seaquist et al. 2013]):** An event during which typical symptoms of hypoglycemia occur, that does not require the assistance of another person and is accompanied by PG >70 mg/dL (3.9 mmol/L). The PG

value of subjects with chronically poor glycemic control can decrease so rapidly that subjects may report symptoms of hypoglycemia before their PG concentration falls below 70 mg/dL (3.9 mmol/L). Events with PG ≤70 mg/dL should not be categorized as relative hypoglycemia. Evaluation and statistical analysis of this category is optional. However, if a subject reports a relative hypoglycemia event where assistance from another person was received or the subject experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycemia event, and report it appropriately.

- **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia were present, but PG measurement was not reported.
- **Overall (or total) hypoglycemia:** This optional category combines most cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). It does not include 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 only be counted once in the category of overall (or total) hypoglycemia.

Only severe hypoglycaemic episodes will be reported separately as AEs. All episodes of severe hypoglycaemia will be reported as SAEs.

The goal of the euglycemic clamp is to maintain glucose concentrations at normal glycemic levels close to a predefined target. Therefore, 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. Glucose monitoring will continue after completion of the euglycemic clamp prior to discharge from the CRU at the discretion of the investigator.

9.4.8.2. Hepatic Safety

If a study subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated total bilirubin ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), 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 ≥ 5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥ 2X ULN on 2 or more consecutive blood tests

- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2.5 mL each will be collected to determine the free 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.

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 free serum insulin lispro will be assayed using a CCI [redacted]

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)

Subjects will participate in a euglycemic clamp for approximately 10 hours following administration of a dose of insulin as described in Section 5.1.

The aim of the euglycemic glucose clamp is to maintain euglycemia through glucose infusion after the administration of a dose of insulin. During the glucose clamp, the GIR will be adjusted to maintain a predetermined target BG concentration for the individual subject. The intent is to maintain BG concentrations approximately at the predose target value, which is defined as 5 mg/dL below the mean predose fasting BG (mean of predose values recorded at approximately -30, -20, and -10 minutes).

Thus, BG concentrations are kept constant while the GIR varies. The varying GIR will reflect the GD activity of insulin.

The subjects will participate in a total of 3 euglycemic clamps in 3 separate study periods. Glucose clamp studies will be performed after an overnight fast of approximately 8 hours. The GIRs required to maintain euglycemia and BG concentrations will be documented throughout the procedure. On the morning of the study, a small catheter will be placed into a forearm vein, ideally at the elbow, for infusion of glucose. The glucose is infused as a 20% dextrose solution. Another catheter will be placed at the wrist or back of the hand, or in the case of difficult venous access, in the forearm as close to the wrist as possible, for blood sampling. Blood samples will be obtained at the bedside for immediate determination of whole BG concentrations using an automated glucose oxidase technique or other appropriate analytical method.

The time of study insulin dosing will be defined as time zero. Following dosing, in conjunction with frequent blood sampling for measurement of BG, glucose will be infused intravenously at a

variable rate in order to maintain euglycemia for approximately 10 hours. If the GIR falls to zero for at least 30 minutes after the clamp has been underway for at least 8 hours, the clamp will be discontinued.

At the end of the clamp (approximately 10 hours after study drug administration) and following collection of the 10-hour study samples, the subject will be fed and will undergo glucose monitoring as deemed appropriate by the investigator. A physician's medical assessment will be required before subjects are discharged from the CRU.

9.7. Immunogenicity Assessments

Samples for potential future immunogenicity testing will be collected as indicated in the Schedule of Activities (Section 2).

Humalog® response is well-characterized historically with clinical and on-market data indicating that immunogenic potential is low and comparable to other marketed insulins such as regular human insulin (Fineberg et al. 1996). Antibodies may form but do not appear to be clinically consequential (Fineberg et al. 2003). Therefore, blood samples will be stored and used to determine antibody production against insulin lispro, as warranted, based on clinical observations and emerging data. Results from these tests are not required for final data review.

Immunogenicity will be assessed by a validated CCI [redacted] to detect anti-insulin lispro antibodies in the presence of lispro. Instead of quantitating the level of anti-insulin lispro antibodies by titer, the CCI [redacted] reports a semiquantitative percent-binding for each positive sample. Additionally, positive samples will be characterized for cross-reactive binding to native insulin. Potential analysis of immunogenicity may be indicated in the statistical analysis plan.

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 LY900014. Any samples remaining after 15 years will be destroyed.

9.8. Genetics

This section is not applicable for this study.

9.9. Biomarkers

This section is not applicable for this study.

9.10. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 15 subjects will be randomized in order that 12 subjects complete all periods of the study (4 per sequence).

Sample size is not based on a statistical power calculation. Sample size is considered suitable to characterize the PK profiles of insulin lispro, and to evaluate the safety and tolerability of single doses of LY900014 administered SC.

If the randomized subjects discontinue from the study prior to its completion, subjects can be replaced. The replacement subject will adopt the original subject's randomization schedule.

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, body weight, BMI, waist and hip circumference, height, race/subrace, and other demographic characteristics will be summarized.

10.3. Statistical Analyses

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

Pharmacokinetic/GD analyses will be conducted on data from all subjects who receive at least one dose of the investigational product and have evaluable PK.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

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 investigational product and protocol procedure AEs will be listed, and 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 investigational product as perceived by the investigator. Symptoms reported to occur prior to 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 regulatory dictionary.

The number of investigational product-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Insulin lispro PK parameter estimates for LY900014 and Humalog will be conducted using standard noncompartmental methods of analysis using CCI [redacted] 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 maximum observed concentration (C_{max}), time to maximum observed drug concentration (t_{max}), time to early half-maximal plasma concentration (early 50% t_{max}), time to late half-maximal drug concentration (late 50% t_{max}), area under the concentration versus time curve (AUC) from time zero to 15 minutes (AUC[0-15min])), AUC from time zero to 30 minutes (AUC[0-30min])), AUC from time zero to 1 hour(AUC[0-1h]), AUC from time zero to 10 hours (AUC[0-10h]), AUC from time 2 to 10 hours (AUC[2-10h]), AUC from time 3 to 10 hours (AUC[3-10h]), AUC from time 0 to the last recorded time (AUC[0-t_{last}]), AUC from time zero to infinity (AUC[0-∞]) will be determined. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary, such as AUC from time zero to 2 hours.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be summarized using standard descriptive statistics.

10.3.3. Glucodynamic Analyses

10.3.3.1. Glucodynamic 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. The analyses will be performed according to the Lilly Global Pharmacokinetics, Pharmacodynamics, and Trial Simulation Divisional Standards.

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 [redacted]. The fitted data for each subject will be used to calculate the following GD parameters: maximum GIR (R_{max}), time to R_{max} (t_{Rmax}), time to half-maximal GIR before t_{Rmax} (early 50% t_{Rmax}), time to half-maximal GIR after t_{Rmax} (late 50% t_{Rmax}), time to onset of insulin action (T_{onset}), the total amount of glucose infused over the duration of the clamp procedure (G_{tot}), the total amount of glucose infused over 1 hour (G_{tot}[0-1h]), and the total amount of glucose infused over 30 minutes (G_{tot}[0-30min]). Additional partial glucose AUCs, such as G_{tot} infused over 2 hours (G_{tot}[0-2h]), 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. Glucodynamic Statistical Inference

Glucodynamic parameters will be summarized using standard descriptive statistics.

10.3.4. Interim Analyses

This is a subject-blind study; the investigator and Lilly study team are unblinded. Data may be analyzed while the trial is ongoing but no changes to the study design are planned. An assessment committee will not be formed. 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

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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.
ADA	American Diabetes Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
BG	blood glucose
blinding	A procedure in which one 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. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not.
BMI	body mass index
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
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
ECG	electrocardiogram
eCRF	electronic case report form

enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
FDA	Food and Drug Administration
GCP	good clinical practice
GD	glucodynamic
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.
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
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
LOESS	locally weighted scatterplot smoothing
MDI	multiple daily injections
PAH	pulmonary arterial hypertension
PG	plasma glucose

PK	pharmacokinetic
randomize	the process of assigning subjects to an experimental group on a random basis
R_{max}	maximum glucose infusion rate
SAE	serious adverse event
SC	subcutaneous
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.
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	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 concentration
t_{Rmax}	time to maximum glucose infusion rate
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Haematology[a]:	Clinical Chemistry[a]:
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin (MCH)	Calcium
Mean cell hemoglobin concentration (MCHC)	Phosphorus
Leukocytes (WBC)	Glucose (fasting)
Absolute counts of:	Blood urea
Neutrophils	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
Platelets	Alkaline phosphatase (ALP)
	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
Urinalysis[a]:	Creatinine
Specific gravity	Gamma-glutamyl transferase (GGT)
pH	
Protein	
Glucose	Pregnancy test[b]
Ketones	FSH[c,d]
Bilirubin	
Urobilinogen	Serology[d]
Blood	Hepatitis B surface antigen
	Hepatitis C antibody
	HIV

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

[a] Performed at a local laboratory.

[b] Female subjects only. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed on Day -1 of Period 1, at follow-up, and on Day -1 of Periods 2 and 3 if the time since the previous pregnancy test is >2 weeks, and processed on site.

[c] Female subjects only, when needed to confirm postmenopausal status.

[d] Performed at screening only.

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 or its designee 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 investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site'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 site 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 personal information collected will be provided in a written document to the subject by the sponsor.

Study and Site Closure

Discontinuation of Study Site

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site 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 or its designee 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[a]**
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 cells; WBC = white blood cells.

[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-ITRY Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	30	1	30
Clinical laboratory tests[a]	7.5	1	7.5
Pharmacokinetics	2.5	75	187.5
Blood discard for cannula patency	0.5	75	37.5
Glucose monitoring (euglycemic clamp)	0.3	10 hours/clamp x 3 clamps (approx. 100 samples/clamp) [b]	90
Immunogenicity	5	4	20
Total			372.5
Total for clinical purposes			380

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

[b] Includes sampling for post-clamp glucose monitoring; additional samples may be drawn if needed for safety purposes.

Appendix 6. Protocol Amendment I8B-MC-ITRY(a) Summary A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Following Single Dose Administration in Healthy Chinese Subjects

Overview

Protocol I8B-MC-ITRY [A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 Following Single Dose Administration in Healthy Chinese 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 described in the following table:

Table ITRY.4. Amendment Summary for Protocol I8B-MC-ITRY Amendment(a)

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities	Blood glucose sampling time during the first 30 minutes of the glucose clamp has been changed from every 5 minutes to every 2.5 to 3 minutes.	Frequency of blood glucose sampling increased to ensure subject safety and clamp quality.
9.4.1. Laboratory Tests	The requirement for the clinical laboratory to be central has been removed.	The change allows flexibility in laboratory selection.
Appendix 5. Blood Sampling Summary	The blood volume required for glucose monitoring has been amended from 72 to 90 mL.	Change reflects additional blood volume required to accommodate more frequent sampling.

Revised Protocol Sections

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

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-ITRY Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	30	1	30
Clinical laboratory tests[a]	7.5	1	7.5
Pharmacokinetics	2.5	75	187.5
Blood discard for cannula patency	0.5	75	37.5
Glucose monitoring (euglycemic clamp)	0.3	10 hours/clamp x 3 clamps (approx. ~~80~~ 100 samples/clamp)[b]	~~72~~90
Immunogenicity	5	4	20
Total			~~354~~372.5
Total for clinical purposes			~~360~~380

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

[b] Includes sampling for post-clamp glucose monitoring; additional samples may be drawn if needed for safety purposes.

9.4.1. Laboratory Tests

Clinical laboratory tests will be analyzed by a ~~central~~ laboratory selected by Lilly.

Study Schedule Protocol I8B-MC-ITRY

	Screening	Euglycemic clamp procedure Periods 1, 2, and 3		Follow-up/Early discontinuation	Instructions/Comments
Procedure	Up to -28 days	Day -1	Day 1[a]	≥14 days after last dose	
Informed consent	X				
Admission to CRU		X			
Overnight fast	X	X		X	Subjects will fast for approximately 8 hours prior to screening and follow-up/early discontinuation and from approximately 8 hours before each dose until the end of the glucose clamp procedure.
Hip and waist circumference		Period 1 only			Measurements taken in triplicate.
Height	X				
Body weight	X	X			
Medical history and physical examination	X				
Medical assessment		X	Predose and before discharge from CRU	X	Medical assessment includes medical review and targeted examination as appropriate.
Vital signs (supine): body temperature, blood pressure and pulse rate	X		Predose and approximately 10 hours postdose (end of the clamp procedure)	X	Single vital signs measurements for safety.
12-lead ECG	X		Predose and approximately 10 hours postdose (end of the clamp procedure)	X	Single ECGs will be collected for safety. Electrocardiograms may be collected at additional times when deemed clinically necessary.

	Screening	Euglycemic clamp procedure Periods 1, 2, and 3		Follow-up/Early discontinuation	Instructions/Comments
Procedure	Up to -28 days	Day -1	Day 1[a]	≥14 days after last dose	
Clinical laboratory tests	X			X	All scheduled clinical laboratory tests will be conducted after at least 8 hours fasting. To monitor subject safety, additional tests may be performed at the discretion of the investigator as needed throughout the study. All testing will be conducted at a local laboratory.
Serology	X				
FSH	X				Female subjects only, when needed to confirm postmenopausal status.
Pregnancy test	X	X		X	Female subjects only. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed on Day -1 of Period 1, at follow-up, and on Day -1 of Periods 2 and 3 if the time since the previous pregnancy test is >2 weeks.
Urine drug screen and alcohol breath test	X				
Study drug administration			X (time = 0)		
Injection-site local tolerability assessments			Immediately postdose, 60, 240, and 600 minutes postdose		
Insulin lispro PK sampling			0 (predose), 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 postdose		

	Screening	Euglycemic clamp procedure Periods 1, 2, and 3		Follow-up/Early discontinuation	Instructions/Comments
Procedure	Up to -28 days	Day -1	Day 1[a]	≥14 days after last dose	
Euglycemic clamp			X 0 to 10 hours postdose		If the GIR falls to zero for at least 30 minutes after the clamp has been underway for at least 8 hours, the clamp will be discontinued. Following completion of the euglycemic clamp, subjects will receive a meal and undergo glucose monitoring as deemed necessary by the investigator prior to discharge.
Blood glucose sampling (euglycemic clamp)			Approximately every 10 minutes for approximately 30 minutes before the start of dosing (for baseline measurement). During clamp, sampling occurs every ~~5~~ 2.5 to 3 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.
Immunogenicity sample			Predose	X	
Discharge from CRU			X		Subjects will be discharged after completion of all study procedures on Day 1, at the discretion of the investigator.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; FSH = follicle-stimulating hormone; GIR = glucose infusion rate; PK = pharmacokinetics.

Note: The site should schedule activities as appropriate. In cases where several study procedures are scheduled at the same time, the order of priority will be as follows: PK samples including blood sampling for blood glucose and laboratory samples per protocol nominal times. Electrocardiograms and vital sign measurements should be scheduled before but as close as possible to the PK sampling times.

[a] There will be a minimum of 3 days between dosing in consecutive periods.

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