Protocol I8B-MC-ITSH

A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 and Humalog across Different Subcutaneous Doses in Healthy Subjects

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LY900014

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly on date provided below.

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1. Protocol Synopsis

Title of Study:
A study to evaluate the pharmacokinetics and glucodynamics of LY900014 and Humalog across different subcutaneous doses in healthy subjects.

Rationale:
In clinical practice, patients with diabetes on insulin therapy will inject their prandial insulins at a range of individualised doses, which may or may not influence the absorption pharmacokinetics (PK), as well as, the glucodynamic (GD) effect. The primary objective of this study is to evaluate the PK and GD effects across 3 dose levels after administration of the commercial formulation of LY900014 in comparison to after administration of Humalog. It will also assess the dose proportionality of insulin lispro PK and GD after administration of the commercial formulation of LY900014.

Objectives/Endpoints:

Objectives	**Endpoints**
Primary To evaluate the insulin lispro PK following subcutaneous (SC) doses of LY900014 compared to Humalog (at doses of 7, 15, and 30 U) in healthy subjects.	Time to early half-maximal plasma concentration (early 50% t_{max}) and area under the concentration versus time curve (AUC) from time zero to 30 minutes
Secondary 1. To evaluate the dose proportionality of the 3 dose levels of LY900014 as assessed by insulin PK and GD measures.	1a. PK: AUC from time zero to 10 hours (AUC[0-10h]), AUC from time zero to infinity (AUC[0-∞]), and maximum observed drug concentration (C_{max}) 1b. GD: Total amount of glucose infused (G_{tot}) and maximum glucose infusion rate (R_{max})
2. To evaluate the GD of LY900014 compared to Humalog following SC doses of 7, 15, and 30 U in healthy subjects using a euglycaemic clamp procedure.	2. Time to half-maximal GIR before tR_{max} (early 50% tR_{max}), G_{tot} over 30 minutes (G_{tot}[0-30min]), G_{tot} over 1 hour (G_{tot}([0-1h]), and time to onset of insulin action (T_{onset})
3. To evaluate the tolerability of LY900014 in healthy subjects.	3. Adverse events (AEs) and injection-site reactions

Summary of Study Design:

Study I8B-MC-ITSH is a Phase 1, randomised, subject- and investigator-blind, 6-period complete crossover study in up to 42 healthy subjects to evaluate the PK and GD characteristics of LY900014 doses in comparison to Humalog at doses of 7, 15, and 30 U.

Treatment Arms and Planned Duration for an Individual Subject:
Subjects will be randomised to 1 of 6 treatment sequences to assess different doses of LY900014 (7, 15, and 30 U) and Humalog (7, 15, and 30 U). The study will include a 28-day screening period, followed by 6 study periods, with

a wash-out period of at least 3 days between each study period. The follow-up visit will take place at least 14 days after the last dose.

Number of Subjects:
Up to 42 healthy men and women may be enrolled to target approximately 34 subjects to complete.

Statistical Analysis:

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:

Safety analyses will be conducted for all enrolled subjects, whether or not they complete all protocol requirements. All investigational product and protocol-procedure AEs will be listed, and if the frequency of events allows, safety data will be summarised using descriptive methodology. 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 summarised using standard descriptive statistics.

Pharmacokinetics:

Pharmacokinetic analyses will be conducted using standard noncompartmental methods of analysis. Pharmacokinetic parameters will be assessed using free serum insulin lispro.

Log-transformed AUC estimates and C_{max} for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of geometric means between LY900014 and Humalog for each dose level, and their corresponding 95% CIs using the mixed-effects model that includes treatment, dose level, dose level-by-treatment interaction, and period as fixed effects and subject as a random effect.

The same model without log transformation will be used for the analysis of the PK time parameters (time to early half-maximal plasma concentration [early 50% t_{max}], time to late half-maximal plasma concentration [late 50% tmax], time to maximum observed drug concentration [t_{max}], and half-life associated with the terminal rate constant in noncompartmental analysis [$t_{1/2}$]). Least-squares means (LSmeans), treatment differences in LSmeans, and the corresponding 95% confidence intervals (CIs) for the treatment differences for each dose level will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The analyses described above will also be performed on the population of subjects who completed and had evaluable PK data for all study periods

The degree of dose proportionality for the insulin lispro in LY900014 will be assessed by fitting the power model to both AUC (AUC[0-10h], and AUC[0-∞]) and C_{max} versus dose for each dose level of LY900014. The estimated ratio of dose-normalised geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. In addition, the slope and its 95% CIs and the geometric LSmeans for each dose level tested will be produced. In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated. Log-transformed C_{max} and AUC LSmeans, and 95% CI estimates for each dose will be back-transformed to provide the geometric means and the corresponding 95% CIs.

The analyses will also be performed using the subset of the subjects who complete all treatment periods with evaluable data.

Glucodynamics:

Glucodynamic assessments will be determined from the glucose clamp procedure, where the glucose infusion rate (GIR) over time will be used as a measure of insulin effect. Glucodynamic analyses will be conducted on those patients who complete at least 1 clamp procedure. A locally weighted scatterplot smoothing function will be applied to all individual GIR versus time profiles in each treatment group and/or period. The fitted data for each patient will be used to calculate the GD parameters.

The GD statistical model will be the same as the model used for the analysis of the PK parameters. The following variables will be log transformed prior to analysis: R_{max}, G_{tot}, G_{tot}(0-30min), G_{tot}(0-1h), and G_{tot} over 10 hours.

The same model without log transformation will be used for the analysis of the GD time parameters (T_{onset}, time to maximum GIR [tR_{max}], early 50% tR_{max}, time to half-maximal GIR after tR_{max}). Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences for each dose level will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The degree of dose proportionality for the GD of LY900014 will be assessed by fitting the power model to G_{tot} and R_{max} parameters. The estimated ratio of dose-normalised geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. In addition, the slope and its 95% CIs and the geometric LSmeans for each dose level tested will be produced. In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated. Log-transformed G_{tot} and R_{max} LSmeans, and 95% CI estimates for each dose will be back transformed to provide the geometric means and the corresponding 95% CIs. The degree of dose proportionality in GD following administration of LY900014 will be assessed by fitting the power model to G_{tot} and R_{max} versus dose for each dose level of LY900014.

Pharmacokinetics and GD analyses will also be performed using the subset of the subjects who complete all treatment periods with evaluable data.

2. Schedule of Activities

Study Schedule for Protocol I8B-MC-ITSH

Procedures	Screening	Euglycaemic Clamp Procedure Periods 1 to 6		FU/ ED[a]	Comments
	Up to Day -28	Day -1	Day 1		
Informed consent	X				Must occur before screening procedures. Screening procedures should take place no later than 28 days after signing the informed consent.
Admission to CRU		X			Enrolment will occur on the first admission.
Overnight fast	X	X			Subjects are expected to fast for approximately 8 hours before screening, and at least 8 hours starting from the evening before each dose until the end of the glucose clamp procedure.
Weight	X	X			Day -1 weight for Period 1 only.
Height	X				
Hip and waist circumference		X			Period 1 only. Record the average of triplicate measurements.
Physical examination/ Medical assessment[b]	X		Predose and before discharge from CRU for each period	X	Full physical examination and medical history at screening. Thereafter, medical review and targeted examination, as appropriate and as deemed necessary by the investigator.
Vital signs (supine): blood pressure and pulse rate[b]	X		Predose and after the end of clamp procedure	X	
12-Lead ECG[b]	X		Predose and after the end of clamp procedure	X	Single ECGs to be collected for safety.
Clinical laboratory tests[b]	X		Predose of Period 1 only	X	Results not required prior to first dosing.
Pregnancy test/urine drug screen/alcohol breath test	X	X		X	Pregnancy test for female subjects of childbearing potential only. Serum pregnancy test at screening. Urine pregnancy test for all other visits. Alcohol breath test and drug screen may be omitted at follow up.
Study drug administration			0 minute		Time of study drug administration = 0 minute. Study drug will be administered at about the same time on Day 1 of each study period.
Injection-site assessments			0, 60, 240, and 600 minutes		Assessment times are relative to study drug administration time (time 0). The 0-minute assessment will start as soon as practicably possible (within 1 minute) following the injection.
Insulin lispro PK sampling			0, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, and 600 minutes		Sampling times are relative to study drug administration time (time 0). The 0-minute sample should be taken within 2 minutes prior to planned dosing.

Procedures	Screening	Euglycaemic Clamp Procedure Periods 1 to 6		FU/ ED[a]	Comments
	Up to Day -28	Day -1	Day 1		
Euglycaemic clamp and blood glucose sampling for procedure			The clamp device will automatically sample blood at a rate of 2 mL/h after connection and record a blood glucose value every minute during the clamp procedure. A manual blood sample will also be taken at least every 30 minutes during the clamp for checking the correct functioning of the clamp device blood glucose readings and for safety.		Blood glucose monitoring will be done every minute starting from calibration after connection to the clamp device, baseline glucose establishment, drug dosing, and clamp up to 10 hours after dosing
C-peptide sampling			0, 60, 120, 240, 360, 480, and 600 minutes		Sampling times are relative to study drug administration (time 0). The 0-minute sample should be taken within 2 minutes prior to planned dosing.
Pharmacogenetic sample		X			Period 1 only.
Immunogenicity sample[b]			Predose for Period 1, Period 3, and Period 5	X	Additional samples may be collected if the investigator considers there is a possibility that an adverse event is immunologically indicated.
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; PK = pharmacokinetics.

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

b Predose assessments, procedures, and sampling may be performed any time before actual dosing on Day 1.

Note: The site should schedule activities as appropriate. In cases when several study procedures are scheduled at the same time, the order of priority will be as follows: PK samples, glucose samples, injection-site assessments, vital signs, ECG, clinical laboratory samples, immunogenicity, C-peptide, and pharmacogenetic samples. If the investigator decides based on clinical judgement not to dose a subject on a given day (for example, 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

In clinical practice, patients with diabetes on insulin therapy will inject their prandial insulins at a range of individualised doses, which may or may not influence the absorption pharmacokinetics (PK), as well as, the glucodynamic (GD) effect. The primary objective of this study is to evaluate the PK and GD effects across 3 dose levels after administration of the commercial formulation of LY900014 in comparison to Humalog®. It will also assess the dose proportionality of insulin lispro PK and GD after administration of the commercial formulation of LY900014.

3.2. Background

The insulin analogue, insulin lispro (Humalog; Eli Lilly and Company), 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 U/kg, peak serum levels were seen 30 to 90 minutes after dosing (Humalog package insert, 2015). However, the general consensus is that rapid-acting insulin, administered either through pumps or syringes/pen injectors, is still not rapid enough to match carbohydrate absorption profiles, which limits efficacy and dosing flexibility. An ultra-rapid-acting prandial insulin would shift the PK and GD profiles so that they have an even faster onset to better match carbohydrate absorption and also may allow important flexibility in the time of dosing relative to meals.

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

Treprostinil is a prostacyclin analogue, administered either through inhalation CCI [redacted], as an intravenous (IV) infusion, or as a continuous SC administration for the treatment of symptomatic pulmonary arterial hypertension (PAH) and has been approved in the US since 2002 CCI [redacted]. 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 (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 have been demonstrated in healthy subjects in 3 previous clinical studies, in approximately 71 healthy subjects across a dose range of 7.5 to 30 U. All 3 studies were Phase 1, randomised, subject-blind studies in which the PK and GD of LY900014 and Humalog 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 compared to Humalog. LY900014 also displayed a dose proportional increase in the insulin lispro exposure (maximum observed drug concentration [C_{max}] and area under the concentration versus time curve from time [AUC]) across this dose range.

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

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

3.3. Benefit–Risk Assessment

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

Potential risks associated with LY900014, derived from the known risks of insulin lispro (Humalog), are hypoglycaemia, hypersensitivity reactions (localised allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral oedema (Humalog package insert, 2015).

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

Following administration of the study insulin, 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 minimise the risk of hypoglycaemia in subjects participating in Study ITSH.

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

4. Objectives and Endpoints

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

Table ITSH.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the insulin lispro pharmacokinetics following SC doses of LY900014 compared to Humalog (at doses of 7, 15, and 30 U) in healthy subjects.	Early 50% t_{max} and AUC(0-30min)
Secondary 1. To evaluate the dose proportionality of the 3 dose levels of LY900014 as assessed by insulin lispro pharmacokinetics and glucodynamic measures.	1a. PK: AUC(0-10h), AUC(0-∞), and C_{max} 1b. GD: G_{tot} and R_{max}
2. To evaluate the GD during euglycaemic clamp procedure following SC doses of 7, 15, and 30 U of LY900014 compared to Humalog in healthy subjects.	2. Early 50% tR_{max}, G_{tot}(0-30min), G_{tot}(0-1h), and T_{onset}
3. To evaluate the tolerability of LY900014 in healthy subjects.	3. AEs and injection-site reactions
Exploratory 1. Explore the formation of antibodies to insulin lispro.	1. Anti-insulin lispro antibodies
2. To assess C-peptide levels following administration of LY900014 and Humalog.	2. C-peptide concentration

Abbreviations: AE = adverse event; AUC(0-30min) = area under the concentration versus time curve from time zero to 30 minutes; AUC(0-10h) = AUC from time zero to 10 hours; AUC(0-∞) = AUC from time zero to infinity; C_{max} = maximum observed drug concentration; early 50% t_{max} = time to early half-maximal plasma concentration; early 50% tR_{max} = time to half-maximal glucose infusion rate before tR_{max}; GD = glucodynamics; G_{tot} = total amount of glucose infused; G_{tot}(0-30min) = G_{tot} over 30 minutes; G_{tot}(0-1h) = G_{tot} over 1 hour; PK = pharmacokinetics; R_{max} = maximum glucose infusion rate; SC = subcutaneous; T_{onset} = time to onset of insulin action.

5. Study Design

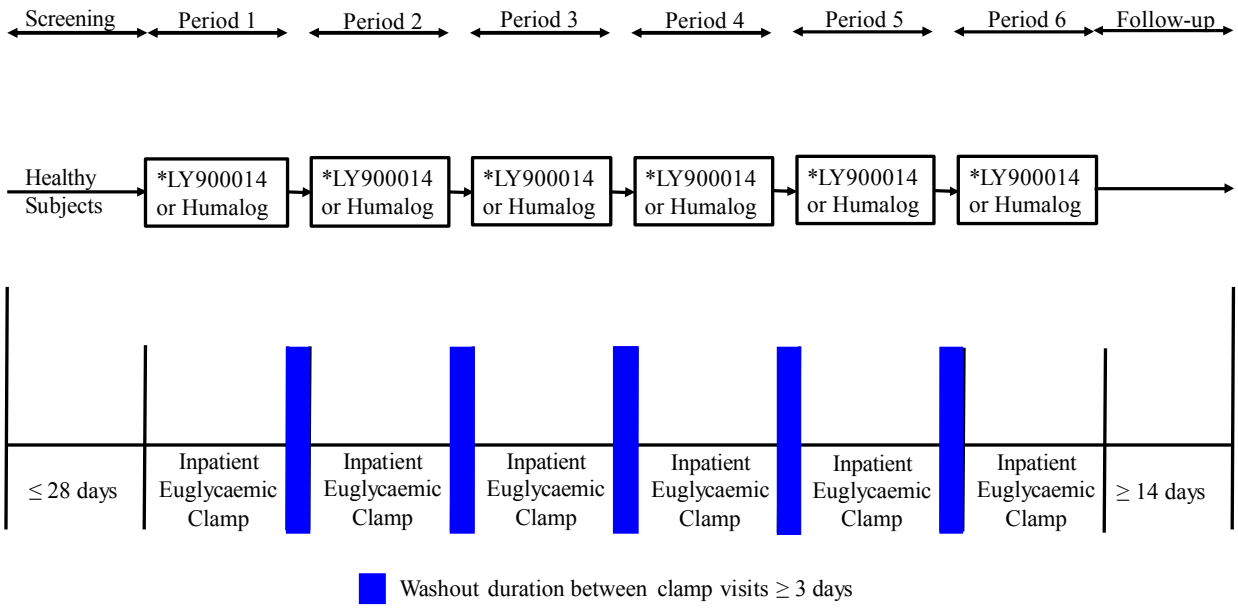
5.1. Overall Design

This is a Phase 1, randomised, subject- and investigator-blind, 6-period complete crossover study in up to 42 healthy subjects to evaluate the PK and GD characteristics across a range of LY900014 doses.

Approximately 34 subjects are expected to complete the study. Each subject will be randomised to 1 of 6 treatment sequences comprising single SC doses of 7, 15, and 30 U of LY900014 or Humalog administered SC in the abdominal wall (Table ITSH.2). A minimum of 3 days between study dosing of each consecutive study period will be required for an individual subject.

Figure ITSH.1 illustrates the study design.

Study governance considerations are described in detail in Appendix 3.



*Single dose of 7, 15, or 30 U of LY900014 or Humalog administered subcutaneously to the abdomen. Euglycaemic clamp procedure after each dose.

Figure ITSH.1. Illustration of study design for I8B-MC-ITSH.

Table ITSH.2. Treatment Sequence Example for I8B-MC-ITSH

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
1	LY 7 U	LY 15 U	H 30 U	LY 30 U	H 15 U	H 7 U
2	LY 15 U	LY 30 U	LY 7 U	H 7 U	H 30 U	H 15 U
3	LY 30 U	H 7 U	LY 15 U	H 15 U	LY 7 U	H 30 U
4	H 7 U	H 15 U	LY 30 U	H 30 U	LY 15 U	LY 7 U
5	H 15 U	H 30 U	H 7 U	LY 7 U	LY 30 U	LY 15 U
6	H 30 U	LY 7 U	H 15 U	LY 15 U	H 7 U	LY 30 U

Abbreviations: H = Humalog; LY = LY900014.

Note: This is only an example table for illustration purpose; subjects will be assigned a treatment sequence according to the actual treatment randomisation schedule provided to the unblinded site pharmacist.

Subjects will be admitted to the clinical research unit (CRU) on the evening before each dosing day and will remain in the CRU for the duration of the clamp period and until discharge by the investigator. Subjects are expected to fast for at least 8 hours before each dose. Following dose administration, each subject will undergo an euglycaemic clamp procedure of up to 10 hours. Upon completion of the clamp procedures, the subjects will be provided a meal and discharged from the CRU in the evening after medical assessments. Subjects may remain in the CRU if deemed necessary for safety monitoring, as determined by the investigator.

Subjects will be required to attend the CRU on at least 8 occasions:

- screening visit (up to 28 days prior to dosing)
- six treatment visits for the dosing and clamp procedure (study Periods 1 to 6) with a minimum period of at least 3 days between consecutive clamp visits
- follow-up visit (at least 14 days after the last dose), or early discontinuation

In the study, safety assessments and an evaluation of local tolerability at injection sites will be performed as specified in the Schedule of Activities (Section 2). Local tolerability assessments will include injection-site reactions within the following categories: pain on palpation, itching, erythema, oedema, and induration/infiltration.

5.2. Number of Participants

A total of 42 subjects may be enrolled for an approximately 34 completing subjects. For purposes of this study, a subject is considered as having completed the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been completed. If a subject discontinues before completion of all 6 dosing periods, replacement subjects may be enrolled. The replacement subject will be assigned the treatment sequence of the discontinued subject and complete that sequence in its entirety.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

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

The use of a crossover design allows each subject to serve as his or her own control, thereby reducing variability. The study is subject- and investigator-blinded to minimise potential bias related to the clamp procedure.

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 LY900014 (see Section 9.6 for a detailed description of the clamp methodology) relative to Humalog. Previous studies have shown that the 10-hour duration of the euglycaemic glucose clamp will allow for a complete assessment of GD activity of LY900014.

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

In patients with diabetes, mealtime insulin requirements can vary substantially depending on carbohydrate content, glycaemic index of the meal, and the insulin sensitivity of patient. Understanding the PK and GD across a broader dose range is important as reliable titration of an insulin product depends on an established dose–response relationship.

5.5. Justification for Dose

The safety, PK, and pharmacology of LY900014 at similar doses and with the similar formulation composition have been assessed in clinical studies in healthy subjects, in patients with T1DM and T2DM using MDI. In addition, clinical studies had evaluated the safety, PK, and pharmacology of SC bolus doses of treprostinil alone. More information can be found in the CCI.

All tested doses of LY900014 (up to 50 U) and treprostinil (CCI) were well tolerated in healthy subjects, patients with T1DM, and patients with T2DM. There were no SAEs related to study treatment in any of the 8 studies. No subject discontinued from the studies because of drug-related AEs. Trial participants in these studies were monitored for changes in vital signs; there were no significant systemic haemodynamic effects of treprostinil at the doses administered based on blood pressure and heart rate. Visual analogue scale pain scores showed that the SC injections of insulin lispro plus treprostinil co-formulations and treprostinil alone were well tolerated. In summary, there were small numbers of TEAEs and injection-site AEs, but there was no clinically significant increase in these or other events compared to placebo or to Humalog and no clinically significant increase in frequency with higher doses of treprostinil. Notably, at the higher doses of treprostinil, there were no clinically significant increase in those AEs associated with systemic absorption as described in the CCI (i.e.,

headache, diarrhoea, nausea, jaw pain, vasodilatation, rash, oedema, and hypotension). This is likely attributable to the relatively lower exposures of treprostinil demonstrated in these clinical studies.

Study ITSH will evaluate 3 insulin lispro dose levels (7, 15, and 30 U), which are within the range of insulin doses that are used for the treatment of both patients with T1DM and T2DM in clinical practice. At the highest dose level of 30 U of LY900014, subjects will be expected to receive approximately CCI treprostinil in a single SC dose, which is within the range evaluated as safe and tolerated in previous studies. The PK profile of treprostinil showed that concentrations of treprostinil in healthy subjects (after administration of up to 30 U of an experimental LY900014 formulation which contained CCI of treprostinil) were quantifiable in only CCI of the samples at 15 minutes postdose and CCI of the samples at 30 minutes postdose occurring around C_{max}. Among subjects with detectable levels, the mean concentrations were only slightly above the detection limit of the assay (lower limit of quantitation = CCI), and there were no detectable levels in any samples at 1 and 2 hours after injection. Thus, the expected treprostinil C_{max} following LY900014 administration would be CCI than the steady-state treprostinil levels in patients with PAH treated with CCI CCI from an average dose of CCI of CCI in clinical trials CCI , CCI .

6. Study Population

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

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

Screening may occur up to 28 days prior to enrolment. 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 enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

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

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

[1a] 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 investigational product (IP)

[1b] female subjects:

- women of childbearing potential may participate and include those who test negative for pregnancy before initiation of treatment based on a urine 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 IP
- women of nonchildbearing potential may participate in the study without using adequate contraceptive methods, and include those who are:
  - infertile due to surgical sterilisation (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as müllerian 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 (positive FSH level) 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 year.

[2] are between 18 and 65 years of age, inclusive, at the time of screening.

[3] have a body mass index (BMI) of 18.0 to 30.0 kg/m^2, inclusive, at the time of screening.

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

[5] have venous access sufficient to allow for blood sampling, IV administration, and clamp procedure as per the protocol.

[6] are nonsmokers, have not smoked for at least 6 months before entering the study, and agree not to smoke (cigars, cigarettes, or pipes) or use smokeless tobacco or nicotine products for the duration of the study.

[7] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[8] are able and willing to give signed informed consent.

6.2. Exclusion Criteria

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

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

[10] are Lilly employees or employees of the CRU.

[11] are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.

[12] have participated, within the past 30 days, in a clinical study involving an IP. If the previous IP has a long half-life, 5 half-lives, or 3 months (whichever is longer) should have passed.

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

[14] have known allergies to treprostinil or insulin lispro, related compounds, or any components of the formulation, or a history of significant atopy.

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

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

[17] have a history or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study drug; or of interfering with the interpretation of data.

[18] have known or ongoing psychiatric disorders deemed to be clinically significant by the investigator.

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

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

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

[22] 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).

[23] use over-the-counter or prescription medication within 7 to 14 days, respectively, prior to dosing apart from vitamin/mineral supplements, occasional paracetamol, topical treatments, thyroid replacement medication, or birth control methods and throughout the study. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the investigator and sponsor.

[24] have donated blood or have blood loss of more than 500 mL within the previous 3 months of study screening.

[25] 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 males or more than 12 g of alcohol per day for females or are unwilling to stop alcohol consumption at least 24 hours before each CRU admission (Day -1) and throughout the duration of each CRU visit.

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

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

For all treatment periods, subjects will fast for at least 8 hours prior to dosing and until the glucose clamp procedure is completed, after which subjects will receive a meal. Water can be consumed freely during this time.

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

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol intake will be allowed at least 24 hours before each CRU admission and while resident within the CRU.

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

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

6.3.3. Activity

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

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

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

This study will evaluate LY900014 (Test) and Humalog (Reference) across 3 SC doses with reference to the amount of insulin lispro present (7, 15, and 30 U). Table ITSH.3 shows the treatment regimens.

The CRU must have resuscitation equipment, emergency drugs, and appropriately trained staff available during the study drug administration.

Table ITSH.3. Treatments Administered for I8B-MC-ITSH

Treatment name	LY900014	Humalog
Insulin lispro dosage concentration	100 U/mL	100 U/mL
Insulin lispro dosage level	7, 15, 30 U	7, 15, 30 U
Route of administration	SC injection	SC injection

Abbreviation: SC = subcutaneous.

The investigator or designee is responsible for

- explaining the correct use of the study drugs to the CRU personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drugs' dispensation and collection
- and returning all unused medications to Lilly or its designee at the end of the study.

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

7.1.1. Packaging and Labelling

Clinical study materials will be labelled 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 CRU unblinded. Each vial will contain 10 mL of either LY900014 or commercially available insulin lispro at a concentration of 100 U/mL. LY900014 will also contain treprostinil at a concentration of CCI . An unblinded pharmacist at the CRU or other CRU personnel who are unblinded will use the insulin vials provided to prepare the blinded syringes for study drug administration.

7.2. Method of Treatment Assignment

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

7.2.1. Selection and Timing of Doses

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

The site of administration of each injection will be recorded. Injection sites selected should be about 5 cm from the umbilicus and the treatment administered SC with the needle applied at about 90° to the surface of the skinfold. An appropriately sized insulin syringe and needle shall be used in all dosing periods to ensure all injections are delivered to a consistent depth target into the SC space. Injections will be rotated among different injection sites on the anterior abdominal wall during the 6 study periods (i.e., left lower quadrant and right lower quadrant).

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

The site of administration of each injection will be recorded in the eCRF.

7.3. Blinding

The study is subject- and investigator-blind with reference to the identity of the study drug administered. The CRU staff will not be blinded to the dose administered due to the difference in volume of injection for the 3 doses being studied.

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

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

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

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

7.4. Dose Modification

Dose adjustments are not allowed in this study.

7.5. Preparation/Handling/Storage/Accountability

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

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

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

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

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

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

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrolment criteria and was inadvertently enrolled, the subject must be discontinued from the study.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

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

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing). 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 eCRF. Late collection outside stipulated time allowances or failure to perform procedures or obtain samples due to clinical issues, such as equipment technical problems, venous access difficulty, or subject defaulting on an agreed scheduled procedure, will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note.

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

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

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

9.1. Efficacy Assessments

Not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study drug or the study, or that caused the subject to discontinue the study drug before completing the study. The subject should be followed until the event resolves, stabilises 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, CRU personnel will record, via electronic data entry, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, CRU personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

If a subject's study drug is discontinued as a result of an AE, CRU personnel must report this to Lilly or its designee via electronic data entry.

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 hospitalisation
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

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

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

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

Lilly collects product complaints on IPs and drug delivery systems used in clinical studies 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 IP so that the situation can be assessed.

9.3. Treatment of Overdose

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

Excess insulin administration may cause hypoglycaemia and hypokalaemia. 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. Hypokalaemia must be corrected appropriately.

Refer to the IB for further information.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

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

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

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

9.4.3. Electrocardiograms

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

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

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the CRU.

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

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

9.4.4. Other Tests

9.4.4.1. Physical Examinations

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

9.4.4.2. Body Weight

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

9.4.4.3. Hip and Waist Circumference

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

9.4.5. Safety Monitoring

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

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

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

9.4.5.1. 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 mmol/L)
  - **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with plasma glucose ≤70 mg/dL (3.9 mmol/L)
- **Unspecified hypoglycaemia:** an event during which plasma glucose ≤70 mg/dL (3.9 mmol/L) but with no available information related to symptoms of hypoglycaemia
- **Probable symptomatic hypoglycaemia:** an event during which symptoms indicative of hypoglycaemia are observed but not accompanied by a plasma glucose determination (but that was presumably caused by plasma glucose ≤70 mg/dL [3.9 mmol/L])
- **Clinically significant hypoglycaemia:** an event during which plasma glucose is <54 mg/dL (3.0 mmol/L), where it is considered sufficiently low to indicate serious, clinically important hypoglycemia.
- **Severe hypoglycaemia:** an event during which patients had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration (≤70 mg/dL [3.9 mmol/L]).
- **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, which do not require the assistance of another person, are accompanied by plasma glucose >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70-mg/dL (3.9 mmol/L) threshold
- **Overall (or total) hypoglycaemia:** This optional category combines most cases of hypoglycaemia except relative hypoglycaemia. Nocturnal and severe hypoglycaemia are special cases of documented or probable hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, that event should only be counted once in this category of overall (or total) hypoglycemia.

The goal of the euglycaemic clamp is to maintain glucose concentrations at normoglycaemic levels close to a predefined target. Therefore, the equivalence of plasma glucose concentrations below 70 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.

9.4.5.1.1. Severe Hypoglycaemia

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

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

9.4.5.2. Hepatic Safety

If a study subject experiences elevated alanine aminotransferase (ALT) ≥3X upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2X ULN, or elevated total bilirubin (TBL) ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase (AST), ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalise and/or are returning to approximate baseline levels.

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

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

9.4.6. Injection-Site Assessments (Local Tolerability)

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

If deemed necessary by the investigator, digital pictures may be taken of the injection site at the time of identification of local intolerability and thereafter as often as judged necessary by the investigator. The pictures should include subject number, visit number, time after dosing, and a ruler for scaling and will be filed on site.

Local tolerability at the injection site will be evaluated and transcribed into the eCRF by means of assessments within the following categories: pain on palpation, itching, erythema, oedema,

and induration/infiltration. If 1 or more symptom(s) of an injection-/infusion-site reaction is reported during the assessment, a single AE for injection-site reaction will be recorded on the AE page of the eCRF.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the serum concentrations of insulin lispro. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock) of each sampling will be recorded.

9.5.1. Bioanalysis

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

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

Bioanalytical samples collected to measure insulin lispro concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining may be used for other exploratory analyses on insulin lispro.

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 glucose infusion rate (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.

At least 30 minutes before the planned administration of study drug, subjects will be connected to the clamp device CCI for continuous blood glucose monitoring to determine their baseline blood glucose. Baseline is defined as the mean of blood glucose concentrations at approximately –6, –4, and –2 minutes (before study drug administration) as measured using CCI. After study drug administration, onset of action occurs when blood glucose drops 5 mg/dL (0.3 mmol/L) from baseline (as measured by CCI). This blood glucose level 5 mg/dL below baseline will be used as the euglycaemic glucose clamp target level throughout the remainder of the clamp procedure. Subjects will not be clamped to a blood glucose target lower than 63 mg/dL. Therefore, subjects with a mean predose baseline fasting blood glucose below 68 mg/dL (equivalent to a fasting plasma glucose of 76 mg/dL [4.21 mmol/L]) will not be dosed to undergo the clamp procedure but may be rescheduled to a later period. In addition, any study procedures conducted up to that time may be repeated in that later period.

After the onset of action has been reached, a variable IV glucose infusion will be initiated in order to keep blood glucose constant at the target level. The GIR necessary to keep the blood glucose 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, blood glucose measurements for verification of CCI measurements will be performed using CCI .

The clamp procedure will continue for up to 10 hours after dose or until after blood glucose concentrations return to baseline without any glucose being administered for at least 30 minutes, whichever is earlier. At the end of the clamp procedure, the subject will be given a meal.

All subjects will be medically assessed before discharge from the CRU (see Schedule of Activities [Section 2]).

9.6.1. Immunogenicity Assessments

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

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and ethics committees (ECs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the study drug. Any samples remaining after 15 years will be destroyed.

9.7. Genetics

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

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

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

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

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

9.8. Exploratory Biomarkers

9.8.1. C-Peptide

Blood samples will be obtained for determination of C-peptide concentrations as specified in the Schedule of Activities (Section 2). These samples and any remaining serum after C-peptide analyses will be discarded. Instructions for the collection and handling of these samples will be provided by the sponsor.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination for Faster PK Absorption

Up to 42 subjects may be enrolled to ensure that at least 34 subjects complete the study.

Thirty-four completing subjects will provide approximately 96% power to demonstrate a 40% increase in the insulin lispro AUC from time zero to 30 minutes (AUC[0-30min]) between LY900014 and Humalog. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The variability was estimated using prior internal studies that showed an average log-scale standard deviation of within-subject difference in AUC(0-30min) of CCI. 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 CCI. This sample size provides approximately 98% 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. 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 at least 85% power to detect at least a 40% increase in total amount of glucose infused (G_{tot}) over 30 minutes (G_{tot}[0-30min]) and G_{tot} over 1 hour (G_{tot}[0-1h]).

10.2. Sample Size Determination for Dose Proportionality

Thirty-four completing subjects will provide greater than 95% power to demonstrate dose proportionality of AUC from time zero to 10 hours (AUC[0-10h]) and AUC from time zero to infinity (AUC[0-∞]). This is based on the assumption of a log-normal distribution and an estimate of intrasubject log-scale standard deviation of CCI. There is also approximately 90% power to demonstrate dose proportionality of C_{max}, assuming an intrasubject log-scale standard deviation of CCI.

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

Standard baseline characteristics of age, sex, ethnicity, race, height, weight, and BMI will be summarised for all randomised patients.

10.3. Statistical Analyses

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

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.

10.3.1. Safety Analyses

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

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

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post hoc analyses and incomplete disclosures of analyses.

10.3.1.1. Clinical Evaluation of Safety

All IP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarised using descriptive methodology.

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

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

10.3.1.2. Statistical Evaluation of Safety

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Insulin lispro PK parameter estimates for LY900014 will be calculated using standard noncompartmental methods of analysis. Free serum insulin lispro concentrations will be used to calculate several PK parameters, including maximum observed drug concentration (C_{max}), time to maximum observed drug concentration (t_{max}), half-life ($t_{1/2}$), time to early half-maximal plasma concentration (early 50% t_{max}), time to late half-maximal drug concentration (late 50% t_{max}), AUC from time zero to 30 minutes [AUC(0-30min)], AUC from time zero to 1 hour[AUC(0-1h)], AUC from time zero to 10 hours [AUC(0-10h)], AUC from time 3 to 10 hours AUC(3-10h) and AUC from time zero to infinity [AUC(0-∞)] will be determined. In addition, the apparent total body clearance of drug calculated after extra-vascular administration

(CL/F), and volume of distribution after extra-vascular administration (Vz/F) also will be determined. Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary, such as AUC from time zero to 2 hours.

The insulin lispro PK parameters for assessing faster insulin lispro absorption are the early 50% t_{max} and AUC(0-30min).

The insulin lispro PK parameters for assessing reduction in the late insulin lispro exposure are the late 50% t_{max} and AUC(3-10h).

The insulin lispro PK parameters for assessing dose proportionality are the C_{max}, AUC(0-10h) and AUC(0-∞).

Although attempts will be made to adhere to the scheduled collection times (Section 2), it is recognised 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 AUCs and C_{max} for insulin lispro will be evaluated to estimate least-squares geometric means, ratios of least-squares geometric means between LY900014 and Humalog for each dose level, and their corresponding 95% CIs using the mixed-effects model that includes treatment, dose level, dose level-by-treatment interaction, and period as fixed effects and subject 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 (LSmeans), treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences for each dose will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem. As a sensitivity analysis, the PK time parameters will be analysed nonparametrically. The median differences between treatments and the 95% CIs for the differences will be presented.

The analyses described above will also be performed on the population of subjects who completed and had evaluable PK data for all study periods.

In addition, the degree of dose proportionality for insulin lispro will be assessed by fitting the power model (Smith et al. 2000) to both AUC (AUC[0-10h] and AUC[0-∞]) and C_{max} versus dose for each dose level of LY900014. The estimated ratio of dose-normalised geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. In addition, the slope and its 95% CI and the geometric least-square means for each dose level tested will be produced. In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated. Log-transformed C_{max} and AUC LSmeans, and 95% CI estimates for each dose will be back-transformed to provide the geometric means and the corresponding 95% CIs.

The analyses will also be performed using the subset of the subjects who complete all treatment periods with evaluable data.

10.3.3. Glucodynamic Analyses

10.3.3.1. Glucodynamic Parameter Estimation

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

A locally weighted scatterplot smoothing (LOESS) function will be applied to all individual GIR versus time profiles in each treatment group and/or period using CCI . The fitted data for each patient will be used to calculate the following GD parameters: 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 (G_{tot}), G_{tot} over 30 minutes ($G_{tot[0\text{-}30min]}$), G_{tot} over 1 hour ($G_{tot[0\text{-}1h]}$), and G_{tot} over 10 hours ($G_{tot[0\text{-}10h]}$). Additional partial glucose AUCs, such as G_{tot} over 2 hours ($G_{tot[0\text{-}2h]}$), G_{tot} from 3hours to 10 hours $G_{tot[3\text{-}10h]}$ may be computed as necessary. The values of these GD parameters will be summarised by treatment and/or period through descriptive statistics. Mean LOESS fits of GIR versus time profiles will be generated. The primary GD parameters for earlier PD onset are early 50% tR_{max}, $G_{tot(0\text{-}30min)}$, $G_{tot(0\text{-}1h)}$, and T_{onset}.

10.3.3.2. Glucodynamic Statistical Inference

The GD statistical model will be the same as the model used for the analysis of the PK parameters. The following variables will be log transformed prior to analysis: R_{max}, G_{tot}, $G_{tot(0\text{-}30min)}$, $G_{tot(0\text{-}1h)}$, and $G_{tot(0\text{-}10h)}$ along with any additional partial G_{tot}. 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 method will be performed for that parameter.

The same model without log transformation will be used for the analysis of the GD time parameters (T_{onset}, tR_{max}, early 50% tR_{max}, late 50% tR_{max}). Least-squares means, treatment differences in LSmeans, and the corresponding 95% CIs for the treatment differences for each dose will be estimated from the model. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

The analyses described above will also be performed on the population of patients who completed and had evaluable GD data for both study periods.

The degree of dose proportionality for the insulin lispro in LY900014 will be assessed by fitting the power model to G_{tot} and R_{max} versus dose for each dose level of LY900014.

The analyses will also be performed using the subset of the subjects who complete all treatment periods with evaluable data.

10.3.4. Pharmacokinetic/Glucodynamic Analyses

Not applicable.

10.3.5. Evaluation of Immunogenicity

The frequency of antibody formation to insulin lispro will be determined. The relationship between the presence (or absence) of antibodies and AEs may be assessed. Likewise, the relationship between the presence of antibodies and the PK parameters and GD response to insulin lispro may be assessed.

10.3.6. C-Peptide

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

10.3.7. Data Review during the Study

This section is not applicable for this study.

10.3.8. Interim Analyses

No formal interim analyses are planned for this study. Data may be accessed by the unblinded Lilly study team and reviewed while the study is ongoing, but no changes to the study design are planned. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

11. References

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

LY900014 Investigator's Brochure. Version approved 03 Mar 2017.

CCI [redacted]

Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17(10):1278-1283.

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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-30min)	AUC from time zero to 30 minutes
AUC(0-10h)	AUC from time zero to 10 hours
AUC(2-10h)	AUC from time 2 to 10 hours
AUC(3-10h)	AUC from time 3 to 10 hours
AUC(0-∞)	AUC from time zero to infinity
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock.
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CP	clinical pharmacologist
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
early 50% t_{max}	time to early half-maximal drug concentration
early 50% tR_{max}	time to half-maximal glucose infusion rate before tR_{max}
EC	ethics committee
ECG	Electrocardiogram

eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
GD	glucodynamic(s)
GGT	gamma-glutamyl transferase
GIR	glucose infusion rate
G_{tot}	total amount of glucose infused
$G_{tot(0\text{-}30min)}$	G_{tot} over 30 minutes
$G_{tot(0\text{-}1h)}$	G_{tot} over 1 hour
$G_{tot(0\text{-}10h)}$	G_{tot} over 10 hours
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorised form, or marketed products used for an unauthorised indication, or marketed products used to gain further information about the authorised form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	Intravenous
late 50% t_{max}	time to late half-maximal drug concentration
late 50% tR_{max}	time to half-maximal GIR after tR_{max}

LOESS	locally weighted scatterplot smoothing
LSmeans	least-squares means
MDI	multiple daily injection
PAH	pulmonary arterial hypertension
PK	pharmacokinetic(s)
randomise	The process of assigning subjects/patients to an experimental group on a random basis.
R_{max}	maximum glucose infusion rate
SAE	serious adverse event
SC	subcutaneous(ly)
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time to maximum observed drug concentration
T_{onset}	time to onset of insulin action
tR_{max}	time to R_{max}
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

- Haematology[a]
  - Haematocrit
  - Haemoglobin
  - Erythrocyte count (RBC)
  - Mean cell volume
  - Mean cell haemoglobin
  - Mean cell haemoglobin concentration
  - Leucocytes (WBC)
  - Absolute counts of
    - Neutrophils
    - Lymphocytes
    - Monocytes
    - Eosinophils
    - Basophils
    - Platelets
- Coagulation[b]
  - International normalised ratio (INR)
  - Activated partial thromboplastin time (aPTT)
- Urinalysis[a]
  - Specific gravity
  - pH
  - Protein
  - Glucose
  - Ketones
  - Bilirubin
  - Urobilinogen
  - Blood
  - Nitrite
  - Leucocytes
  - Microscopy[f]
- Clinical Chemistry[a]
  - Sodium
  - Potassium
  - Bicarbonate
  - Chloride
  - Calcium
  - Phosphate
  - Glucose
  - Blood urea nitrogen (BUN)
  - Total protein
  - Albumin
  - Total bilirubin
  - Alkaline phosphatase (ALP)
  - Aspartate aminotransferase (AST)
  - Alanine aminotransferase (ALT)
  - Gamma-glutamyl transferase (GGT)
  - Creatinine
  - Uric acid
- Serology[b]
  - Hepatitis B surface antigen
  - Hepatitis C antibody
  - HIV
  - FSH[c]
- Pregnancy test[d]
- Ethanol/Alcohol breath test[e]
- Urine drug screen[e]

Abbreviations: CRU = clinical research unit; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

a Performed at screening, Period 1 Day 1, and follow-up.

b Only at screening. Hepatitis B, hepatitis C, and HIV tests may be waived if results of the same test have been obtained from the subject within the past 6 months before screening.

c Only at screening in menopausal women if necessary.

d All females of childbearing potential: Serum pregnancy test at screening, urine pregnancy test at all other visits.

e Performed locally at the site at screening and repeated prior to each CRU admission. Urine drug screen: amphetamine, cannabis, cocaine, barbiturates, methadone, benzodiazepines, tricyclic antidepressants, methamphetamine, opiates, and phencyclidine.

f If clinically indicated, per investigator's discretion.

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

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

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

Recruitment

Study-specific recruitment material should be approved by Lilly.

Ethical Review

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

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

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

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

Regulatory Considerations

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

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

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

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the CRU. 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 ECs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I8B-MC-ITSH Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	10	1	10
Clinical laboratory tests[a]	7	2	14
Pharmacokinetic samples serum insulin lispro	1	24 samples × 6 periods = 144	144
Clamp device sampling for glucose[b]	NA	NA	138
Blood glucose during clamp period (Super GL)[c]	0.3	276	82.8
C-peptide	2	7 samples × 6 periods = 42	84
Immunogenicity	5	4	20
Pharmacogenetics	10	1	10
Total for clinical purposes			502.8
Total for clinical purposes rounded up to the nearest 10 mL			510

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

b Clamp device sampling: 30- to 60-minute calibration, 30-minute baseline plus 10-hour clamp = 11.5 hours × 6 periods = 69 hours × 2 mL/hour = 138 mL.

c Blood glucose during clamp period (Super GL): 30- to 60-minute calibration, 30-minute baseline plus 10-hour clamp = 11.5 hours × 6 periods = 69 hours × up to 4 samples/hour = 276 blood samples × 0.3 mL/blood sample = 82.8 mL.