Protocol/Statistical Analysis Plan: I8B-MC-ITRR

Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro Following Single Dose Administration in Elderly and Younger Adults With Type 1 Diabetes Mellitus

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Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro Following Single Dose Administration in Elderly and Younger Adults with Type 1 Diabetes Mellitus

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Confidential Information

LY900014

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1. Protocol Synopsis

Title of Study:

Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro Following Single Dose Administration in Elderly and Younger Adults with Type 1 Diabetes Mellitus

Rationale:

LY900014 is an ultra-rapid-acting insulin lispro formulation with increased initial absorption compared to commercially available insulin lispro formulation (Humalog®; Eli Lilly and Company). LY900014 aims at mimicking the physiological prandial insulin secretion pattern better than the currently available treatments, which may more effectively control postprandial glucose excursions and allow increased flexibility in the time of dosing relative to a meal.

The aim of this study is to compare the insulin lispro pharmacokinetic (PK) and glucodynamic (GD) profiles of LY900014 with those of insulin lispro (Humalog) during a euglycaemic glucose clamp in elderly and younger adults with type 1 diabetes mellitus (T1DM).

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To evaluate the PK of insulin lispro following administration of a single 15-U SC dose of LY900014 compared to insulin lispro (Humalog) within each T1DM population (elderly and younger adults).	• Early 50% t_{max} and $AUC_{(0\text{-}30min)}$
Secondary • To compare the GD during a euglycaemic clamp of LY900014 and insulin lispro (Humalog) following administration of a single 15-U SC dose in elderly and younger adults with T1DM. • To evaluate the safety and tolerability of the novel LY900014 formulation.	• Early 50% TR_{max}, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1hour)}$, and T_{onset} • AEs

Abbreviations: AE = adverse event; $AUC_{(0\text{-}30min)}$ = area under the concentration versus time curve from time zero to 30 minutes; early 50% t_{max} = time to early half-maximal plasma concentration; early 50% TR_{max} = time to early half-maximal glucose infusion rate; GD = glucodynamics; $Gtot_{(0\text{-}30min)}$ = total amount of glucose infused over 30 minutes; $Gtot_{(0\text{-}1hour)}$ = total amount of glucose infused over 1 hour; PK = pharmacokinetics; SC = subcutaneous; T1DM = type 1 diabetes mellitus; T_{onset} = time to onset of insulin action.

Summary of Study Design:

Study I8B-MC-ITRR is a randomized, subject- and investigator-blind, 2-treatment, 2-period, crossover study in elderly and younger adults with T1DM.

Treatment Arms and Duration:
LY900014 (test): Single 15-U dose
Insulin lispro (Humalog) (reference): Single 15-U dose

Number of Subjects: Up to 42 younger adult (aged 18 to 45 years inclusive) and 42 elderly (aged ≥65 years) subjects may be enrolled to ensure that at least 34 subjects in each age group complete the study.

Statistical Analysis: The primary statistical analyses for PK will be conducted on subjects who receive at least 1 dose of study drug and have measurable insulin lispro concentrations. The primary statistical analysis for GD will be conducted on those subjects who complete at least 1 clamp procedure. Supportive analyses will be done on the key parameters for the subjects who complete all treatment periods with evaluable data. Safety analyses will be conducted for all enrolled subjects who received at least 1 dose of study drug, whether or not they completed all protocol requirements.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided.

Safety: All investigational and protocol procedure adverse events (AEs) will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety parameters that will be assessed include safety laboratory parameters, vital signs, and electrocardiogram parameters as well as injection-site reactions. The parameters will be listed and summarized using standard descriptive statistics.

Pharmacokinetics: Subjects who receive at least 1 dose of study drug and have measurable insulin lispro concentrations will be included in the PK analysis dataset. PK parameter estimates for insulin lispro will be calculated using standard noncompartmental methods of analysis.

Log-transformed maximum observed concentration (C_{max}), clearance, and area under the plasma concentration-time curve estimates for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog (reference), and their corresponding 95% CIs for each age group using the statistical model that includes treatment, sequence, and period as fixed effects and subject within sequence as a random effect. The same model without log transformation will be used for time to early half-maximal plasma concentration (early 50% t_{max}), time to late half-maximal plasma concentration (late 50% t_{max}), and time to maximum concentration (t_{max}) to estimate least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for each age group. The treatment ratios and the corresponding 95% CIs for these time parameters will be calculated using Fieller's theorem.

As treprostinil plasma concentrations after administration of LY900014 are expected to be very low, a descriptive statistical analysis may be conducted if sufficient data are available for this analysis. The primary analysis of the treprostinil concentrations will be focused on assessing t_{max} and C_{max}.

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

A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and/or period. The fitted data for each subject will be used to calculate the GD

parameters. 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 statistical model will be similar to the model used for the analysis of the PK parameters. The variables of maximum GIR (R_{max}), total amount of glucose infused (Gtot), total amount of glucose infused over 30 minutes ($Gtot_{[0\text{-}30min]}$), total amount of glucose infused over 1 hour ($Gtot_{[0\text{-}1h]}$), and total amount of glucose infused over 10 hours ($Gtot_{[0\text{-}10h]}$) will be log-transformed prior to analysis. The time variables including time to onset of insulin action (T_{onset}), time to R_{max} (TR_{max}), time to half-maximal GIR before TR_{max} (early 50% TR_{max}), and time to half-maximal GIR after TR_{max} (late 50% TR_{max}) will be analyzed using the same model without log transformation to estimate least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs. The treatment ratios and the corresponding 95% CIs for these time parameters will be calculated using Fieller's theorem.

Immunogenicity:

The immunogenicity data will be listed. The relationship between treatment-emergent antidrug antibodies and AEs will be evaluated. The relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may also be evaluated.

2. Schedule of Activities

Study Schedule: Protocol I8B-MC-ITRR

Procedures	Screening	Euglycaemic Clamp Procedure Periods 1 and 2		FU/ED[a]	Instructions/Comments
	Up to Day -28	Day -1	Day 1		
Informed consent[b]	X				
Subject admission to CRU		X			
Standardized dinner		X			All subjects will receive short-acting insulin either via an injection or via a bolus dose from the insulin pump before the start of a standardized dinner and 6 hours prior to dosing.
Fasting	X	X		X	Subjects are expected to fast for at least 8 hours before screening and FU, and at least 8 hours before each dose until after the glucose clamp procedure is completed. (Up to 20 g of carbohydrates will be allowed to prevent hypoglycaemia.)
Height	X				
Weight	X		Predose for Period 1 and Period 2	X	
Waist and hip circumference[d]		X			
Alcohol breath test	X	X		X	
Run-in and stabilization of glucose			X		To start approximately 1-6 hours prior to study drug dosing.
Medical assessment and physical examination	X	X	Before discharge from CRU for each period	X	Physical examination and medical history at screening. Thereafter, medical review and targeted examination, as appropriate.
Vital signs: body temperature, blood pressure, and pulse rate	X	X	Predose, 0.5 and 2 hours after dose and at the end of the clamp procedure	X	Vital signs can be collected after the subject is supine for at least 5 minutes. Body temperature at screening only. Predose vital signs may be collected up to 2 hours before the start of the clamp procedure.
Randomization		X			Only at Period 1

Procedures	Screening	Euglycaemic Clamp Procedure Periods 1 and 2		FU/ED[a]	Instructions/Comments
	Up to Day -28	Day -1	Day 1		
12-Lead ECG	X		Predose and at the end of the clamp procedure	X	Predose ECGs can be collected up to 2 hours before the start of the clamp procedure. Subjects must be supine for at least 10 minutes before ECG collection and remain supine but awake during ECG collection.
Clinical laboratory tests	X		Predose for Period 1 only	X	Fasting laboratory test for screening, Period 1, and FU. To monitor patient safety, additional tests may be performed at the discretion of the investigator, as needed throughout the study.
Pregnancy test/urine drug screen[c]	X	X		X	Pregnancy test for all female subjects. Urine drug screen for all subjects at CRU admission.
Study drug administration			X		Time = 0 minutes
Injection-site local tolerability assessments			0, 60, and 240 minutes postdose and at the end of clamp procedure		Time 0: assessments of injection-site reaction will occur immediately following the injection.
VAS assessment of injection site pain			0, 20, and 60 minutes postdose		Time 0: assessments of injection-site pain will occur immediately following the injection.
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 study drug administration time (0 minutes).
Treprostinil PK sampling			15, 30, 60, and 120 minutes		Sampling times are relative to study drug administration time (0 minutes).
Blood glucose sampling for euglycaemic clamp			Blood glucose monitoring every minute starting from the run-in and throughout the duration of the clamp until 10 hours after dosing		
Pharmacogenetic sample			Predose for Period 1 only		Refer to sample collection instructions provided by the sponsor.
Immunogenicity sample			Predose for Period 1 and Period 2	X	
Discharge from CRU			X		After completion of all study procedures and medical assessment on Day 1. Investigator's discretion to discharge on Day 2.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; ICF = informed consent form; PK = pharmacokinetic; VAS = visual analog scale.

[a] Procedures should be performed at least 14 days after the last dose of study drug.

[b] Screening shall be completed within 28 days of dose of study drug. The ICF will be signed at least 1 day prior to screening.

[c] A FSH test will be performed for women who are menopausal

[d] The average of triplicate measurements.

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. ECGs and vital sign measurement should be scheduled before but as close as possible to the PK sampling times. VAS and injection-site assessments can be done after PK sampling 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.

3. Introduction

3.1. Study Rationale

The use of LY900014 in elderly subjects (≥65 years of age) is anticipated. Study I8B-MC-ITRR (ITRR) is being conducted in accordance with regulatory guidance to conduct clinical trials of medicines that are likely to have significant use in the elderly.

LY900014 is an ultra-rapid-acting insulin lispro formulation, which has shown an increased initial absorption compared to commercially available insulin lispro formulation (Humalog®, Eli Lilly and Company). LY900014 aims at mimicking the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions and allow increased flexibility of the time of dosing relative to a meal.

A population of elderly subjects is selected as changes in the body composition due to aging (such as increased body fat, reduced lean body mass, decreased total body water) may alter the pharmacokinetic (PK) profile of insulin lispro in LY900014.

Minimal data are available for the evaluation of the PK and glucodynamics (GD) of insulin lispro after LY900014 administration in subjects ≥65 years of age. Therefore, the aim of this study is to compare the PK and GD profiles of insulin lispro from LY900014 with those of insulin lispro (Humalog) during a euglycaemic glucose clamp in elderly subjects and younger adults with type 1 diabetes mellitus (T1DM) and also in a population of younger adults to support prescribing information and gain further data in this population.

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 subcutaneous (SC) doses of insulin lispro ranging from 0.1 to 0.4 units/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/GD of insulin analogs so that they have an even faster onset to better match carbohydrate absorption and also may allow important flexibility in the time of dosing relative to meals.

LY900014 represents a new formulation that contains insulin lispro, treprostinil, citrate, and other excipients. This formulation involves the novel use of a small amount of treprostinil (Remodulin®) as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient to elicit a systemic effect. Treprostinil is a prostacyclin analog, administered either through inhalation (Tyvaso®), as an intravenous (IV) infusion, or as a continuous SC administration for the treatment of symptomatic pulmonary arterial hypertension and has been approved in the United States (US) since 2002 and in Germany since 2007 (Remodulin package insert, 2014). Each of the other excipients (such as sodium citrate and magnesium chloride) in the LY900014 formulation is listed in the US Food and Drug Administration's (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 has been demonstrated in healthy subjects in 2 previous clinical studies, CCI [redacted]. Both were Phase 1, randomized, subject-blind studies in which the PK and GD of LY900014 and Humalog insulin lispro were evaluated during a euglycaemic glucose clamp following SC administration. The total insulin lispro exposure and GD effect were similar for LY900014 and Humalog insulin lispro; however, LY900014 demonstrated a faster and earlier insulin lispro absorption and faster elimination compared to Humalog insulin lispro.

Preliminary data from 3 ongoing Phase 1b studies CCI [redacted] showed LY900014 was well tolerated in subjects with T1DM using either multiple daily injections (MDI) or insulin pump treatment. 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 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.

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

3.3. Benefit/Risk Assessment

Study I8B-MC-ITRR will not offer any direct benefits to the subjects participating in the study. The data from previous studies CCI [redacted] and preliminary data from ongoing studies CCI [redacted] 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)- the active pharmaceutical ingredient in LY900014, are hypoglycaemia, 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).

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 Remodulin package insert (2014) (that is, headache, diarrhea, nausea, jaw pain, vasodilatation, rash, edema, anorexia, vomiting, asthenia, abdominal pain, and hypotension). The exposures of treprostinil in LY900014 for participants in this study are expected to be undetectable compared to those observed in the dose ranges previously explored with SC bolus administration of treprostinil and are expected to be substantially lower than those observed in the treatment of pulmonary arterial hypertension.

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 small amounts of treprostinil (Remodulin) in the LY900014 formulation.

Additionally, local and systemic toxicity profiles of Humalog and Remodulin do not suggest the potential for additive or synergistic toxicity.

Following administration of the study insulins, subjects will receive IV glucose infusion at a variable rate to maintain euglycaemia up to 10 hours after insulin lispro administration. The aim of the clamp procedure is to maintain blood glucose within the normal glycaemic 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 hypoglycaemia in subjects participating in Study ITRR.

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

More detailed information about the known and expected benefits and risks of Humalog insulin lispro may be found in the Humalog package insert (2015).

4. Objectives and Endpoints

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

Table ITRR.1. Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the PK of insulin lispro following administration of a single 15-U SC dose of LY900014 compared to insulin lispro (Humalog) within each T1DM population (elderly and younger adults).	• Early 50% t_{max} and $AUC_{(0\text{-}30min)}$
Secondary • To compare the GD during a euglycaemic clamp of LY900014 and insulin lispro (Humalog) following administration of a single 15-U SC dose in elderly and younger adults with T1DM. • To evaluate the safety and tolerability of the novel LY900014 formulation.	• Early 50% TR_{max}, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1hour)}$, and T_{onset} • AEs
Exploratory • To evaluate whether the difference between LY900014 and insulin lispro in PK and PD parameters is similar between elderly and younger adults.	• Early 50% t_{max} and $Gtot_{(0\text{-}30min)}$

Abbreviations: AE = adverse event; $AUC_{(0\text{-}30min)}$ = area under the concentration versus time curve from time zero to 30 minutes; early 50% t_{max} = time to early half-maximal plasma concentration; early 50% TR_{max} = time to early half-maximal glucose infusion rate; GD = glucodynamics; $Gtot_{(0\text{-}30min)}$ = total amount of glucose infused over 30 minutes; $Gtot_{(0\text{-}1h)}$ = total amount of glucose infused over 1 hour; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; T1DM = type 1 diabetes mellitus; T_{onset} = time to onset of insulin action.

5. Study Design

5.1. Overall Design

This is a Phase 1, randomized, subject- and investigator-blind, 2-treatment, 2-period, crossover study that compares the PK and GD of insulin lispro from LY900014 and insulin lispro (Humalog) following administration of a single 15-U SC dose in elderly and younger adults with T1DM who are either on multiple daily insulin injections or on CSII via a sponsor-approved insulin pump. Study ITRR will be conducted at 1 or more sites.

Figure ITRR.1 illustrates the study design.

Subjects will be randomized to 1 of 2 treatment sequences according to the actual randomization table provided to the site. Each subject will participate in a screening visit, 2 clinical research unit (CRU) inpatient dosing visits, and a follow-up visit. Before each dose, a run-in period of 1 to 6 hours to stabilize blood glucose will occur. Dosing visits will be separated by a wash-out period of 3 to 15 days, during which subjects will resume their normal insulin treatment with the exemption of the insulin switch 48 to 72 hours prior to dosing as mentioned below. At each visit, subjects will receive either LY900014 or insulin lispro and undergo a euglycaemic clamp procedure where the time-concentration and time-action profiles of the study treatment will be evaluated simultaneously for up to 10 hours using an automated clamp device. Briefly, the aim of the euglycaemic clamp is to maintain euglycaemia 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 euglycaemic target; therefore, the glucose infusion rate (GIR) reflects the GD effect of the insulin.

Prior to each dosing visit, subjects with T1DM on multiple daily insulin injections have to discontinue their basal insulin, according to the following guidance:

- For subjects using insulin degludec or insulin glargine U300, the last injection of insulin degludec should occur no later than 72 hours prior to dosing.
- For subjects using insulin detemir or glargine, the last injection of insulin detemir or glargine should occur no later than 48 hours prior to dosing.
- For subjects using neutral protamine Hagedorn (NPH) insulin or other intermediate-acting insulin, the last injection of NPH insulin or other intermediate-acting insulin should occur no later than 24 hours prior to dosing.
- Subjects requiring any infusion via CSII of insulin lispro (Humalog) will switch to insulin glulisine (Apidra®) at least 8 hours prior to dosing. Basal infusion rate via CSII should not occur later than 3 hours prior to dosing.
- Any injection or bolus infusion via CSII of more than 6 U of short-acting insulin should not occur between 11 and 6 hours prior to dosing. Any bolus injection or bolus infusion via CSII should occur no later than 6 hours prior to dosing.

All subjects will be instructed to perform at least 4-point daily self-monitoring plasma glucose (SMPG), as well as continue their short-acting insulin during lead-in. The SMPG and prandial insulin doses should be recorded in the patient's diary, which will serve as a source document.

5.1.1. Inpatient Dosing Visits

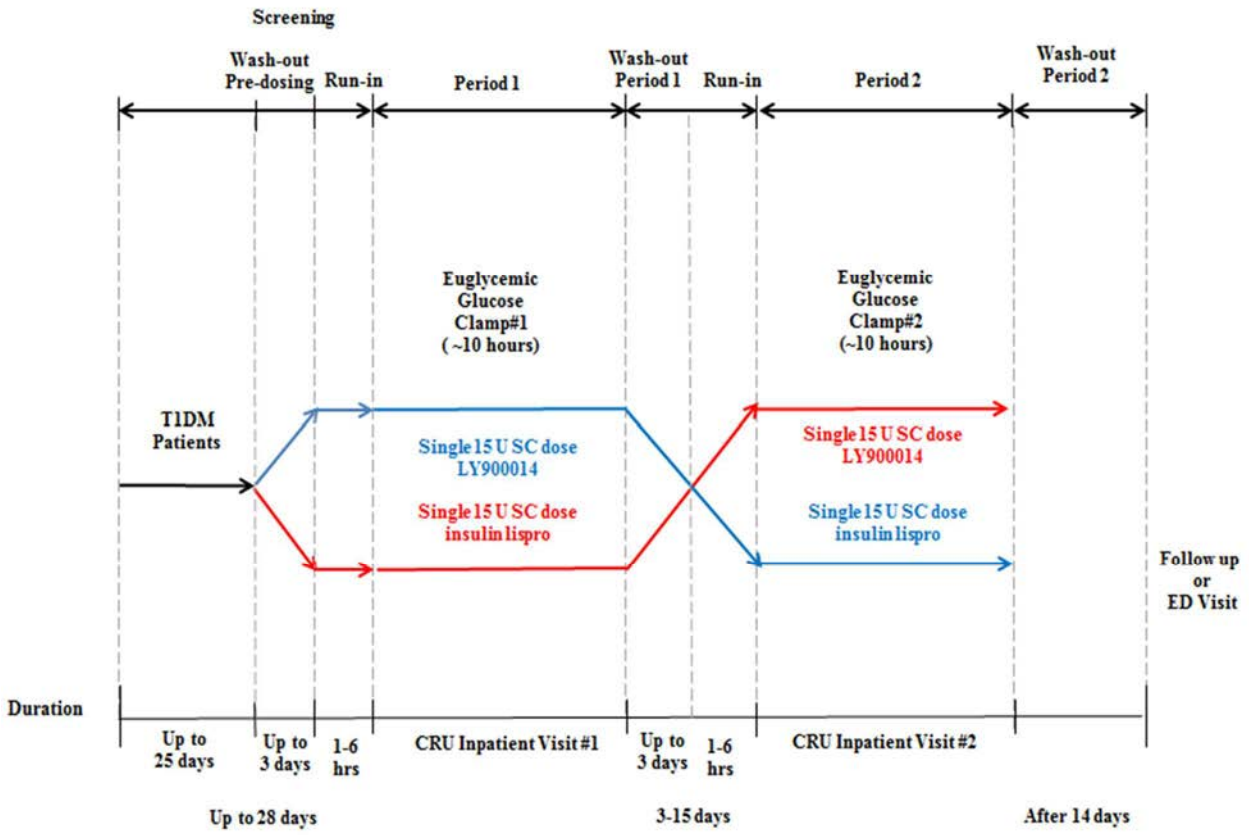
The patient will check into the CRU on Day -1 of each period in the early evening (at approximately 1700 hours). Subjects on multiple daily insulin injections would have discontinued their basal insulin but subjects using pump therapy (CSII) should arrive at the CRU with their basal rate running. All subjects will receive short-acting insulin either via an injection or via a bolus dose from the insulin pump before the start of a standardized dinner within the CRU. This prandial dose should be administered no later than 6 hours prior to the planned study drug dosing the next day. After dinner (at approximately 2200 hours), the subject is required to fast until the completion of the clamp procedure the following day. Consumption of food or beverages other than water later than approximately 2200 hours on the evening before dosing is not allowed, with the exception of minor intake of rapidly absorbable carbohydrates (not more than 20 g) if necessary to prevent hypoglycaemia (if carbohydrates have been ingested, subjects' blood glucose measurement will have to confirm that they are not hypoglycaemic). If hypoglycaemia (blood glucose level ≤3.5 mmol/L [≤ 63 mg/dL] or plasma glucose ≤3.9 mmol/L [≤70 mg/dL]) or more than 20 g of carbohydrates are needed to prevent hypoglycaemia less than 24 hours prior to dosing, the dosing visit can be rescheduled 1 to 7 days later. Each of the dosing visits can only be rescheduled once.

Prior to study treatment dosing, the patient will be connected to the clamp device for continuous glucose monitoring and the start of the baseline run-in period. Variable IV infusion of either glucose (20% dextrose solution) or insulin (insulin glulisine [Apidra]) will be started to reach a target blood glucose level. Once the target blood glucose level is attained and remains stable, with the predose activities as specified in the Schedule of Activities completed, the patient will receive a dose and undergo the clamp procedure proper. More information on the clamp methodology can be found in Section 9.6.

5.1.2. Outpatient Procedure

After completing each period, subjects will resume their previous insulin regimen. The investigator will provide instructions for transition back to a normal insulin regimen. Subjects will return for the second dosing period within a 3- to 15-day interval, during which they will have to perform at least 4-point daily SMPG. The basal insulin will have to be discontinued as described previously.

After completing all study treatment dosing and clamp procedures, subjects will resume their former insulin regimen and SMPG routine. A CRU visit for follow-up or early discontinuation should occur at least 14 days after the last dose of study drug.



Abbreviations: CRU = clinical research unit; ED = early discontinuation; SC = subcutaneous; T1DM = type 1 diabetes mellitus.

Figure ITRR.1. Illustration of study design for Protocol I8B-MC-ITRR.

5.2. Number of Participants

Up to 42 younger adult and 42 elderly subjects may be enrolled to ensure that at least 34 subjects in each age group complete the study.

If subjects drop out of the study before completion of both clamp periods, replacement subjects may be enrolled; the replacement subjects will assume the same treatment sequence as the subjects who dropped out and will complete that treatment sequence in its entirety.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

The use of a crossover design allows each patient to serve as his or her own control, thereby reducing variability. The study is subject- and investigator-blind to minimize potential bias.

A euglycaemic 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).

A population of elderly subjects is selected as changes in the body composition due to aging (such as increased body fat, reduced lean body mass, decreased total body water) may alter the PK profile of insulin lispro in LY900014.

Based on the PK properties of treprostinil ($t_{1/2}$ = approximately 1 hour) and Humalog ($t_{1/2}$ = 0.79 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

Based on previous studies of both insulin lispro (Humalog) and LY900014, the 15-U dose is within the clinical dose range and should provide measurable PK and GD profiles for both study insulins. The safety, PK, and pharmacology of LY900014 at similar doses and with similar formulation composition have been assessed in 2 clinical studies in healthy subjects CCI and in ongoing studies in patients with T1DM using MDI CCI or insulin pump treatment CCI and type 2 diabetes mellitus using MDI CCI In patients with T1DM, the weight-based total daily insulin dose for a large majority of patients is 0.4 to 0.8 U/kg/day of which approximately 50% is delivered as the basal insulin dose and the other 50% is divided among preprandial insulin doses (Herbst and Hirsch 2002; Heller et al. 2009). Therefore, a reasonably high estimate for total daily preprandial insulin dose in T1DM is 0.4 U/kg/day. It is estimated that the lowest body weight for either population would be around 56 kg. Thus, the 15-U dose of LY900014 within this study would delivery approximately a 0.26-U/kg dose and would not exceed this high estimate for the total daily preprandial insulin dose.

A 15-U dose of LY900014 contains CCI of treprostinil in a single SC dose, which is within the range evaluated as safe and tolerated in all previous studies CCI . The PK of treprostinil in LY900014 following SC administration of 15 U of LY900014 was assessed previously in CCI , treprostinil exposure was not detectable for the 15-U dose of LY900014 CCI Based on the treprostinil exposures observed in CCI , treprostinil blood concentrations in this study are expected to be CCI

6. Study Population

Eligibility of subjects for study enrollment 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 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 and/or enrollment:

[1] are male or female subjects with T1DM for at least 1 year. A diagnosis of T1DM is based on medical history with a fasting C-peptide ≤0.30 nmol/L.

[1a] Male subjects:

agree to use an effective method of contraception for the duration of the study and for 1 month following the last dose of the investigational product.

[1b] Female subjects:

women of childbearing potential may participate and include those who test negative for pregnancy before initiation of treatment based on a serum pregnancy test and agree to use 1 highly effective method of contraception or a combination of 2 effective methods of contraception during the study and for 1 month following the last dose of the investigational product.

women of nonchildbearing potential may participate in the study without using adequate contraceptive methods, and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis;
- or postmenopausal, defined as women aged <52 years and being amenorrhoeic for more than 1 year with a serum follicle-stimulating hormone (FSH) level compatible with postmenopausal status or aged ≥52 years and being amenorrhoeic for less than 1 year and with a serum FSH level compatible with postmenopausal status or aged ≥52 years being amenorrhoeic for more than 1 year

[2] are aged 18 to 45 years (both inclusive) (younger adult group) or at least 65 years (elderly group) at the time of screening.

[3] have a body mass index (BMI) of 18.5 to 30.0 kg/m^2, inclusive, at screening.

[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 to allow for glucose infusion and blood sampling procedures as per 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 approved by Lilly and the ethical review board (ERB) governing the site.

[8] have a glycated hemoglobin (HbA_1c) <9.0% at screening.

[9] have had no episodes of severe hypoglycaemia in the last 6 months (see Section 9.4.7.1).

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 or employees of the investigational site/CRU.

[12] are currently enrolled in a clinical trial 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 trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[14] have previously completed or withdrawn from this study.

[15] have known allergies to treprostinil (Remodulin), insulin lispro, insulin glulisine (Apidra), related compounds, or any components of the formulation, or a 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. Elderly patients with clinically significant bradycardia will be excluded.

[17] have a supine blood pressure at screening outside the range of 90 to 140mmHg for systolic or 50 to 95 mmHg for diastolic (1 repeat is allowed) as determined by the investigator, or results with unacceptable deviations that are judged by the investigator to be clinically significant for the population, or have a heart rate outside the range of 50 to 90 beats/minute.

[18] have a history or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine (apart from T1DM), 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 urinary drug screening.

[21] show evidence of an acute infection with fever or infectious disease at the time of study entry.

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

[23] show evidence of hepatitis C and/or positive hepatitis C antibody (the presence of hepatitis C antibodies in the setting of normal liver function tests and a negative hepatitis C polymerase chain reaction are not an exclusion).

[24] show evidence of hepatitis B and/or positive hepatitis B surface antigen (the presence of antibodies to the hepatitis B surface antigen is not an exclusion).

[25] are women who are pregnant or lactating.

[26] have significant lipohypertrophy in the target abdominal injection area as judged by the investigator.

[27] have, except for current regimen of insulin therapy and concomitant medication(s) (for example, antihypertensive medication, lipid-lowering agent, thyroid hormone replacement medication, hormonal contraception, hormonal replacement therapy), regular use of or intended use of any over-the-counter or prescription medications or nutritional supplements that treat hyperglycaemia or insulin resistance or that promote weight loss within 14 days before dosing.

[28] are currently a smoker, used tobacco products on a regular basis in the 6 months before screening, or are intending to smoke during the study period.

[29] are receiving chronic (lasting longer than 14 consecutive days) systemic or inhaled glucocorticoid therapy (excluding topical, intra-articular, and intraocular preparations), or have received such therapy within the 4 weeks before screening.

[30] have donated blood of more than 450 mL or more in the last 3 months or provided any blood donation within the last month before screening.

[31] have a significant history of alcoholism or drug abuse as judged by the investigator or consuming more than 24 g of alcohol per day for men, or more than 12 g of alcohol per day for women (1 unit of alcohol is defined as 10 mL [8 g] of pure alcohol).

[32] 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.

[33] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

[34] have a history of renal impairment (exclusion only if glomerular filtration rate [estimated GFR] <60 mL/minute/1.73 m^2 [GFR is estimated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine equation], or have a serum creatinine level ≥126 µmol/L [male] or ≥111 µmol/L [female]).

[35] have a history of deep vein thrombosis of the leg or repeated episodes of deep leg vein thrombosis in first-degree relatives (parents, siblings, or children) as judged by the investigator.

[36] have proliferative retinopathy or maculopathy and/or severe neuropathy; in particular, autonomic neuropathy as judged by the investigator based on a recent (<1.5 years) ophthalmologic examination.

[37] any significant changes in insulin regimen and/or unstable blood glucose control within the past 3 months prior to screening as assessed by the investigator.

[38] require daily insulin treatment >1.5 U/kg/body weight.

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

In both treatment periods, subjects will fast for at least 8 hours prior to dosing until after the glucose clamp procedure is completed, after which subjects will receive a meal. Water can be consumed freely during this time. If the clamp procedure is completed in less than 10 hours, then the meal should be delayed until the last PK sample has been taken, unless the investigator deems it necessary to administer the meal for safety reasons.

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 will be encouraged to follow their normal diets.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects should refrain from caffeine-containing food/beverages (for example, cola, chocolate drinks, tea, coffee, energy drinks containing methylxanthine [caffeine, theophylline, or theobromine]) for at least 12 hours before each dose and throughout the duration of each CRU visit.

No alcohol will be allowed at least 24 hours before each CRU admission (Day –1) and throughout the duration of each CRU visit (see Additional Exclusion Criterion [31]). Between dosing visits, daily alcohol should not exceed 3 units for males and 1.5 units for females (a unit is defined in Exclusion Criterion [31], Section 6.2).

Smoking (cigars, cigarettes, or pipes) and the use of smokeless tobacco will not be permitted during the study (see Exclusion Criterion [28]).

6.3.3. Activity

Subjects are encouraged to maintain their regular exercise habits; however, subjects engaging in strenuous physical exercise (for example, weightlifting, football, cycling/swimming/running at a level higher than normal) within 48 hours prior to (planned) dosing will be excluded from this study, as judged by the investigator to interfere 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 may be rescreened 1 time. Any further rescreening must be done in consultation with the sponsor. Individuals who still do not meet participation criteria after rescreening (screen failure) may not be rescreened.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of LY900014 administered once by SC injection with insulin lispro administered once by SC injection. Table ITRR.2 shows the treatment regimens.

Table ITRR.2. Treatments Administered

Treatment Name	LY900014	Insulin lispro (Humalog)
Dosage Formulation	100 U/mL	100 U/mL
Dosage Level	15 U	15 U
Treprostinil concentration and approximate treprostinil dose administered	CCI CCI	NA
Route of Administration	SC injection	SC injection

Abbreviation: SC = subcutaneous.

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 trial materials.

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. LY900014 will be supplied by Lilly or its representative, in accordance with current good manufacturing practices and will be supplied with lot numbers. Reference drug will be commercially available insulin lispro (Humalog) supplied by Lilly.

The study insulins will be provided to the site unblinded. CCI [redacted]. An unblinded pharmacist at the site or other site personnel who are unblinded will use the insulin vials provided to prepare the blinded syringes.

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 patient's case report form (CRF). For each patient, the doses will be administered at approximately the same time on Day 1 of each study period.

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

The site of administration of each injection will be recorded. The insulin used in this study will be injected using syringes and vials. Injection sites selected should be about 5 cm from the

umbilicus and the treatment is administered SC. An appropriate size of needle shall be used to ensure all injections are delivered to a consistent target depth into the SC space; if an 8-mm (or greater) needle is used to administer the injection, the skinfold should be pinched. Injection sites will be rotated between the left lower quadrant and right lower quadrant on the anterior abdominal wall during the 2 study periods.

7.3. Blinding

This is a subject- and investigator-blind study. The Lilly clinical pharmacologist/Lilly study team is unblinded.

Emergency codes will be available to the investigator. An unblinded pharmacist or other site personnel is required to prepare the insulin doses for administration. A code, which reveals the treatment group for a specific study subject, may be opened during the study only if the patient's well-being requires knowledge of the patient's treatment assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding a patient's treatment assignment is warranted for medical management of the event. Patient's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical pharmacologist or clinical research physician (CRP) prior to unblinding a study patient's treatment assignment unless this could delay emergency treatment of the patient. If a study patient's treatment assignment is unblinded, Lilly must be notified immediately.

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

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

All insulin products must be stored at the investigative site under refrigerated conditions (between 2°C and 8°C) in a locked and secure place. Insulin must not be frozen.

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

7.6. Treatment Compliance

The study drugs will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Subjects on stable concomitant medication(s) at the time of study entry should continue their regular, unchanged dose throughout the study. Subjects receiving multiple daily insulin injections will discontinue their basal and prandial insulin regimens as described in the Study Design, prior to receiving study treatment (Section 5.1). Similarly, the patient's insulin regimen should resume in between dosing periods and discontinued prior to the next period following the guidance in Section 5.1.

Subjects should not use over-the-counter or prescription medications (other than their current regimen of insulin therapy and concomitant medication(s) [for example, anti-hypertensive medication, lipid-lowering agent, thyroid hormone replacement medication]) or nutritional supplements that affect blood glucose or the body's sensitivity to insulin or that promote weight loss 14 days before dosing (apart from vitamin/mineral supplements, occasional acetaminophen [paracetamol], ibuprofen, or hormonal replacement therapy) or throughout the study (refer to Section 6.2).

Subjects should not be receiving chronic (lasting longer than 14 consecutive days), systemic, or inhaled glucocorticoid therapy (excluding topical, intra-articular, and intraocular preparations), or have received such therapy within the 4 weeks before screening.

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

If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator, and when possible, after consultation with a Lilly clinical pharmacologist. Any additional medication used during the course of the study must be documented.

Any changes in concomitant medications from screening will be recorded upon admission to the CRU.

7.8. Treatment After the End of the Study

Insulin lispro (Humalog) and LY900014 will not be made available from the sponsor to subjects after conclusion of the study. Subjects will resume their previous insulin regimen after the study procedure has been completed.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Subjects who discontinue the investigational product early will have procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

The criteria for enrollment must be followed explicitly. If the investigator site identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor will be notified. If the sponsor identifies a subject who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified.

If the subject was enrolled but did not receive study drug, the subject will be discharged from the study without receiving study drug; if the subject received the single dose of the study drug prior to realizing the subject did not meet enrollment criteria, they will continue to be monitored per protocol.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

- Enrollment in any other clinical trial 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 patient should be discontinued from the study
- Subject Decision
    - the patient requests to be withdrawn from the study
- Participation in the study needs to be stopped for safety reasons in the case of a severe hypoglycaemic episode

Subjects who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

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 (including tolerance limits for timing).

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

Appendix 4 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon merging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the electronic CRF (eCRF). Late collection outside the stipulated time allowances or failure to obtain samples due to clinical issues (such as venous access), technical issues (such as equipment problems), or subject defaulting on a scheduled procedure will not be considered as protocol deviations but the site will still be required to notify the sponsor in writing via a file note.

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.

Investigators must document their review of each laboratory safety report.

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 patient.

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

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 patient to discontinue the investigational product before completing the study. The patient 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 patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. 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 the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device, 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 patient'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 1 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
- events considered significant by the investigator based upon appropriate medical judgment

Study site personnel must alert Lilly, 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 begins after the patient has signed informed consent and has received the 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 patient summary CRF 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 the 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 identifies as related to the investigational product or procedure. US 21 Code of Federal Regulations 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. 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 hypoglycaemia and hypokalemia. Mild episodes of hypoglycaemia usually can 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 hypoglycaemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

9.4. Safety

9.4.1. Physical Examinations

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

9.4.2. Body Weight

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

9.4.3. 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.

9.4.4. Laboratory Tests

Laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

9.4.5. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2) and as clinically indicated.

9.4.6. Electrocardiograms

For each patient, 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 patient receives the first dose of the investigational product should be reported to Lilly, or its designee, as an AE via eCRF.

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities. ECGs must be recorded and reviewed before receiving study treatment. Subjects must be supine for at least 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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

If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the patient can continue in the study. The investigator, or a qualified designee, is responsible for determining if any change in patient 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.

9.4.7. Safety Monitoring

The Lilly clinical pharmacologist 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 clinical pharmacologist or research physician will consult with the functionally independent Global

Patient Safety therapeutic area physician or clinical research scientist when appropriate, and periodically review:

- trends in safety data
- laboratory analytes
- AEs

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.

9.4.7.1. Glucose Monitoring

Hypoglycaemia will be described using the following definitions:

- **Documented hypoglycaemia:**
  - **Symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by plasma glucose ≤70 mg/dL (3.9 mM)
  - **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with plasma glucose ≤70 mg/dL (3.9 mM)
- **Unspecified hypoglycaemia**: an event during which plasma glucose is ≤70 mg/dL (3.9 mM) but no information relative to symptoms of hypoglycaemia was recorded
- **Probable symptomatic hypoglycaemia:** an event during which symptoms indicative of hypoglycaemia are not accompanied by a plasma glucose determination (but that was presumably caused by plasma glucose ≤70 mg/dL [3.9 mM])
- **Severe hypoglycaemia:** an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status, and cannot assist in their care, is semiconscious or unconscious, or experiences coma with or without seizures, and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal level is considered sufficient evidence that the event is induced by a low plasma glucose concentration (≤70 mg/dL [3.9 mM])
- **Nocturnal hypoglycaemia:** any hypoglycaemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycaemia) that occurs between bedtime and waking
- **Relative hypoglycaemia:** an event during which typical symptoms of hypoglycaemia, that do not require the assistance of another person, are accompanied by plasma glucose >70 mg/dL (3.9 mM), but these levels may be quickly approaching the 70 mg/dL (3.9 mM) threshold
- **Overall (or total) hypoglycaemia:** This optional category combines all cases of hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, the event is only counted once in this category

The goal of the euglycaemic clamp is to maintain blood glucose concentrations at normoglycaemic levels close to a pre-defined target. Therefore, plasma glucose concentrations

below 70 mg/dL (equivalent to blood glucose 63 mg/dL) will not routinely be recorded as hypoglycaemic events during the glucose clamp procedure. However, at the discretion of the investigator, decrease in glucose concentrations may be recorded as a hypoglycaemic event based on clinical concern, or related to technical issues resulting in hypoglycaemia.

9.4.7.1.1. Severe Hypoglycaemia

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

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

9.4.8. 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).

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

Additional assessments will be performed until resolution, as judged necessary by the investigator.

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

An injection-site reaction should be recorded as either an AE or an SAE according to respective definitions/criteria.

9.4.8.1. Pain Measurements Using the Visual Analog Scale

Pain measurements will be assessed using the electronic version of the 100-mm validated visual analog scale (VAS) (or electronic VAS [eVAS]) for pain. The VAS is a well validated tool (Williamson and Hoggart 2005) to assess injection-site pain.

The eVAS (van Duinen et al. 2008) is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually “no pain” and “worst imaginable pain.” The patient will be asked to mark the 100-mm line electronically to indicate pain intensity associated with each injection on a scale of 0 (no pain) to 100 mm (worst imaginable pain) according to the Study Schedule and as clinically indicated.

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 wellbeing of the subject. Analgesia can be prescribed in response to pain and must be documented in the concomitant medication section of the CRF.

9.4.9. 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 by a validated assay designed to detect antidrug antibodies in the presence of insulin lispro.

Serum from the blood sample will be divided into 3 aliquots; the first aliquot is used for initial testing and the remaining aliquots will be stored at -70°C, and retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the study insulins. Any samples remaining after 15 years will be destroyed.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 2.5 mL each will be collected to determine serum concentrations of insulin lispro, and samples of approximately 2.0 mL each will be collected to determine plasma concentrations of treprostinil. 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

Serum concentrations of insulin lispro will be measured using a CCI [redacted] specific for insulin lispro at a laboratory approved by the sponsor. Plasma concentrations of treprostinil will be measured using a validated CCI [redacted] at a laboratory approved by the sponsor. Samples will be retained for a maximum of 1 year after the last subject visit. During this time, plasma and serum remaining may be used for other exploratory analyses on insulin lispro or treprostinil.

9.6. Glucodynamics (Euglycaemic Glucose Clamp)

The aim of the euglycaemic 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.

Subjects with T1DM will participate in euglycaemic glucose clamps on 2 separate visits. All glucose clamp procedures will be performed after an overnight fast of at least 8 hours.

Approximately 1-6 hours before the planned administration of study drug, subjects will be connected to the clamp device for continuous blood glucose monitoring and receive a variable IV infusion of either insulin glulisine or glucose to obtain a steady blood glucose clamp target of 100mg/dL (±20%) (5.5 [±1.1] mmol/L). The target blood glucose level of 5.5 mmol/L (100 mg/dL)±20% (upper and lower limits included) must be kept at -60 to -30 minutes before trial product administration, followed by a target blood glucose level of 5.5 mmol/L (100

mg/dL)±10% (upper and lower limits included) the last 30 minutes prior to trial product administration without any glucose infusion. The intravenous insulin infusion (if any) is lowered as much as possible to keep the BG concentrations at the target without having to infuse glucose. The insulin infusion is tapered off and should be stopped 10 minutes prior to dosing. Baseline is defined as the mean of blood glucose concentrations at –6, –4, and –2 minutes before trial product administration as measured using CCI , and the onset of action occurs when blood glucose drops to 0.3 mmol/L (5 mg/dL) from baseline. If there are no stable BG measurements using CCI in the last minutes before intended dosing, dosing should be postponed and the run-in period will be prolonged. If the target blood glucose level cannot be established before 1400 hours, the visit will be terminated and the subject may be rescheduled for a new dosing visit 1 to 7 days later. After the onset of action has been reached, a variable IV glucose infusion will be initiated in order to keep BG constant at the target level (5.5 mmol/L; 100 mg/dL). The GIR necessary to keep the BG concentration at the target level will be recorded every minute throughout the glucose clamp. Frequently or at least every 30 minutes throughout the glucose clamp, BG measurements for safety will be performed using CCI .

The clamp procedure will continue for up to 10 hours after dose or until after blood glucose concentrations increased to >200 mg/dL (11.1 mmol/L) without any glucose being administered for at least 30 minutes, whichever is earlier.

At the end of the clamp procedure, the patient will receive a medical assessment, and be given a meal along with their prandial insulin treatment. Their basal insulin regimen may be restarted accordingly, albeit subjected to the stopping guidance as described in Section 5.1, prior to the next dosing visit, if applicable.

The sample(s) will be stored for up to a maximum of 1 year after the last patient visit for the study at a facility selected by the sponsor.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, 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 response to LY900014 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 patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs/institutional review boards impose shorter time limits, for the study at a facility selected by Lilly or its designee. 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. Biomarkers

Not applicable for this study.

9.9. Health Economics

Not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 42 younger adult and 42 elderly subjects may be enrolled to ensure that at least 34 subjects in each age group complete the study. Thirty-four completing subjects in each age group will provide approximately 95%% power to demonstrate a 40% increase in the insulin lispro area under the plasma concentration-time curve from time zero to 30 minutes ($AUC_{[0\text{-}30min]}$) between LY900014 and Humalog within each age group. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The variability was estimated by analyzing a Lilly internal study that showed a log-scale standard deviation of within-subject difference in $AUC_{(0\text{-}30min)}$ of 0.5. Analysis of internal data showed a log-scale standard deviation of within-subject difference in time to early half-maximal plasma concentration (early 50% t_{max}) of 0.5, which provides approximately 95% power to show a 30% reduction in early 50% t_{max}, testing with an alpha level of 0.05 and a 2-sided CI.

In addition, the study is adequately powered to evaluate the GD parameters within each age group. There is approximately 80% power to detect a 20% decrease in both time to onset of insulin action (T_{onset}) and time to half-maximal GIR before TR_{max} (early 50% TR_{max}), and approximately 85% power to detect at least a 40% increase in total amount of glucose infused over 30 minutes ($Gtot_{[0\text{-}30min]}$) and total amount of glucose infused over 1 hour ($Gtot_{[0\text{-}1h]}$).

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly.

The primary statistical analyses for PK will be conducted on those subjects who receive at least 1 dose of study drug and have measurable insulin lispro concentrations. The primary statistical analysis for GD will be conducted on those subjects who complete at least 1 clamp procedure. Supportive analyses will be done on the key parameters for the subjects who complete all treatment periods with evaluable data. Safety analyses will be conducted for all enrolled subjects who receive at least 1 dose of study drug, whether or not they complete all protocol requirements.

Any change in 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.

Summary statistics (including number of subjects, mean, standard deviation or standard error, minimum, and maximum) will be presented for continuous variables. A linear mixed-effect model will be used for continuous variables unless otherwise stated in the below subsections. The primary comparison between LY900014 and insulin lispro for each age group will be performed using the model that includes treatment, sequence, and period as fixed effects, and subject within sequence as a random effect. Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided.

An exploratory analysis on the interaction between treatment and age group will be assessed using data from both age groups by a model similar to that for each age group, with the addition of age group and the interaction of treatment by age group as fixed effects. This test will be used to compare whether the LY900014 versus insulin lispro treatment effect is similar between the elderly and younger adult groups.

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 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 Dictionary for Regulatory Activities.

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 and vital signs, as well as evaluation of injection-site reactions. The parameters will be listed, and may be summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

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

The primary study assessment will be the intensity of pain at each injection site immediately after the injection (time 0) 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 separately by age group, using the statistical model that includes treatment, sequence, and period as fixed effects and subject within sequence as a random effect. It is possible that VAS scores will be zero; 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.

A descriptive summary will be provided for the following categories of scores: 0, 1-10, 11-20, 21-30, 31-40, etc. up to the maximum category by treatment for each time point.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Subjects who receive at least 1 dose of study drug and have measurable insulin lispro concentrations will be included in the PK analysis dataset.

PK analyses will be conducted using standard noncompartmental methods of analysis using [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 early 50% t_{max}, time to late half-maximal plasma concentration (late 50% t_{max}), maximum observed concentration (C_{max}), t_{max}, $t_{1/2}$, and area under the plasma concentration-time curve from time zero to the last recorded time, $AUC_{(0\text{-}30min)}$, area under the plasma concentration-time curve from time zero to 1 hour, area under the plasma concentration-time curve from time zero to 10 hours, and area under the plasma concentration-time curve from time zero to infinity. Other parameters may be calculated as deemed appropriate. Additional partial area under the plasma concentration-time curves (AUCs) may be computed as necessary. The primary insulin lispro PK parameters for faster insulin lispro absorption analysis are early 50% t_{max} and $AUC_{(0\text{-}30min)}$.

Given the predicted low systemic concentrations of treprostinil, the PK analysis of treprostinil from the LY900014 dosing will be conducted using the available data. The primary analysis of the treprostinil concentrations will be focused on assessing time to maximum concentration (t_{max}) and C_{max}.

Although attempts will be made to adhere to the scheduled collection times (Section 2), 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 using summary statistics.

10.3.2.2. Pharmacokinetic Statistical Inference

Log-transformed C_{max} and AUC estimates for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog (reference), and their corresponding 95% CIs for each age group using the statistical model that includes treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters (early 50% t_{max}, late 50% t_{max}, t_{max}, and $t_{1/2}$). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow and Liu 2009).

As treprostinil plasma concentrations after administration of LY900014 are expected to be very low, a descriptive statistical analysis may be conducted if sufficient data are available for this analysis.

10.3.3. Glucodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

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

A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and age group using S-PLUS software (version 8.2). The fitted data for each subject will be used to calculate the following GD parameters: T_{onset}, maximum GIR (R_{max}), time to R_{max} (TR_{max}), early 50% TR_{max}, time to half-maximal GIR after TR_{max} (late 50% TR_{max}), total amount of glucose infused (Gtot), $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1h)}$, and total amount of glucose infused over 10 hours ($Gtot_{[0\text{-}10h]}$). Additional partial glucose AUCs, such as total amount of glucose infused over 2 hours, may be computed as necessary. The values of these GD parameters will be summarized by treatment group and age group through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated. The primary GD parameters for analysis are early 50% TR_{max}, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1h)}$, and T_{onset}.

10.3.3.2. Glucodynamic Statistical Inference

The statistical model will be the same as the model used for the analysis of the PK parameters. The variables will be log-transformed prior to analysis and will include R_{max}, Gtot, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1h)}$, and $Gtot_{(0\text{-}10h)}$. For GD parameters that have at least 1 subject with a value equal to zero, a value equal to the smallest non-zero observed GD value for that parameter divided by 2 will be added to all values, and the analysis of the log-transformed data will be performed.

Similarly to the PK time parameters, the GD time parameters (T_{onset}, TR_{max}, early 50% TR_{max}, and late 50% TR_{max}) will be evaluated without log transformation. Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

10.3.4. Evaluation of Immunogenicity

The immunogenicity data will be listed. The relationship between treatment-emergent antidrug antibodies and AEs will be evaluated. The relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may also be evaluated.

10.3.5. Interim Analyses

An interim analysis may be conducted after all subjects in the younger adult group have completed the study to analyze the safety, PK and GD data in order to support regulatory submission. The Lilly clinical pharmacologist/Lilly study team is unblinded. The individuals and unblinded data are as specified in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

Data may be analyzed while the trial is ongoing, but no changes to the study design are planned. The results may help Lilly expedite final delivery and to enable planning of future studies. An assessment committee will not be formed.

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.
AUC	area under the plasma concentration-time curve
$AUC_{(0\text{-}30min)}$	AUC from time zero to 30 minutes
Blinding	A procedure in which one or more parties to the trial 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. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed concentration
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 trial-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.
CRF	case report form
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
CSII	continuous subcutaneous insulin infusion
early 50% t_{max}	time to early half-maximal plasma concentration
early 50% TR_{max}	time to half-maximal GIR before TR_{max}

ECG	Electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
eVAS	electronic visual analog scale
FDA	Food and Drug Administration
GCP	good clinical practice
GD	glucodynamic(s)
GFR	glomerular filtration rate
GIR	glucose infusion rate
Gtot	total amount of glucose infused
$Gtot_{(0\text{-}30min)}$	total amount of glucose infused over 30 minutes
$Gtot_{(0\text{-}1h)}$	total amount of glucose infused over 1 hour
$Gtot_{(0\text{-}10h)}$	total amount of glucose infused over 10 hours
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial 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.
interim analysis	An interim analysis is an analysis of clinical trial 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 trial, 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 trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	Intravenous
late 50% t_{max}	time to late half-maximal plasma concentration
late 50% TR_{max}	time to half-maximal GIR after TR_{max}
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 trial.
LOESS	locally weighted scatterplot smoothing
NPH	neutral protamine Hagedorn
PK	pharmacokinetic(s)
R_{max}	maximum GIR
SAE	serious adverse event
SC	subcutaneous/subcutaneously
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 trial.
SMPG	self-monitoring plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
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 to maximum concentration
T_{onset}	time to onset of insulin action
TR_{max}	time to R_{max}
US	United States
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]	Clinical chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	C-peptide, fasting[b]
Absolute counts of	Glucose, fasting
Neutrophils	Blood urea nitrogen (BUN)
Lymphocytes	Uric acid
Monocytes	Total cholesterol
Eosinophils	Total protein
Basophils	Albumin
Platelets	Total bilirubin
HbA1c[b]	Alkaline phosphatase (ALP)
Urinalysis[a]	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	Creatinine
Protein	Gamma-glutamyl transferase (GGT)
Glucose	
Ketones	Ethanol breath test[b,c]
Bilirubin	Urine drug screen[b,c]
Urobilinogen	Hepatitis B surface antigen[b]
Erythrocytes/hemoglobin	Hepatitis C antibody[b]
Nitrite	HIV[b]
Leucocytes	Pregnancy test[e]
Microscopy[d]	FSH[b]
Coagulation[b]	
Prothrombin time (PT)	
Partial thromboplastin time (PTT)	

Abbreviations: FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

[a] Results will be validated by the local laboratory at the time of initial testing.

[b] Performed at screening only. Hepatitis B and HIV tests may be waived if they have been performed within the 6 months before screening (with reports available for review). FSH test only applicable at screening in menopausal women, if necessary.

[c] Urine drug screen and ethanol breath test may be repeated prior to admission to the clinical research unit. Urine drug screen: amphetamine, cannabis, cocaine, barbiturates, methadone, benzodiazepines, tricyclic antidepressants, methamphetamine, opiates, and phencyclidine.

[d] If clinically indicated, at investigator's discretion.

[e] All females: serum pregnancy test at screening; urine pregnancy test for all other visits.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the patient understands the potential risks and benefits of participating in the study.
- ensuring that informed consent is given by each patient 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 patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonization (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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences 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 CRFs, 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 CRF 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 patient 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.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, 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 judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. 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. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I8B-MC-ITRR Sampling Summary

Purpose	Maximum Blood Volume Per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	11	1	11
Clinical laboratory tests[a]	9	2	18
Pharmacokinetics – insulin lispro	2.5	50	125
Pharmacokinetics - treprostinil	2.0	8	16
Clamp device sampling for glucose[b]	N/A	N/A	64
Immunogenicity	5	3	15
Pharmacogenetics	10	1	10
Blood glucose during clamp period (Super GL)[c]	0.3	128	38.4
Total	-	-	297.4
Total for clinical purposes [rounded up to nearest 10 mL]			300

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

[b] Clamp device sampling: 6 hour run-in plus 10 hour clamp = 16 hours x 2 periods = 32 hours x 2 mL/hour = 64 mL.

[c] Blood glucose during clamp period (Super GL): 6 hour run-in plus 10 hour clamp = 16 hours x 2 periods = 32 hours x up to 4 samples/hour = 128 blood samples x 0.3 mL/blood sample = 38.4 mL

Appendix 5. Protocol Amendment I8B-MC-ITRR(c) Summary Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro Following Single Dose Administration in Elderly and Younger Adults with Type 1 Diabetes Mellitus

Overview

Protocol I8B-MC-ITRR(b), Pharmacokinetics and Glucodynamics of LY900014 Compared to Insulin Lispro Following Single Dose Administration in Elderly and Younger Adults with Type 1 Diabetes Mellitus, has been amended. The new protocol is indicated by Amendment (c) 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:

- Text in Sections 1, 5.2, and 10.3 has been amended to indicate an increase in sample size in each group such that up to 6 additional young adults and 6 additional elderly subjects may be enrolled. This change is intended to ensure there is sufficient statistical power to make robust comparisons between the study groups. As such, estimations of statistical power have been adjusted throughout and confidence intervals have been increased to 95% two-sided, with an alpha level of 0.05.
- Text in Sections 1 and 10.3 has been amended to indicate that all enrolled subjects who received at least 1 dose of the study drug will be included in safety analysis, whether or not they completed all protocol requirements.
- In Sections 1 and 10, descriptions of the statistical PK and PD analyses have been updated to be consistent with the latest approved Statistical Analysis Plan, as well as analyses conducted for other studies in this programme. In particular, PK and GD time parameters such as t_{max} will be evaluated without log transformation, and there will be no sensitivity analysis for GD parameters.
- Text in Sections 1 and 10.3.4 has been updated to clarify that immunogenicity data in addition to TEADA will be evaluated.
- The Schedule of Activities (Section 2) has been amended to indicate that 2 of the procedures (clinical laboratory tests and the collection of immunogenicity samples) will be performed prior to dosing but, for practical reasons, not necessarily within the previously indicated 2-hour time window.
- Text in Section 7.2.1 has been amended to instruct that subjects' skinfold should be pinched if needles sized 8 mm or greater are used.

- In Section 9.4.7.1, the term “total hypoglycaemia” has been replaced with “overall (or total) hypoglycaemia” to keep consistency with the terminology used in external publications.
- Text in Section 10.3.1.2.1 has been adjusted to clarify that injection-site pain scores will be analyzed for each age group separately.

Revised Protocol Sections

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

1. Protocol Synopsis

Number of Subjects: Up to 42~~36~~ younger adult (aged 18 to 45 years inclusive) and 42 ~~36~~ elderly (aged ≥65 years) subjects may be enrolled to ensure that at least 34 ~~28~~ subjects in each age group complete the study.

Statistical Analysis: The primary statistical analyses for PK will be conducted on subjects who receive at least 1 dose of study drug and have measurable insulin lispro concentrations. The primary statistical analysis for GD will be conducted on those subjects who complete at least 1 clamp procedure. Supportive analyses will be done on the key parameters for the subjects who complete all treatment periods with evaluable data. Safety analyses will be conducted for all enrolled subjects who received at least 1 dose of study drug, whether or not they completed all protocol requirements.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided.

Pharmacokinetics:

Log-transformed ~~time to early half-maximal plasma concentration (early 50% tmax), time to late half-maximal plasma concentration (late 50% tmax), time to maximum concentration (tmax),~~ maximum observed concentration (C_{max}~~max~~), clearance, and area under the plasma concentration-time curve estimates for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog (reference), and their corresponding 95% ~~90% confidence intervals (~~CIs~~)~~ for each age group using the statistical model that includes treatment, sequence, and period as fixed effects and subject within sequence as a random effect. The same model without log transformation will be used for time to early half-maximal plasma concentration (early 50% t_{max}~~max~~), time to late half-maximal plasma concentration (late 50% t_{max}~~max~~), and time to maximum concentration (t_{max}~~max~~) to estimate least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for each age group. The treatment ratios and the corresponding 95% CIs for these time parameters will be calculated using Fieller's theorem. ~~For the primary inference, LY900014 will be concluded to have a significantly faster PK action compared to Humalog (reference) if the upper confidence bound of the 2-sided 90% CI of the ratio of geometric means of early 50% tmax is less than 1, or if the lower confidence bound of the 2-sided 90% CI of the ratio of geometric means of area under the plasma concentration-time curve from time zero to 30 minutes is greater than 1.~~

Glucodynamics:

The GD statistical model will be similar to the model used for the analysis of the PK parameters. The variables of ~~will be log-transformed prior to analysis and will include time to onset of insulin action (T_{onset}),~~ maximum GIR (R_{max}), ~~time to R_{max} (TR_{max}), time to half-maximal GIR before TR_{max} (early 50% TR_{max}), time to half-maximal GIR after TR_{max} (late 50% TR_{max}),~~ total amount of glucose infused (Gtot), total amount of glucose infused over 30

minutes ($Gtot_{(0\text{-}30min)}$), total amount of glucose infused over 1 hour ($Gtot_{(0\text{-}1h)}$), and total amount of glucose infused over 10 hours ($Gtot_{[0\text{-}10h]}$) will be log transformed ~~log transformed~~ prior to analysis. The time variables including time to onset of insulin action (T_{onset}~~onset~~), time to R_{max} (TR_{max}), time to half-maximal GIR before TR_{max} (early 50% ~~TR~~TR_{max}), and time to half-maximal GIR after TR_{max} (late 50% ~~TR~~TR_{max}) will be analyzed using the same model without log transformation to estimate least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs. The treatment ratios and the corresponding 95% CIs for these time parameters will be calculated using Fieller's t~~T~~heorem. ~~If subjects have a GD parameter with a value equal to zero, then a nonparametric analysis will be used instead~~.

Immunogenicity:

~~Treatment-emergent antidrug antibodies (TEADAs)~~ The immunogenicity data will be listed. The relationship between treatment-emergent antidrug antibodies and AEs will be evaluated. The relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may also be evaluated.

2. Schedule of Activities

Procedures	Screening	Euglycaemic Clamp Procedure Periods 1 and 2		FU/ED[a]	Instructions/Comments
	Up to Day -28	Day -1	Day 1		
Clinical laboratory tests	X		Predose for Period 1 only ~~(up to 2 hours before dosing)~~	X	Fasting laboratory test for screening, Period 1, and FU. To monitor patient safety, additional tests may be performed at the discretion of the investigator, as needed throughout the study.
Immunogenicity sample			Predose for Period 1 and Period 2	X	~~Predose up to 2 hours before dosing~~

5.2 Number of Participants

Up to 42~~36~~ younger adult and 42 ~~36~~ elderly subjects may be enrolled to ensure that at least 34 ~~28~~ subjects in each age group complete the study.

7.2.1 Selection and Timing of Doses

The site of administration of each injection will be recorded. The insulin used in this study will be injected using syringes and vials. Injection sites selected should be about 5 cm from the umbilicus and the treatment is administered SC ~~with the needle applied at about 90~~°. An appropriate size of needle shall be used to ensure all injections are delivered to a consistent target depth into the SC space; ~~without pinching the skinfold. If~~ if an 8-mm (or greater) ~~insulin syringes are~~ needle is used to administer the injection, the skinfold needs to be pinched. ~~An appropriate size of needle shall be used to ensure all injections are delivered to a consistent target depth into the SC space.~~ Injection~~s~~ sites will be rotated between the left lower quadrant and right lower quadrant on the anterior abdominal wall during the 2 study periods.

9.4.7.1 Glucose Monitoring

- **Overall (or ~~Total~~ total) hypoglycaemia:** This optional category combines all cases of hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, the event is only counted once in this category

10.1 Sample Size Determination

Up to 42~~36~~ younger adult and 42~~36~~ elderly subjects may be enrolled to ensure that at least 34 ~~28~~ subjects in each age group complete the study. Thirty-four ~~Twenty-eight~~completing subjects in each age group will provide approximately 95% power to demonstrate a 40% increase in the insulin lispro area under the plasma concentration-time curve from time zero to 30 minutes ($AUC_{[0\text{-}30min]}$) between LY900014 and Humalog within each age group. Testing will be done at an alpha level of 0.05~~0.1~~ with a 2-sided confidence interval (CI). The variability was estimated by analyzing a Lilly internal study that showed a log-scale standard deviation of within-subject difference in $AUC_{(0\text{-}30min)}$ of 0.5. Analysis of internal data showed a log-scale standard deviation of within-subject difference in time to early half-maximal plasma concentration (early 50% t_{max}) of 0.5, which provides approximately 95% power to show a 30% reduction in early 50% t_{max}, testing with an alpha level of 0.05~~0.1~~ and a 2-sided CI.

In addition, the study is adequately powered to evaluate the GD parameters within each age group. There is approximately 80% power to detect a 20% decrease in both time to onset of insulin action (T_{onset}) and time to half-maximal GIR before TR_{max} (early 50% TR_{max}), and approximately ~~90~~85% power to detect at least a 40% increase in total amount of glucose infused over 30 minutes ($Gtot_{[0\text{-}30min]}$) and total amount of glucose infused over 1 hour ($Gtot_{[0\text{-}1h]}$).

10.3 Statistical Analyses

The primary statistical analyses for PK will be conducted on those subjects who receive at least 1 dose of study drug and have measurable insulin lispro concentrations. The primary statistical analysis for GD will be conducted on those subjects who complete at least 1 clamp procedure. Supportive analyses will be done on the key parameters for the subjects who complete all treatment periods with evaluable data. Safety analyses will be conducted for all enrolled subjects who receive at least 1 dose of study drug, whether or not they complete all protocol requirements.

Summary statistics (including number of subjects, mean, standard deviation or standard error, minimum, and maximum) will be presented for continuous variables. A linear mixed-effect model will be used for continuous variables unless otherwise stated in the below subsections. The primary comparison between LY900014 and insulin lispro for each age group will be performed using the model that includes treatment, sequence, and period as fixed effects, and subject within sequence as a random effect. Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided.

10.3.1.2.1 Statistical Evaluation of the Intensity of Injection-Site Pain

A mixed-effect model will be used to analyze the time 0 (immediately after dosing) data separately by age group, using the statistical model that includes treatment, sequence, ~~age group~~

~~(if applicable), the 2-way interaction between treatment and age group (will be included only when age group is included in the model),~~ 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 zero; 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.

10.3.2.2 Pharmacokinetic Statistical Inference

Log-transformed ~~early 50% t_{max}, late 50% t_{max}, t_{max},~~ C_{max}, ~~$t_{1/2}$~~ and AUC estimates for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog (reference), and their corresponding 95%~~90%~~ CIs for each age group using the statistical model that includes treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters (early 50% t_{max}, late 50% t_{max}, t_{max}, and $t_{1/2}$). Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow and Liu 2009).

~~For the primary inference, LY900014 will be concluded to have a significantly faster PK action compared to insulin lispro (Humalog) if the upper confidence bound of the 2-sided 90% CI of the ratio of geometric means of early 50% t_{max} is less than 1, or if the lower confidence bound of the 2-sided 90% CI of the ratio of geometric means of $AUC_{(0\text{-}30min)}$ is greater than 1.If model assumptions are severely violated for the time parameters, early 50% t_{max}, late 50% t_{max}, and t_{max} will be analyzed using the Wilcoxon signed-rank test. The difference in medians between LY900014 and insulin lispro and the 90% CIs for the difference will be presented.~~

10.3.3.2 Glucodynamic Statistical Inference

The statistical model will be the same as the model used for the analysis of the PK parameters. The variables will be log-transformed prior to analysis and will include R_{max}, Gtot, $Gtot_{(0\text{-}30min)}$, $Gtot_{(0\text{-}1h)}$, and $Gtot_{(0\text{-}10h)}$. For GD parameters that have at least 1 subject with a value equal to zero, a value equal to the smallest non-zero observed GD value for that parameter divided by 2 will be added to all values, and the analysis of the log-transformed data will be performed. ~~In addition, as a sensitivity analysis, a nonparametric analysis will be performed for that parameter.~~

Similarly to the PK time parameters, ~~The~~ the GD time parameters (T_{onset}, TR_{max}, early 50% TR_{max}, and late 50% TR_{max}) will be evaluated without log transformation ~~using a linear mixed-effects model assuming that model assumptions are satisfied with treatment, sequence, and period as fixed effects, and subject within sequence as a random effect~~. Least-squares means, treatment differences in least-squares means, and the corresponding 95% CIs for the treatment differences will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem. ~~Fieller's Theorem may be applied to calculate the CI of treatment comparison ratio.~~

10.3.4 Evaluation of Immunogenicity

~~Treatment-emergent antidrug antibodies (TEADAs)~~The immunogenicity data will be listed. The relationship between treatment-emergent antidrug antibodies and AEs will be evaluated. The relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may also be evaluated.

11. References

Chow SC, Liu JP. Design and analysis of bioavailability and bioequivalence studies. 3rd ed. Florida: Taylor and Francis Group, LLC; 2009:p88-90.

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