Protocol: Protocol I8B-MC-ITSL(a) A Mixed Meal Tolerance Test Study to Evaluate the Pharmacokinetics and Pharmacodynamics of LY900014 Compared to Humalog Following a Single Dose in Adults with Type 1 Diabetes

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# Protocol I8B-MC-ITSL(a)
# A Mixed Meal Tolerance Test Study to Evaluate the Pharmacokinetics and Pharmacodynamics of LY900014 Compared to Humalog Following a Single Dose in Adults with Type 1 Diabetes

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## Confidential Information



LY900014

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
12 December 2017
Amendment (a) Electronically Signed and Approved by Lilly
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# 1. Protocol Synopsis

**Title of Study:**
A Mixed Meal Tolerance Test Study to Evaluate the Pharmacokinetics and Pharmacodynamics of LY900014 Compared to Humalog Following a Single Dose in Adults with Type 1 Diabetes

**Rationale:**
This study in patients with type 1 diabetes mellitus (T1DM) aims to compare the pharmacokinetic (PK) profiles of insulin lispro after administration of LY900014 and Humalog and their impact on postprandial blood glucose during a standardised mixed meal tolerance test (MMTT). Furthermore, this study plans to characterise the PK and pharmacodynamics (PD) of insulin aspart analogues NovoRapid® and FIASP® in patients with T1DM under identical study conditions. A non-diabetic healthy subject cohort is included in the study to characterise "normal" insulin secretory and glucose response during an identical standardised meal. Healthy subjects will not receive any of the study drugs.

Evaluation of these meal-time insulins in the context of a standardised test meal cannot be used to infer clinical efficacy with the same rigour as a glycated haemoglobin assessment following long-term treatment. However, assessment of these analogue insulin formulations under identical conditions provides a unique opportunity to obtain comparative information on the PK and PD in a setting appropriate for evaluation of meal-time insulin.

**Objective(s)/Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary**<br>1. To evaluate the differences in PK between LY900014 and Humalog following a single dose in patients with T1DM | 1. Early 50% $t_{max}$ and AUC(0-30min) |
| **Secondary**<br>1. To characterise the PK profiles of LY900014, Humalog, NovoRapid and FIASP following a single dose in patients with T1DM<br>2. To evaluate the differences in PD between LY900014 and Humalog following a single dose in patients with T1DM<br>3. To characterise the PD response to LY900014, Humalog, NovoRapid and FIASP, as assessed by the MMTT, in patients with T1DM | 1. Early 50% $t_{max}$<br>2. ΔAUC(0-1h), ΔAUC(0-5h)<br>3. ΔAUC(0-1h), ΔAUC(0-5h) |

Abbreviations: AUC(0-30min) = area under the concentration versus time curve from time 0 to 30 minutes; ΔAUC = area under the baseline subtracted glucose concentration versus time curve; ΔAUC(0-1h) = ΔAUC from time 0 to 1 hour postmeal; ΔAUC(0-5h) = ΔAUC from time 0 to 5 hours postmeal; early 50% $t_{max}$ = time to early half-maximal drug concentration; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics; T1DM = type 1 diabetes mellitus.

**Summary of Study Design:**

Study I8B-MC-ITSL is a clinical pharmacology, patient- and investigator-blind, randomised, 4-treatment, 4-period crossover study in patients with T1DM. The study also involves healthy subjects who will undergo a single MMTT but will not receive any study drug.

**Treatment Arms and Planned Duration for an Individual Patient with T1DM:**
Patients will be screened over a 14-day period prior to start of a 7- to 14-day lead-in (insulin transition) period. Patients will then participate in a dose-finding assessment (1 to 7 days prior to MMTT in Period 1) and subsequently randomised to 1 of 4 treatment sequences according to the actual randomisation table provided to the clinical research unit (CRU). In each study period, patients will undergo a MMTT. Each patient will receive a single individualised subcutaneous (SC) injection of LY900014, Humalog, FIASP or NovoRapid immediately before the standardised test meal. All treatment procedures will be inpatient stays of approximately 2 days per period and require a maximum of 6 weeks to complete 4 periods. Each study dosing will be separated by a minimum of 21 hours and may occur on consecutive days; however, patient inclusion is subject to required screening criteria. The follow-up or early discontinuation visit should occur at least 14 days after the last dose of the study drug.

**Treatment Arms and Planned Duration for an Individual Healthy Subject:**

Subjects will be screened over a 28-day period prior to the MMTT. Subjects will be admitted to the CRU the evening before the MMTT. Each subject will receive a standardised test meal on Day 1. Subjects will remain inpatient in the CRU for 2 days.

**Treatment (applicable to patients):**

For a given patient, the single individualised dose will be the same for all the treatments.

**LY900014:** Single individualised SC dose per assessment period

**Humalog:** Single individualised SC dose per assessment period

**FIASP**: Single individualised SC dose per assessment period

**NovoRapid**: Single individualised SC dose per assessment period

**Number of Patients and Subjects:**
Up to 74 patients with T1DM may be enrolled so that approximately 64 patients complete the study. Replacement patients will adopt all 4 assigned crossover treatments of the original patient's randomisation schedule.

For the healthy subject cohort, sufficient subjects will be enrolled to have 12 healthy subjects complete the study.

**Statistical Analysis:**

Primary statistical analyses of PK and PD parameters will be conducted on the set of patients who complete all treatment periods with identical prandial insulin does for the MMTTs during the study. Supportive analyses may be done on the key parameters for the patients who complete at least 2 treatment periods. Safety analyses will be conducted on the set of patients receiving at least 1 dose of the study drug to which they are randomised, regardless of whether or not they completed all protocol requirements.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided. No multiplicity test adjustment will be made for secondary objectives.

**Safety:** All investigational product- and protocol procedure-related adverse events will be listed, and if the frequency of events allows, safety data will be summarised using descriptive methodology. Safety parameters will be listed and summarised using standard descriptive statistics.

**Pharmacokinetic:**

The mixed-effects model will be used for the analysis of the PK time parameters (time to early half-maximal drug concentration [early 50% $t_{max}$], time to late half-maximal drug concentration [late 50% $t_{max}$] and time to maximum observed drug concentration [$t_{max}$]) without log transformation. Least-squares means (LSmeans), treatment differences in LSmeans and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance. The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem.

Log-transformed area under the concentration versus time curves (AUCs), maximum observed drug concentration ($C_{max}$) for insulin lispro/aspart may be evaluated to estimate geometric means, ratios of geometric means and their corresponding 95% CIs using the same mixed-effect model as PK time parameters.

**Pharmacodynamics:**

Data will be analysed for the patients during each MMTT. The change from baseline values (the average of -30, -15 and 0 minutes) represented as the 0-hour time point following the start of the MMTT for each patient will be calculated. The area under the baseline subtracted glucose concentration versus time curve from time 0 to 1 hour post-meal (ΔAUC[0-1h]), area under the baseline subtracted glucose concentration versus time curve from time 0 to 2 hours post-meal (ΔAUC[0-2h]) and area under the baseline subtracted glucose concentration versus time curve from time 0 to 5 hours post-meal (ΔAUC[0-5h]) will be calculated. In addition, the change from baseline maximum glucose observed during the 5 hours post-meal and change from baseline 1 hour glucose and 2 hour glucose after the start of the meal will be calculated. Other partial ΔAUCs may be calculated, as deemed appropriate.

Summary statistics will be presented by treatment. All PD parameters (including ΔAUCs, glucose changes from baseline and time parameters) on the original scale will be analysed using the mixed-effects model that includes treatment, sequence and period as fixed effects and patient within sequence as a random effect. The p-value on the difference between LS means will be used to determine statistical significance and the corresponding 95% CIs for the LSmean ratios from Fieller's theorem will be presented.

# 2. Schedule of Activities

**Study Schedule Protocol I8B-MC-ITSL for Patients with T1DM**

| | Screening | Lead-In | Dose-Finding Assessment | Study Period (Periods 1 to 4) | | Follow-up/Early Discontinuation | Comments |
|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 14 days prior to lead-in** | **7-14 days prior to dose-finding assessment** | **1-7 days prior to Period 1, Day 1** | **Day -1** | **Day 1** | **≥14 days after discharge** | |
| Informed consent | X | | | | | | At least 1 day before screening procedures. Screening procedures should take place no later than 28 days after signing the informed consent. |
| Medical history and physical examination | X | | | | | | |
| Height | X | | | | | | At screening only. |
| Weight | X | | | X | | X | Period 1 only. |
| Vital signs (supine): blood pressure and pulse rate | X | | | | Predose and 420 minutes postdose | X | |
| 12-lead ECG (supine) | X | | | | Predose (Period 1) | X | Single ECGs will be collected for safety. |
| Clinical laboratory tests | X | | X | | Predose for Period 1 only | X | Fasting laboratory test. All clinical laboratory tests will be analysed at a local laboratory (see Section 9.4.2). |
| Alcohol breath test | | | | X | | | Alcohol breath test to be done at admission for all periods. |

| | Screening | Lead-In | Dose-Finding Assessment | Study Period (Periods 1 to 4) | | Follow-up/Early Discontinuation | Comments |
|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 14 days prior to lead-in** | **7-14 days prior to dose-finding assessment** | **1-7 days prior to Period 1, Day 1** | **Day -1** | **Day 1** | **≥14 days after discharge** | |
| Lead-in/insulin transition activities | | X | | | | | Once patients have completed screening procedures, they will switch from prescribed basal insulin to site-provided insulin glargine. Patients will receive general diabetes training. A patient diary will be provided for recording dosing and other required information (Section 5.1.1.1). Lead-in period may be extended by 2 days as needed. |
| Patient admission to CRU | | | | X | | | Admitted to CRU on the evening of Day -1 for all study periods. If the dose-finding assessment occurs from Day -2, the patient may continue to remain inpatient in the CRU until the completion of study MMTT for Period 1. |

| | Screening | Lead-In | Dose-Finding Assessment | Study Period (Periods 1 to 4) | | Follow-up/Early Discontinuation | Comments |
|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 14 days prior to lead-in** | **7-14 days prior to dose-finding assessment** | **1-7 days prior to Period 1, Day 1** | **Day -1** | **Day 1** | **≥14 days after discharge** | |
| Dose-finding MMTT | | | X | | | | Patients will undergo dose-finding assessment with Humalog and a standardised test meal. Dose-finding MMTT will occur after the insulin transition. Dose-finding assessment should occur between 1 and 7 days prior to MMTT in Period 1. To take place between 0700 hours and 1100 hours. See Section 5.1.1.2 for rescheduling. |
| Randomisation | | | | X | | | To take place before run-in of Period 1 Day 1. |
| Pregnancy test | X | | | X | | X | For female patients only. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at the time of admission in Periods 1 to 4 and at follow-up (see Appendix 2). |
| Standardised dinner | | | | X | | | Approximately at 1900 hours. The evening dinner will be identical for every period. |

| | Screening | Lead-In | Dose-Finding Assessment | Study Period (Periods 1 to 4) | | Follow-up/Early Discontinuation | Comments |
|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 14 days prior to lead-in** | **7-14 days prior to dose-finding assessment** | **1-7 days prior to Period 1, Day 1** | **Day -1** | **Day 1** | **≥14 days after discharge** | |
| Medical assessment | | | | X | Predose and before discharge from CRU | X | Medical assessment includes medical review and targeted examination, and as appropriate review of concomitant medication, patient diary and MMTT exclusion criteria (see Section 6.2.1). |
| Glucose stabilisation/run-in | | | | | X | | From approximately 7 hours to 30 minutes before dosing: IV infusion of glucose (dextrose solution) and/or insulin glulisine to achieve a target blood glucose level of 135±15 mg/dL (7.5±0.8 mmol/L). Blood glucose concentrations will be monitored at a minimum of 30-minute intervals (see Sections 9.6.1 and 5.1.1.3). See Section 6.2.3 for rescheduling. |

| | Screening | Lead-In | Dose-Finding Assessment | Study Period (Periods 1 to 4) | | Follow-up/Early Discontinuation | Comments |
|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 14 days prior to lead-in** | **7-14 days prior to dose-finding assessment** | **1-7 days prior to Period 1, Day 1** | **Day -1** | **Day 1** | **≥14 days after discharge** | |
| Blood glucose sampling (MMTT) | | | 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300 minutes post-meal | | -30, -15, 0 minutes pre-meal, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300 minutes post-meal | | 0-minute time point sample to be taken at the start of the meal. |
| Study MMTT | | | | | X | | Standardised test meal will be administered at approximately 0700 hours (with allowance up to 1100 hours) and should be consumed within 15 minutes (see Section 5.1.1.3). MMTT may occur on consecutive days. |
| Study drug administration | | | | | X | | Immediately before the start of meal according to the randomisation schedule: Study drug will be administered at approximately the same time on Day 1 of Periods 1 to 4. There will be at least 21 hours between study doses. |

| | Screening | Lead-In | Dose-Finding Assessment | Study Period (Periods 1 to 4) | | Follow-up/Early Discontinuation | Comments |
|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 14 days prior to lead-in** | **7-14 days prior to dose-finding assessment** | **1-7 days prior to Period 1, Day 1** | **Day -1** | **Day 1** | **≥14 days after discharge** | |
| Insulin lispro/insulin aspart PK sampling | | | | | 0 (predose), 1, 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300, 360 and 420 minutes postdose | | Sampling times are relative to the time of study drug administration in each period. |
| Discharge from CRU | | | | | X | | Patients may be discharged after all study procedures are completed. Patients may be offered a meal following completion of all PK and PD assessments. |

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics.

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

**Study Schedule Protocol I8B-MC-ITSL for Healthy Subjects**

| | Screening | Study Period | | Comments |
|---|---|---|---|---|
| **Procedure** | Days -28 to -2 | Day -1 | Day 1 | |
| Informed consent | X | | | At least 1 day before screening procedures. Screening procedures should take place no later than 28 days after signing the informed consent. |
| Medical history and physical examination | X | | | |
| Height | X | | | At screening only. |
| Weight | X | X | | |
| Vital signs (supine): blood pressure and pulse rate | X | | | |
| 12-lead ECG (supine) | X | | | Single ECGs will be collected for safety. |
| Clinical laboratory tests | X | | | Fasting laboratory test. Laboratory tests will be analysed at a local laboratory. |
| Oral glucose tolerance test | X | | | Plasma glucose measurements before ingestion of glucose beverage and at 1 and 2 hours after the start of ingestion of glucose beverage. |
| Subject admission to CRU | | X | | Admitted to CRU on the evening of Day -1. |
| Pregnancy test | X | X | | For female subjects only. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at admission to the CRU (see Appendix 2). |
| Standardised dinner | | X | | Approximately at 1900 hours. |
| Medical assessment | | X | Before discharge from CRU | Medical assessment includes medical review and targeted examination, and as appropriate review of concomitant medication and MMTT exclusion criteria (see Section 6.2.2). |
| Blood glucose sampling (MMTT) | | | -30, -15, 0 minutes pre-meal, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, 240, 300 minutes post-meal | 0-minute time point sample to be taken at the start of the meal. |

| | Screening | Study Period | | Comments |
|---|---|---|---|---|
| **Procedure** | Days -28 to -2 | Day -1 | Day 1 | |
| MMTT | | | X | Standardised test meal will be administered at approximately 0700 hours (with allowance up to 1100 hours) and should be consumed within 15 minutes (see Section 5.1.2). |
| Endogenous insulin sampling | | | 0 (pre-meal), 1, 2, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 90, 120, 150, 180, 240, 300, 360 and 420 minutes postmeal | Sampling times are relative to the time of meal administered. |
| Discharge from CRU | | | X | Subjects may be discharged after all study procedures are completed. Subjects may be offered a meal following completion of all PK and PD assessments. |

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics.

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

# 3. Introduction

## 3.1. Study Rationale

A prandial insulin with faster-on and/or faster-off characteristics might reduce glycaemic excursions and the incidence of postprandial hypoglycaemia compared to currently available insulin analogues. LY900014 is an ultra-rapid-acting insulin lispro formulation that has shown an increased early absorption compared to commercially available insulin lispro (Humalog®; Eli Lilly and Company). LY900014 aims to closely mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose excursions. FIASP® is a new commercially available fast-acting insulin aspart formulation that displays increased early absorption compared to commercially available insulin aspart (FIASP® SmPC, 2017; NovoRapid® SmPC, 2017).

This study in patients with type 1 diabetes mellitus (T1DM) aims to compare the pharmacokinetic (PK) profiles of insulin lispro after administration of LY900014 and Humalog and their impact on postprandial blood glucose during a standardised mixed meal tolerance test (MMTT). Furthermore, this study plans to characterise the PK and pharmacodynamics (PD) of insulin aspart analogues NovoRapid and FIASP in patients with T1DM under identical study conditions. A non-diabetic healthy subject cohort is included in the study to characterise "normal" insulin secretory and glucose response during an identical standardised test meal. Healthy subjects will not receive any of the study drugs during the study.

Evaluation of these meal-time insulins in the context of a standardised test meal cannot be used to infer clinical efficacy with the same rigour as a glycated haemoglobin (HbA1c) assessment following long-term treatment. However, assessment of these analogue insulin formulations under identical conditions provides a unique opportunity to obtain comparative information on the PK and PD in a setting appropriate for evaluation of meal-time insulin.

## 3.2. Background

The insulin analogue insulin lispro (Humalog) has been shown to be absorbed more quickly than regular human insulin (Humalog package insert, 2017). In healthy volunteers given subcutaneous (SC) doses of insulin lispro ranging from 0.1 to 0.4 units (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 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/PD of insulin analogues so that they have an even faster onset to better match carbohydrate absorption and also allow greater flexibility in the time of dosing relative to meals.

LY900014 represents a new formulation that contains insulin lispro, treprostinil, citrate, and other excipients. This formulation involves the novel use of a microdose of treprostinil (CCI [redacted]) as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient to elicit a systemic effect. Treprostinil is a prostacyclin 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 and in Germany since 2006 (AMIS database [WWW]). Sodium citrate is also included in the formulation to further enhance the absorption of insulin lispro, at least in part by enhancing vascular permeability. Each of the other excipients (such as magnesium chloride) in the LY900014 formulation is listed in the US Food and Drug Administration (FDA)'s Generally Recognized as Safe Food Additives database and in the FDA's Inactive Ingredients in Approved Drugs database. Furthermore, the excipient concentration in LY900014 is within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

To date, LY900014 has been administered to approximately 89 patients with diabetes (60 T1DM and 29 type 2 diabetes mellitus [T2DM]) across three Phase 1b studies and approximately 118 healthy volunteers across five Phase 1 studies. A further 24 patients with T1DM have received LY900014 in the ongoing CCI [redacted] Across these studies, LY900014 has consistently demonstrated a faster time-action profile than Humalog; however, the total insulin lispro exposure was similar between LY900014 and Humalog. In patients with T1DM, LY900014 reduced the time to early half-maximal drug concentration (early 50% $t_{max}$), a measure of insulin absorption, by 36.5% ($p<0.0001$) compared to Humalog. LY900014 displayed proportional increases in insulin lispro exposure (area under the concentration versus time curve [AUC] and maximum observed drug concentration [$C_{max}$]) with dose. The faster early insulin lispro absorption was maintained across the dose range studied (7.5 to 30 U). In patients with T1DM or T2DM treated with multiple daily injections (MDIs) of insulin therapy, LY900014 significantly reduced postprandial glucose excursions compared to Humalog when both were dosed through SC injection at the start of a standardised test meal. Additionally, through the use of MDIs of LY900014 for up to 2 weeks in patients with either T1DM or T2DM, it was found that LY900014 was well tolerated. There were no serious adverse events (SAEs) related to study treatment or discontinuations from the studies because of a drug-related adverse event (AE). Small numbers of treatment-emergent adverse events were reported, and there were no notable increases in these events in relation to any of the LY900014 formulations compared to those in relation to Humalog. There were no reported cases of severe hypoglycaemia related to LY900014 in these studies. Additionally, there were no reported incidences of local or systemic allergic reactions.

FIASP and NovoRapid (insulin aspart injection) are different formulations of the rapid-acting insulin analogue, insulin aspart, which when administered either SC or IV lowers blood glucose in patients with T1DM and T2DM. Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid at position B28, and is produced using recombinant DNA technology utilising *Saccharomyces cerevisiae*. In addition to the excipients in NovoRapid, FIASP also has arginine and nicotinamide as excipients (FIASP® SmPC, 2017; NovoRapid® SmPC, 2017).

## 3.3. Benefit/Risk Assessment

This study will not offer any direct benefits to the patients or healthy subjects participating in the study. The data from previous studies in healthy subjects and 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 studies that have evaluated treprostinil (CCI as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those AEs associated with systemic absorption of treprostinil, as described in the CCI CCI The exposures of treprostinil in LY900014 for participants in ongoing and future clinical studies are expected to be much lower than those observed in the dose ranges previously explored with SC bolus administration of treprostinil. Accordingly, treprostinil exposure in diabetic patients is generally below the detection limit CCI and is substantially lower (at least ~200-fold lower) than those observed in adults for the treatment of PAH. No known potential risks are associated with the microdoses of treprostinil in the LY900014 formulation.

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

Potential risks associated with NovoRapid or FIASP, are hypoglycaemia, hypokalaemia hypersensitivity reactions (localised allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), weight gain and peripheral oedema (FIASP® SmPC, 2017; NovoRapid® SmPC, 2017).

The study includes inpatient procedures during which participants will be continuously monitored. In the event patients experience hypoglycaemia during the MMTT, then the hypoglycaemia event will be treated as described in Section 9.4.8. If a patient experiences elevated blood glucose level following food intake for more than 1 hour, insulin glulisine will be administered IV (see Section 9.4.8 for treatment guidelines). Patients will maintain their basal insulin regimen of site-provided insulin glargine during the entire study including the MMTT days. Appropriate measures will be taken to minimise the risk of hyperglycaemia (including conduct of a dose-finding assessment to ensure that the individualised dose is appropriate for the standardised test meal).

The healthy subjects in the study will not have any study drug intervention and therefore no potential risks associated with any of the study drugs are applicable.

Healthy subjects will undergo inpatient procedures (a single MMTT), during which participants will be continuously monitored.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY900014 is to be found in the Investigator's Brochure (IB).

More detailed information about the known and expected benefits and risks of FIASP and NovoRapid may be found in the following: FIASP Summary of Product Characteristics and NovoRapid Summary of Product Characteristics.

# 4. Objectives and Endpoints

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

**Table ITSL.1. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| 1. To evaluate the differences in PK between LY900014 and Humalog following a single dose in patients with T1DM | 1. Early 50% $t_{max}$ and AUC(0-30min) |
| **Secondary** | |
| 1. To characterise the PK profiles of LY900014, Humalog, NovoRapid and FIASP following a single dose in patients with T1DM | 1. Early 50% $t_{max}$ |
| 2. To evaluate the differences in PD between LY900014 and Humalog following a single dose in patients with T1DM | 2. ΔAUC(0-1h), ΔAUC(0-5h) |
| 3. To characterise the PD response to LY900014, Humalog, NovoRapid and FIASP, as assessed by the MMTT, in patients with T1DM | 3. ΔAUC(0-1h), ΔAUC(0-5h) |
| **Tertiary/Exploratory** | |
| 1. To characterise "normal" insulin secretory and glucose response to the MMTT in non-diabetic healthy subjects | 1. Insulin and glucose concentrations |
| 2. To evaluate the tolerability of SC doses of LY900014 in patients with T1DM | 2. AEs and hypoglycaemic events |

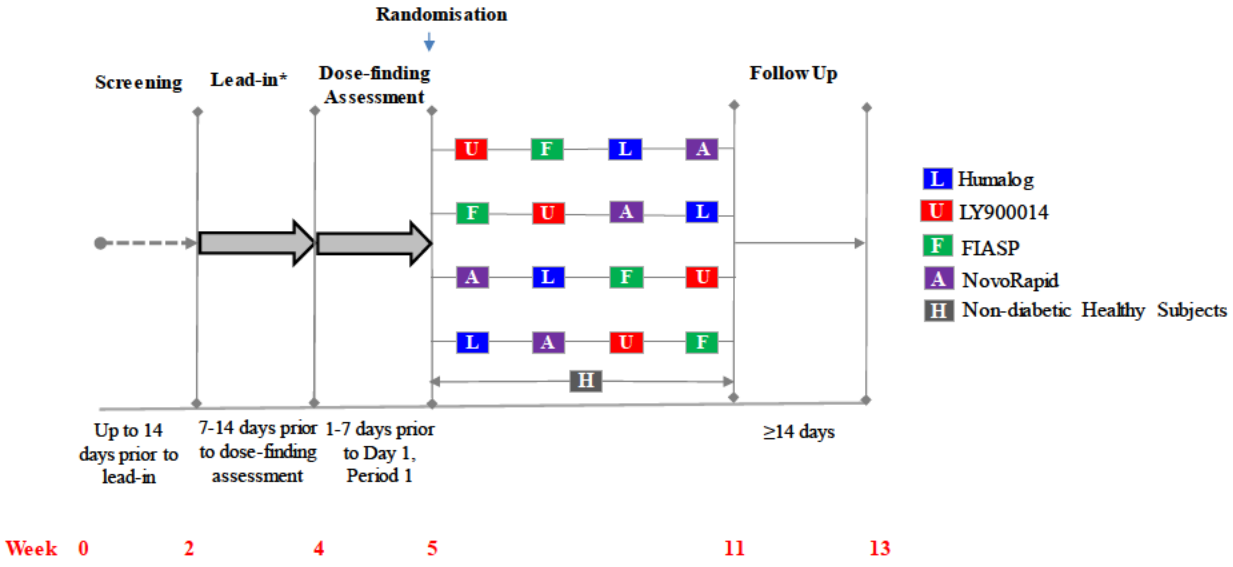
Abbreviations: AE = adverse event; AUC(0-30min) = area under the concentration versus time curve from time 0 to 30 minutes; ΔAUC = area under the baseline subtracted glucose concentration versus time curve; ΔAUC(0-1h) = ΔAUC from time 0 to 1 hour post-meal; ΔAUC(0-5h) = ΔAUC from time 0 to 5 hours post-meal; early 50% $t_{max}$ = time to early half-maximal drug concentration; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; T1DM = type 1 diabetes mellitus.

# 5. Study Design

## 5.1. Overall Design

Study I8B-MC-ITSL (ITSL) is a clinical pharmacology, patient- and investigator-blind, randomised, 4-treatment, 4-period crossover study in patients with T1DM to compare insulin lispro PK and PD profiles of the postprandial blood glucose during a standardised MMTT following LY900014 in comparison to Humalog in patients with T1DM following single SC injections administered just before a standardised MMTT. This study will also characterise the PK and PD of insulin aspart analogues NovoRapid and FIASP in patients with T1DM under identical study conditions. A non-diabetic healthy subject cohort, which approximately matches to the cohort of patients with T1DM with regard to the mean body mass index (BMI) and age, is included with the intention of characterising the insulin secretory response to a standardised MMTT within normal physiology. These subjects will undergo a single in-house MMTT and will not receive any of the study drugs. Study ITSL may be conducted at 1 or more clinical research units (CRUs).

Figure ITSL.1 illustrates the study design.




Abbreviation: MMTT = mixed meal tolerance test.
*Lead-in period 7 to 14 days prior to dose-finding assessment to enable transition to insulin glargine; patients continue use of insulin glargine and usual prandial insulin analogues throughout the study during lead-in and between MMTT assessments.
Dose-finding MMTT with Humalog is performed between 1 and 7 days prior to MMTT in Period 1.
4-period crossover: the 4 MMTT assessments may occur on successive days, but all should be completed within 6 weeks.
Intravenous glucose insulin infusion is provided from 7 hours to 30 minutes prior to MMTT to achieve a stable baseline glucose target in the patients with type 1 diabetes mellitus.
Single MMTT is performed in non-diabetic healthy subject cohort; no lead-in period is required.

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

### *5.1.1. Patients with T1DM*

Each patient will be randomised on Day -1 of Period 1 to one of 4 treatment sequences (see Figure ITSL.1) comprising single SC doses of LY900014, Humalog, NovoRapid, and FIASP, administered immediately before the start of a standardised MMTT (time=0 min) (see Section 6.3.1).

Prior to Period 1, a dose-finding test will be performed to confirm that the patient's insulin to carbohydrate ratio is appropriate for the standardised MMTT for the study. The current study will use individualised dosing based on the dose-finding assessment, and this unit dose will be the same for each insulin (Humalog, LY900014, NovoRapid and FIASP) administration during the 4 MMTTs. The 4 MMTT assessments can occur on consecutive days but not more than 14 days apart, and all the 4 MMTT assessments should be completed within 6 weeks.

Patients will be required to visit the CRU on at least 7 occasions (no more than 11 occasions if dose finding and/or 1 MMTT are rescheduled) as noted in the Schedule of Activities (see Section 2):

- Screening visit
- Lead-in (insulin transition) period (see Section 5.1.1.1)
- 4 inpatient CRU study visits (including dose-finding assessment [see Section 5.1.1.3])
- A follow-up visit at least 14 days after the last dose or early discontinuation

Eligible patients who have fulfilled the entry criteria and completed all screening procedures will return to the CRU 7 to 14 days prior to the dose-finding assessment visit to begin a lead-in (insulin transition) period. When patients visit the CRU to begin the lead-in period, patients will receive and review instructions on general diabetes education including measurement of self-monitored plasma glucose (SMPG), and on the insulin transition (see Section 9.4.7). During the insulin transition period, patients will transition from their current basal insulin therapy to the CRU-provided insulin glargine (see Section 5.1.1.1). Following insulin transition, patients will return to the CRU for dose-finding assessment (see Section 5.1.1.2) from 1 to 7 days prior to Day 1 of Period 1. The dose-finding assessment will involve the use of Humalog administered immediately (not more1 minute) before a standardised MMTT to inform the dose of prandial insulin (LY900014, Humalog, FIASP, or NovoRapid) to be used during the study MMTT assessments. Upon completion of the dose-finding assessment, patients will be randomised to 1 of 4 treatment sequences. Prior to the MMTT in each study period, patients will undergo a run-in period (see Section 5.1.1.3) to achieve a predetermined glucose target of 135±15 mg/dL (7.5±0.8 mmol/L). Once the glucose target is achieved, patients will proceed with the MMTT in which a single individualised SC dose of LY900014, Humalog, FIASP, or NovoRapid will be administered immediately before the standardised test meal (see Section 5.1.1.3).

Each dose of study drug (LY900014, Humalog, FIASP, and NovoRapid) will be separated by a minimum of 21 hours during all the treatment periods. The maximum duration allowed for all 4 treatment periods is approximately 6 weeks. Patients will continue using CRU-provided insulin glargine and their usual rapid- or fast-acting insulin analogues (prandial insulin) during the entire study including the lead-in period and between MMTTs (see Section 7.7 for use of concomitant medications and basal insulin). During the washout periods, patients will be instructed to perform regular monitoring of blood glucose (see Section 9.4.7).

Following completion of all study procedures in each period, patients may be offered a meal and discharged from the CRU at the discretion of the investigator.

#### 5.1.1.1. Lead-in and Insulin Transition

After completing all screening procedures according to the Schedule of Activities (Section 2), patients will return to the CRU for the lead-in visit and receive instructions on the insulin transition. The lead-in CRU visit is to take place 7 to 14 days prior to the dose-finding assessment. At the lead-in CRU visit, patients will transition from their current regimen of basal insulin to the CRU-provided insulin glargine according to the following guidance:

- 7 to 14 days prior to their admission to the CRU for the dose-finding assessment, patients will switch from neutral protamine Hagedorn (NPH) insulin, insulin detemir, insulin degludec or insulin glargine to the CRU-provided once-daily evening dose of insulin glargine. The starting dose will be at the investigator's discretion using patients' current insulin regimen as the reference.
- Adjustments may be made in consultation with the investigator following feedback obtained from the patient during at least twice-weekly telephone follow-up as part of the insulin-transition period.
- Once a stable dose has been established, patients will remain on it till completion of the study.

Patients can continue current therapy with any prandial insulin throughout the study.

Additionally, at the lead-in CRU visit, patients will be provided with general diabetes training including, but not limited to proper insulin-injection technique, correct self-monitoring of plasma glucose (PG) using a standardised glucometer, interpretation of results and symptoms, and treatment of hypoglycaemia. In addition to the study insulin, the CRU will also provide the glucometer, test strips, control solution and lancets. A diary will also be provided as described in Section 9.4.7.

#### 5.1.1.2. Dose-Finding Assessment

After transitioning to a stable dose of insulin glargine, patients will return to the CRU anytime between 1 and 7 days prior to MMTT in Period 1 for the dose-finding assessment. The dose-finding assessment may begin between 0700 and 1100 hours. Patients will have fasted for at least 10 hours prior to the standardised test meal (see Section 5.1.1.3). The dose-finding test will be performed to confirm that the patient's insulin to carbohydrate ratio is appropriate for the standardised MMTT for the study. The objective of the dose-finding assessment is to determine an appropriate, individualised prandial insulin dose to be administered with the standardised test meal during the study MMTT (see Section 5.1.1.3). The prandial insulin selected from the dose-finding assessment will be same for all insulins (Humalog, LY900014, NovoRapid and FIASP) assessed within the study.

The patient's blood glucose level will be measured to select a Humalog dose for the dose-finding assessment as follows:

- if the patient's blood glucose level is within the range of 70 to 180 mg/dL (3.9 to 10.0 mM), the patient will be given Humalog at the dose the patient would have taken at home
- the dose-finding meal test should not be carried out if the patient's blood glucose level is not within the range of 70 to 180 mg/dL (3.9 to 10.0 mM) prior to start of the dose-finding meal test. The dose-finding meal test may be rescheduled as judged by the investigator (see Section 6.2.3).

Immediately (within 1 minute) after the Humalog dose has been selected and administered, patients will receive a standardised test meal as described in Section 6.3.1. Patients are expected to complete each standardised test meal within 15 minutes of starting it.

The patient's blood glucose level will be measured every 20 minutes for 5 hours post-meal to select a Humalog dose for the study MMTT as follows:

- if the patient's blood glucose level is within the range of 70 to 240 mg/dL (3.9 to 13.3 mM) for 5 hours post-meal, the selected Humalog dose will be used for the prandial insulin dose (LY900014, Humalog, FIASP and NovoRapid) to be administered along with the MMTTs in all the periods but can still be adjusted if necessary based on the clinical judgement of the investigator.
- if the patient's blood glucose level is not within the range of 70 to 240 mg/dL (3.9 to 13.3 mM), the dose of Humalog will be adjusted based on the investigator's judgement or if the investigator is unable to make a decision regarding the Humalog dose after completing the initial test, the dose-finding assessment may be repeated once within 7 days of the initial assessment.
- if, during the dose-finding assessment, the patients' blood glucose level drops below pre-test baseline, the investigator may make further adjustments of the insulin dose. Refer to Section 9.4.8 for treatment of hyperglycaemia and hypoglycaemia.

Following completion of procedures associated with the dose-finding assessment, patients may be offered a meal. Dose-finding assessment should occur between 1 and 7 days prior to MMTT in Period 1. If the dose-finding assessment occurs from Day -2, the patient may continue to remain inpatient in the CRU until the completion of study MMTT on Day 1 of Period 1.

#### 5.1.1.3. Inpatient Procedures

**Run-In**

On the day before each MMTT day (that is, Day -1 in each of the 4 periods), patients will arrive at the CRU in the early evening (approximately 1700 hours) except for patients who undergo the dose-finding assessment from Day -2 of Period 1. Patients will be advised to bring their prandial insulin when they arrive at the CRU, which will be administered before the start of a standardised dinner.

Before the start of the run-in period, cannulation of 2 veins will be performed. A variable IV infusion of glucose (20% dextrose solution) and/or insulin glulisine will be initiated (~2400 hours) in order to obtain a blood glucose target level of 135±15 mg/dL (7.5±0.8 mmol/L). Any insulin infusion should be tapered off and stopped at least 30 minutes prior to start of the standardised test meal. For the last 30 minutes prior to study drug administration, the target blood glucose concentration should be within the range without any glucose infusion. If this target blood glucose range is not attained before 1100 hours, the meal test will be halted and may be performed on a separate visit; each meal test can only be repeated once (see Section 6.2.3 for rescheduling).

**Study MMTT**

Each patient's individual, short-acting insulin may be administered on Day -1 before the start of a standardised dinner (at approximately 1900 hours). If a correction dose of short-acting insulin needs to be administered after the meal, no more than 6 U of short-acting insulin should be administered between 7 and 12 hours before the scheduled intake of standardised test meal.

The meal test may start in the early morning at approximately 0700 hours with allowance up to 1100 hours, if required, to ensure the patient's blood glucose level is stable and on target, with the pre-meal activities as specified in the Schedule of Activities (Section 2). LY900014, Humalog, FIASP, or NovoRapid SC bolus injection will be administered immediately before the start of MMTT during each of the 4 treatment periods according to the randomisation schedule. The individualised dose for each patient will be the same for all the 4 treatment periods. For each MMTT, the patient should stay in a semi-supine position for 2 hours post-meal. The patient will not be allowed to consume water for 2 hours after the MMTT assessment begins; however, water may be consumed freely 2 hours post-meal.

A standardised MMTT will be administered on Day 1 during each of the 4 treatment periods. Patients are expected to complete each standardised test meal within 15 minutes of starting it. Patients will be without further food intake from the start of the meal to completion of blood collection (approximately 420 minutes) unless required to treat hypoglycaemia (see Section 9.4.8).

Following completion of the assessment period and sample collection (approximately 420 minutes), patients will be offered a meal. Patients will continue with the CRU-provided insulin glargine along with their usual bolus prandial insulin. Patients will be observed following administration of the meal and discharged at the investigator's discretion.

After completion of the last treatment period (Period 4), the patients will resume their pre-study basal insulin.

### *5.1.2. Healthy Subjects*

The cohort of healthy subjects will be approximately matched to the cohort of patients with T1DM as far as possible with regard to the mean BMI and age. The healthy subjects will be assessed for the PK and PD effects of their endogenous insulin. They will not be administered any study drugs, but will undergo MMTT as described below.

The subjects will be required to visit the CRU on at least 3 occasions as noted in the Schedule of Activities (see Section 2):

- Informed consent
- Screening visit (including an oral glucose tolerance test [Appendix 6]) up to 28 days prior to MMTT
- An inpatient CRU study visit

Eligible healthy subjects who have satisfied the entry criteria and completed all screening procedures will return to the CRU on Day -1 of the inpatient visit. Subjects will be offered a standardised dinner (at approximately 1900 hours).

On Day 1, the MMTT may start at approximately 0700 hours, with the pre-meal activities as specified in the Schedule of Activities (Section 2). A standardised MMTT will be performed on Day 1 and the subjects are expected to complete the standardised test meal within 15 minutes of starting it. The subjects should stay in a semi-supine position for 2 hours post-meal. The subjects will not be allowed to consume water for 2 hours after the MMTT assessment begins; however, water may be consumed freely 2 hours post-meal.

Subjects will be without further food intake from the start of the meal to completion of blood collection (approximately 420 minutes) unless required to treat hypoglycaemia (see Section 9.4.8).

Following completion of the assessment period and sample collection (approximately 420 minutes), subjects will be offered a meal. Subjects will be observed following administration of the meal and discharged at the investigator's discretion.

Study governance considerations are described in detail in Appendix 3.

## 5.2. Number of Participants

Up to 74 patients with T1DM may be enrolled so that approximately 64 patients complete the study. Replacement patients will adopt all 4 assigned crossover treatments of the original patient's randomisation schedule.

For the healthy subject cohort, sufficient subjects will be enrolled to have 12 healthy subjects complete the study.

For purposes of this study, a patient/subject completes the study when all scheduled procedures shown in the Schedule of Activities (see Section 2) have been finished.

## 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 patient/subject.

## 5.4. Scientific Rationale for Study Design

This study has a 4-period crossover design to reduce the variability of insulin PK and PD as each patient will serve as his/her own control. Also, the total number of patients needed with a crossover design is less than the number needed with a parallel group design. A maximum duration of approximately 6 weeks is allowed for patients to complete all 4 assigned periods to minimise the risk of insulin resistance/changes in mean glycaemic control during the study.

This study is being conducted in patients with T1DM, as this is the target population for the study drugs. Additionally in patients with T1DM there is no interference of endogenous

insulin. A healthy subject cohort is being included to characterise the normal physiological insulin secretory response to a single standardised MMTT.

Randomisation and blinding are used to avoid bias introduced through an association between allocation order of study drugs and patient characteristics. The Lilly clinical pharmacologist (CP)/Lilly study team will be unblinded.

In each study period, patients will undergo a run-in period before the MMTT using a variable insulin and glucose IV infusion. This run-in period will allow for improved comparability of the postprandial glucose response to a mixed meal after treatment with LY900014, Humalog, FIASP, and NovoRapid when administered immediately before the start of the meal. This run-in aims to achieve similar preprandial glucose levels for all patients before the start of the standardised test meal and thereby reduces the variability of the postprandial glucose response. Insulin glulisine has been chosen for IV optimisation of blood glucose during the run-in because it does not cross-react with either the insulin lispro- or insulin aspart-specific assay used for the PK analysis.

Under this design, if 2 periods occur on consecutive days, the interval between the last bolus on the first day and the first bolus on the second day is much longer compared to the length of time that the treatment (LY900014, Humalog, FIASP or NovoRapid) lasts in the bloodstream; therefore, no carryover effect is expected. This enables PK and PD data from the breakfast meal tests of each period to be analysed independently and separately.

At least 21 hours between the doses of study drug allows for a complete washout of study drug administered with the MMTT and glucose response and prevents carryover effects.

## 5.5. Justification for Dose

The bolus dose of insulin (LY900014, Humalog, FIASP, or NovoRapid) will be individualised to cover the carbohydrate content in this standardised test meal. This dose of insulin is reflective of clinically relevant, individualised insulin dosing, similar to the manner in which patients would determine the insulin dose for the carbohydrate content in a meal. For each patient, the individualised prandial insulin dose for each standardised test meal must be kept identical throughout the crossover periods.

# 6. Study Population

Eligibility of patients or 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 for patients may occur up to 14 days prior to the lead-in period. Patients who are not enrolled within 35 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Screening for healthy subjects may occur up to 28 days prior to Day 1. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

## 6.1. Inclusion Criteria

Patients or subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrolment:

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

for the non-diabetic healthy subjects: are overtly healthy males or females with normal glucose tolerance (see Section 6.1.2), as determined through medical history and physical examination.

a. Male patients:

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

b. Female patients:

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

ii. Otherwise, women of child-bearing potential participating in the study must agree to use 1 highly effective method of contraception until discharge from final treatment period.

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

2. A highly effective method of contraception includes a combined (oestrogen and progestogen containing) or progestogen-only hormonal contraception administered orally, intravaginally or transdermally and is associated with inhibition of ovulation. Alternatively, patients may use either an intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, or the partner should have been vasectomised.

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

1. infertile due to surgical sterilisation (hysterectomy, bilateral oophorectomy or bilateral salpingectomy), congenital anomaly such as Mullerian agenesis; or

2. post-menopausal – defined as a woman being amenorrhoeic for more than 1 year without an alternative medical cause and a serum follicle-stimulating hormone (FSH) level compatible with post-menopausal status. An FSH level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

[2] are aged 18 to 70 years, both inclusive.

[3] have a BMI of 18.5 to 30.0 kg/$m^2$, both inclusive.

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

[5] have venous access sufficient to allow for glucose infusion and blood sampling as per the protocol.

[6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures including the ability to consume the standardised test meal.

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

### *6.1.1. Additional Inclusion Criteria for T1DM*

[8] have an HbA1c ≤9.0% at screening.

[9] have had no episodes of severe hypoglycaemia in the past 6 months (see Section 9.4.6.2).

[10] are on stable prandial insulin and basal insulin (NPH insulin, insulin glargine or insulin detemir or insulin degludec) for at least 3 months before screening with a total insulin dose demand of ≤1.5 U/kg/day.

### *6.1.2. Additional Inclusion Criteria for Healthy Subjects*

[11] have a fasting PG of ≤100 mg/dL, and post-challenge PG of ≤140 mg/dL following oral glucose tolerance test (Appendix 6) and HbA1c <5.7% at screening.

## 6.2. Exclusion Criteria

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

[12] 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.

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

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

[15] have participated, within the past 30 days or 5 half-lives (whichever is longer) in a clinical study involving an investigational product.

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

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

[18] have a supine blood pressure at screening outside the range of 90 to 160 mmHg for systolic or 50 to 100 mmHg for diastolic (1 repeat is allowed) as determined by the investigator, or results with unacceptable deviations that are judged by the investigator to be clinically significant for the population, or have a heart rate outside the range of 50 to 90 beats/minute.

[19] have known or ongoing psychiatric disorders.

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

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

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

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

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

[25] are women who are pregnant or lactating.

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

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

[28] are currently smoking more than 5 cigarettes (or nicotine equivalent) per day.

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

[30] have a significant history of alcoholism or drug abuse as judged by the investigator.

[31] currently consumes more than 24 g of alcohol per day for men, or more than 12 g of alcohol per day for women (1 unit of alcohol is defined as 10 mL [8 g] of pure alcohol).

[32] are unwilling to comply with the dietary requirements/restrictions during the study: (i) comply with the fasting requirements of the study, (ii) consume only the meals/snacks provided during the inpatient visits.

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

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

### *6.2.1. Additional Exclusion Criteria for T1DM*

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

[36] patients with T1DM having proliferative retinopathy or maculopathy and/or severe neuropathy; in particular, autonomic neuropathy as judged by the investigator based on a recent (<1.5 years) ophthalmologic examination.

[37] have a history or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, haematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data.

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

[39] have type 2 diabetes and use other injectable or oral medications to treat hyperglycaemia (such as GLP-1 receptor agonists, metformin, or SGLT2 inhibitors)

[40] have known allergies to treprostinil (CCI [redacted], insulin lispro, insulin glulisine, insulin glargine, FIASP, insulin aspart-related compounds or any components of the formulation, or a history of significant atopy.

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

### *6.2.2. Additional Exclusion Criteria for Healthy Subjects*

[42] have a history or current 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 investigational product; or of interfering with the interpretation of data.

[43] are healthy nondiabetic volunteers that currently use any medications that impact insulin secretion or elevate glucose (such as beta blockers, thiazide diuretics, and niacin)

### *6.2.3. Additional Exclusion Criteria for Inpatient Dosing Days*

Patients or subjects who fulfil 1 or more inpatient dosing-day exclusion criteria will be excluded from study drug administration for that MMTT day. A single inpatient treatment period can be rescheduled 1 to 14 days later. Each treatment period can only be rescheduled once.

The following exclusion criteria apply to the day before each MMTT day:

[44] any medical condition or AE that could interfere with glucose metabolism, as judged by the investigator.

[45] during the run-in period and up to 2 hours prior to the start of the MMTT, episodes of non-severe hypoglycaemia (symptoms or BG ≤70 mg/dL [3.9 mmol/L]) can be treated with 15 to 20 g of carbohydrate. If a hypoglycaemia episode requires more than approximately 20 g of carbohydrate within 8 hours of the start of the MMTT or the patient experiences a severe hypoglycaemia episode up to 1 week prior to MMTT (as defined in Section 9.4.6.2 and 9.4.6.3), the MMTT must be rescheduled.

[46] bolus injection of more than 6 U of a prandial insulin between 7 and 12 hours before standardised test meal.

[47] any use of caffeine-containing food/beverages (for example, cola, chocolate drinks, tea, coffee, energy drinks containing methylxanthine [caffeine, theophylline, or theobromine]) for at least 12 hours before each standardised test meal and throughout the duration of each CRU visit.

## 6.3. Lifestyle and/or Dietary Requirements

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

### *6.3.1. Meals and Dietary Restrictions*

Patients and subjects will be provided standardised liquid meals for the MMTTs, as outlined in the Schedule of Activities (Section 2). A standardised evening meal on the day prior to the MMTT and a meal following completion of the MMTT will also be provided. Patients and subjects will be fasted (except for water) for at least 10 hours before each standardised test meal and consume each meal within approximately 15 minutes. The standardised test meal will use CCI ®. The standardised test meal will consist of 2 cans of 8 fl/oz CC CI (approximately 100 g of carbohydrates total in each standardised test meal). Patients and subjects will not be allowed to consume water for 2 hours after consuming the standardised test meal apart from the fluid provided with the meal; however, water may be consumed freely afterwards.

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

Following completion of study procedures, patients and subjects will be offered a meal. The CRU personnel will record dose and time of prandial insulin administered to patients with T1DM with end-of-study meal.

### *6.3.2. Caffeine, Alcohol and Tobacco*

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

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

No tobacco products including cigarette, cigars, pipes and nicotine replacement will be permitted during the inpatient visits.

### *6.3.3. Activity*

Patients and subjects will be encouraged to maintain their regular exercise and insulin regimen adaptation (for patients with T1DM only) during the outpatient period; however, they should not undertake vigorous or prolonged exercise at least 24 hours before each dosing day at the CRU. While in-patient, movement will be restricted to retain the integrity of connections to 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 involves a comparison of LY900014 administered through SC injection with Humalog, FIASP and NovoRapid. Insulin glargine (non-investigational drug) with a dose strength of 100 U/mL will be provided as the basal insulin from lead-in until the follow-up visit. Table ITSL.2 shows the treatment regimens.

**Table ITSL.2. Treatments Administered**

| **Treatment Name** | LY900014 | FIASP | Humalog[a] | NovoRapid |
|---|---|---|---|---|
| **Dosage Strength** | 100 U/mL (vial) | 100 U/mL (vial) | 100 U/mL (vial) | 100 U/mL (vial) |
| **Unit Dose Strength(s)** | Single dose, individualised dosing | Single dose, individualised dosing | Single dose, individualised dosing | Single dose, individualised dosing |
| **Route of Administration** | Subcutaneous | Subcutaneous | Subcutaneous | Subcutaneous |
| **Timing of Dose** | Bolus immediately before start of the MMTT | Bolus immediately before start of the MMTT | Bolus immediately before start of the MMTT | Bolus immediately before start of the MMTT |

Abbreviation: MMTT = mixed meal tolerance test.

[a] Two vials per patient will be used: 1 for the dose-finding MMTT and 1 for the test assessment. Single individualised dose during dose-finding MMTT and a single dose per the randomisation schedule.

The investigator or designee is responsible for

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

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

Each dose of study drug will be prepared by the investigator or designee and treatments will be administered using an insulin U-100 SC syringe. Each insulin vial will be labelled appropriately and dispensed to qualified study site personnel for administration. All study drugs will be given through SC injection by qualified and appropriately trained CRU personnel, at the CRU, as designated by the investigator. For SC dose administration, an insulin syringe will be used for the dose administration with an appropriate size of needle to ensure all injections are delivered to a consistent target depth into the SC space; if an 8-mm (or greater) needle is used to administer the injection, the skinfold should be pinched.

Injections will be rotated among different injection sites on the anterior abdominal wall during the 4 study periods (that is, left lower and upper quadrants, and right lower and upper quadrants). Study injections should be given by a limited number of individuals for consistency.

### *7.1.1. Packaging and Labelling*

The study insulin (LY900014, Humalog, FIASP, and NovoRapid) will be provided to the CRU in unblinded vials.

During the lead-in (insulin transition) period and between each MMTT, insulin glargine will be provided to the patients in pens.

All clinical study materials provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed and remaining at the end of the study will be maintained.

The investigational products will be labelled according to the country's regulatory requirements.

## 7.2. Method of Treatment Assignment

The study drug to be injected on a given treatment day will be determined according to the randomisation schedule.

### *7.2.1. Selection and Timing of Doses*

The SC dose of insulin (LY900014, Humalog, FIASP and NovoRapid) will be individualised per patient to cover the carbohydrate content of the standardised test meal based on the results from the dose-finding assessment (see Section 5.1.1.2). The individualised insulin dose of LY900014, Humalog, FIASP or NovoRapid for each patient must be kept identical for the standardised test meals throughout the crossover periods.

Patients will be provided with the appropriate insulin glargine for self-administration during the outpatient period(s) of the study. Patients will be instructed to select and rotate their injection sites in the abdominal area and to administer the SC treatment.

The doses during the inpatient period will be administered immediately before a standardised test meal and will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the patient's electronic case report form (eCRF).

## 7.3. Blinding

This is a patient- and investigator-blind study. The CRU personnel who administer the drug will not be blinded and will be separate and distinct from those who are involved in patient care. The sponsor including the Lilly CP/Lilly study team will be unblinded. Blinding will be maintained throughout the conduct of the study as described in a separate blinding document.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient'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 during the study MMTT procedure. However, dose adjustments may be made during the insulin transition period or between MMTTs based on the recommendation of the CRU investigator (see Section 7.7).

### *7.4.1. Special Treatment Considerations*

Lilly will provide insulin glargine during the lead-in period and throughout the study. Patients can continue current therapy with their prandial insulin therapy throughout the study.

Commercially available insulin glulisine and 20% dextrose will be used during the run-in period to stabilise blood glucose prior to the start of the meal test. Insulin glulisine may also be used to treat hyperglycaemia during the meal test (see Section 5.1.1.3).

## 7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all investigational products 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 or study materials, and only authorised CRU personnel may supply or administer investigational products. All investigational products 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 personnel.

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

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

## 7.6. Treatment Compliance

The investigational products will be administered at the CRU, and documentation of treatment administration will occur at the CRU.

Every attempt will be made to select patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the CRU.

The specifications in this protocol for the timings of safety, PK and PD sampling are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the eCRF. Failure to obtain samples due to clinical issues, such as problems with venous access, will not be considered a protocol violation, but written documentation will have to be provided to the sponsor for all missing samples (regardless of reasons) to facilitate data reconciliation before completion of the study.

Any major modifications that might affect the conduct of the study, patient safety and/or data integrity will be detailed in a protocol amendment.

## 7.7. Concomitant Therapy

Patients will continue the basal insulin regimen established during the insulin transition period throughout the entire study except when presenting safety issues or to prevent any medical problems (see Section 7.4); in this case, the investigator will as far as practically possible discuss a change in the regimen with the Lilly CP. Any change in the basal insulin regimen will be captured in the patients' diary and eCRF.

Patients can continue current therapy with prandial insulin throughout the study.

In both patients with T1DM and healthy subjects, any chronic systemic or inhaled glucocorticoid therapy (excluding topical, intra-articular and intraocular preparations) should be excluded. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

In general for both patients with T1DM and healthy subjects, the addition of new concomitant medications should be avoided; however, paracetamol (maximum 4 g/24 hours) may be administered at the discretion of the investigator for treatment of headache, etc. If the need for concomitant medication (other than paracetamol) arises, inclusion or continuation of the patient or subject may be at the discretion of the investigator after consultation with a Lilly CP or clinical research physician (CRP). Any medication used during the course of the study must be documented.

Patients with T1DM and healthy subjects may continue their stable concomitant medication at the time of study entry at regular, unchanged doses during the study; for example, antihypertensive medications, lipid-lowering agents, thyroid hormone replacement medications, hormonal contraception or hormonal replacement therapies.

Patients with T1DM and healthy subjects should not initiate new over-the-counter or prescription medications or nutritional supplements that affect blood glucose or the body's sensitivity to insulin or that promote weight loss 14 days before dosing or throughout the study.

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

## 7.8. Treatment after the End of the Study

Patients will revert to their previous insulin regimen after the final study MMTT and associated procedures have been completed.

Not applicable to healthy subjects.

# 8. Discontinuation Criteria

Patients or subjects discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 2 of this protocol.

## 8.1. Discontinuation from Study Treatment

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

- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >5X upper limit of normal (ULN) for healthy subjects, 8X ULN for patients
- ALT or AST >3X ULN for healthy subjects, 5X ULN for patients sustained for more than 2 weeks or
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalised ratio >1.5 or
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

### *8.1.1. Discontinuation of Inadvertently Enrolled Patients or Subjects*

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

## 8.2. Discontinuation from the Study

Patients or subjects will be discontinued under the following circumstances:

- Enrolment in any other clinical study involving an investigational product 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)
- positive drug screen, positive pregnancy test administered on Day -1 of Period 1 or any use of prescription or non-prescription medication according to Exclusion Criterion [38].
- Investigator Decision
    - if the patient or subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the

study indication, discontinuation from the study occurs prior to introduction of the new agent

- Subject Decision
    - the patient or subject requests to be withdrawn from the study.

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

## 8.3. Patients or Subjects Lost to Follow-up

A patient or 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 patients or 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).

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

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

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

## 9.1. Efficacy Assessments

This section is not applicable for this study.

## 9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient or subject to discontinue the investigational product before completing the study. The patient or subject should be followed up 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 patient's or subject's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, the CRU personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

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

Hypoglycaemic events are AEs of special interest and will be collected and reported throughout the trial as described in Section 9.4.6.3. All hypoglycaemic events will be recorded in the hypoglycaemia module of the eCRF, this allows for the collection of comprehensive safety information relating to these events.

### *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 (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or 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, the 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 patient or subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

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

Pregnancy (maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to 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 investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

### *9.2.2. Complaint Handling*

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

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

## 9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY900014, Humalog, FIASP or NovoRapid 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, Humalog, FIASP and/or NovoRapid Product Label (Humalog package insert, 2015; NovoRapid® product monograph, 2016; FIASP® SmPC, 2017).

## 9.4. Safety

### *9.4.1. Physical Examination*

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

### *9.4.2. Laboratory Tests*

For each patient and subject, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2). Patients will be fasted for at least 8 hours prior to the clinical laboratory tests.

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

### 9.4.3. Vital Signs

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

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

If orthostatic measurements are required, patients and subjects should be supine for at least 5 minutes and stand for at least 2 minutes.

If the patient or subject feels unable to stand, supine vital signs only will be recorded.

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.

### 9.4.4. Electrocardiograms

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

For each patient and subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Patients and subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the CRU as soon after the time of ECG collection as possible, and ideally while the patient or subject is still present, to determine whether the patient or subject meets entry criteria at the relevant visit(s) and for immediate patient or 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 patient or subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in patient and 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.

## *9.4.5. Other Tests*

### 9.4.5.1. Body Weight and Height

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

## *9.4.6. Safety Monitoring*

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- adverse events.

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

### 9.4.6.1. Hepatic Safety

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

### 9.4.6.2. Glucose Monitoring

Hypoglycaemia will be described using the following definitions (IHSG 2017):

- **Documented Glucose Alert Level (Level 1), PG ≤70 mg/dL (3.9 mmol/L):**
  - **Symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
  - **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with PG ≤70 mg/dL (3.9 mmol/L)

  - **Unspecified hypoglycaemia:** an event during which PG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded.
- **Documented Clinically Significant Hypoglycaemia (Level 2) PG <54 mg/dL (3.0 mmol/L):**
  - **Symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by PG ≤54 mg/dL (3.0 mmol/L)
  - **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with PG ≤54 mg/dL (3.0 mmol/L)
  - **Unspecified hypoglycaemia:** an event during which PG ≤54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycaemia was recorded.
- **Severe hypoglycaemia (Level 3):** an event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. During these episodes, the patient has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L])
  - **Severe hypoglycaemia requiring medical attention**: a severe hypoglycaemic event when patients require therapy by health care providers (emergency medical technicians, emergency room personnel, etc.).

**Other Hypoglycaemia:**

- **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 PG >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 all cases of hypoglycaemia. If an event of hypoglycaemia falls into multiple subcategories, the event is counted only once in this category
- **Probable symptomatic hypoglycaemia:** An event during which symptoms of hypoglycaemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

#### 9.4.6.3. 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 patient to have required assistance and is not predicated on the report of a patient simply having received assistance.

All hypoglycaemic events are AEs of special interest and will be recorded in the hypoglycaemia module of the eCRF (see Section 9.2 for details). All episodes of severe hypoglycaemia must be reported as SAEs.

### *9.4.7. Self-Monitored Plasma Glucose during Outpatient Period*

Self-monitored plasma glucose testing will consist of a minimum of daily 4-point SMPG profiles (preprandial for 3 meals [that is, breakfast, lunch and dinner] and at bedtime) using the glucometer provided by the site. Patients will be instructed to use a diary to document any AEs, hypoglycaemic events, insulin doses and the SMPG values.

During the lead-in (insulin transition) and washout period, hyperglycaemia will be monitored daily by fasting fingerstick glucose tests and documented in a diary. Each patient will be instructed to contact the CRU personnel if his/her fasting fingerstick glucose level is >200 mg/dL. The patient will be managed as considered appropriate by the investigator based on the actual glucose value (for example, return to the CRU for evaluation). If the patient has a fasting fingerstick glucose level >200 mg/dL on 2 consecutive days, the patient will be instructed to return to the CRU the following day to have a fasting PG performed. If the fasting PG >240 mg/dL is confirmed, the patient will be withdrawn from the study.

### *9.4.8. Treatment of Hyperglycaemia and Hypoglycaemia*

Patients and subjects will be without food intake from the start of the MMTT to completion of blood collection (approximately 420 minutes) unless required to treat hypoglycaemia (see Section 9.4.6.2 for definition of hypoglycaemia) with either rapidly absorbable oral carbohydrates or IV glucose.

Patients may consume up to 20 g of carbohydrates to treat or prevent hypoglycaemia during the fasting periods. If carbohydrates are administered and consumed, this must be captured in the patient's diary and eCRF.

During the MMTT, if a patient experiences hyperglycaemia (blood glucose concentration ≥306 mg/dL [17 mM]) for more than 1 hour, insulin glulisine may be administered IV.

In cases where treatment of either hypo- or hyperglycaemia require intervention, samples for blood glucose will be taken and PK samples will be collected as planned.

## 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 and plasma or serum concentrations of insulin aspart in patients with T1DM. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

### *9.5.1. Bioanalysis*

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

Serum concentrations of insulin lispro will be measured using a validated CCI [redacted] method specific for insulin lispro at a laboratory approved by the sponsor.

Plasma or serum concentrations of insulin aspart in patients with T1DM will be measured using a validated CCI [redacted] method specific for insulin aspart at a laboratory approved by the sponsor.

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

## 9.6. Pharmacodynamics

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

Blood samples (approximately 0.2 mL each) will be obtained for the measurement of glucose at the times specified in the Schedule of Activities (Section 2) using a validated method (for example, glucose analyser) that will be readily available at the CRU during the inpatient periods in order to provide real-time glucose measurement. Repeat samples for counter-checking of apparent spurious results may be taken where indicated. Samples will be disposed of upon confirmation of results.

### *9.6.1. Glucose Samples (Run-In Period)*

Blood glucose concentrations will be monitored at a minimum of 30-minute intervals during the run-in period on Day 1 (from approximately 7 hours before dosing).

### *9.6.2. Glucose Samples (MMTT)*

Blood samples will be obtained for the measurement of glucose at the times specified in the Schedule of Activities (Section 2). These glucose measurements will be used for patient safety management as well as for PD evaluations.

## 9.7. Genetics

Not applicable.

## 9.8. Biomarkers

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine endogenous insulin concentrations in plasma in healthy subjects using a commercially available validated enzyme-linked immunosorbent assay. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

## 9.9. Health Economics

This section is not applicable for this study.

# 10. Statistical Considerations and Data Analysis

## 10.1. Sample Size Determination

An initial 74 patients with T1DM may be enrolled so that approximately 64 patients complete the study. Sixty-four completing patients will provide at least 95% power to demonstrate a 2-fold increase in the serum insulin lispro AUC from time 0 to 30 minutes (AUC[0-30min]) between LY900014 and the Humalog. Testing will be done at an alpha level of 0.05 with a 2-sided confidence interval (CI). The sample size will also provide greater than 95% power to demonstrate a 35% reduction of early 50% $t_{max}$ between LY900014 and Humalog. The estimated standard deviation of within-subject difference on the log scale is 0.35 for AUC(0-30min) and 0.3 for early 50% $t_{max}$, according to an analysis of internal Lilly data (Study I8B-FW-ITRG) for LY900014 and Humalog administered in a repeat-dose study.

With this sample size, there is more than 95% power to detect a 40% reduction in postprandial glucose incremental area under the baseline subtracted glucose concentration versus time curve from time 0 to 1 hour ($\Delta$AUC[0-1h]) between LY900014 and Humalog. With similar assumptions, the study is also adequately powered for the comparison between LY900014 and NovoRapid.

With 64 completing patients, there is more than 95% power to detect a 20% reduction of early 50% $t_{max}$ between LY900014 and FIASP. In addition, there is approximately 80% power to demonstrate a 25% reduction in postprandial glucose incremental AUC from time 0 to 1 hour between LY900014 and FIASP. The power calculation is based on published results of FIASP studies and internal Lilly data.

Patients who are randomised but drop out before completing assigned treatment may be replaced to ensure that approximately 64 patients complete the study.

For the healthy cohort, 12 non-diabetic healthy subjects will be evaluated for their glucose and insulin secretory response to the MMTT. No treatment will be provided for this cohort. The sample size for the healthy cohort was chosen to provide sufficient data in order to evaluate the objectives of the study, and is not intended to achieve any a priori statistical requirements.

## 10.2. Populations for Analyses

### *10.2.1. Study Participant Disposition*

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

### *10.2.2. Study Participant Characteristics*

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

## 10.3. Statistical Analyses

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

Primary statistical analyses of PK and PD parameters for the cohort of patients with T1DM will be conducted on the set of patients who complete all treatment periods with identical prandial insulin doses for the MMTTs during the study, as the PK parameters and PD response is dependent on the insulin dose which is individualised for each patient. Supportive analyses may be done on the key parameters for the patients who complete at least 2 treatment periods.

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.

Safety analyses will be conducted on the set of patients receiving at least 1 dose of the study drug to which they are randomised, regardless of whether or not they completed all protocol requirements.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. No multiplicity test adjustment will be made for secondary objectives.

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

### *10.3.1. Safety Analyses*

#### 10.3.1.1. Clinical Evaluation of Safety

All treatment- and protocol procedure-related 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 study drug as perceived by the investigator during the inpatient period. 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 investigational product-related SAEs will be reported.

#### 10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed, and 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

Patients who complete at least 1 MMTT and have measurable insulin concentrations will be included in the analysis dataset for the PK analyses. Pharmacokinetic analyses will be conducted using standard noncompartmental methods of analysis ([redacted]) on a computer that meets or exceeds the minimum system requirements for these programs. It is possible that other validated equivalent PK software programs may be utilised if appropriate, warranted and approved by global PK management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

Serum insulin lispro and plasma or serum insulin aspart concentrations will be used to calculate several PK parameters, including time to early half-maximal drug concentration (early 50% $t_{max}$), time to late half-maximal drug concentration (late 50% $t_{max}$), maximum observed drug concentration ($C_{max}$), time to maximum observed drug concentration ($t_{max}$), AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-tlast]), AUC(0-30min), AUC from time 0 to 1 hour (AUC[0-1h]), AUC from time 0 to 7 hours (AUC[0-7h]) and AUC from time zero to infinity (AUC[0-$\infty$]). Additional partial AUCs may be computed as necessary, such as AUC from time 0 to 2 hours (AUC[0-2h]) and AUC from time 3 to 7 hours (AUC[3-7h]).

In addition, a graphical comparison of the "normal" insulin secretory response using the endogenous insulin levels following the MMTT from healthy subjects to the insulin lispro/aspart profile following these insulin analogues (LY900014, Humalog, FIASP or NovoRapid) in patients with T1DM will be performed. Additional analysis may be performed, if needed.

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

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.

### 10.3.2.2. Pharmacokinetic Statistical Inference

Patients who did not keep identical prandial insulin doses for the MMTTs across all periods will be excluded from the statistical analysis of the PK parameters.

The PK time parameters (early 50% $t_{max}$, late 50% $t_{max}$ and $t_{max}$) in the original scale will be analysed by the mixed-effect model that includes treatment (LY900014, Humalog, FIASP, NovoRapid), treatment sequence and period as fixed effects and patient within sequence as a random effect. Least-squares means (LSmeans), treatment differences in LSmeans and the corresponding 95% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance.

The treatment ratios and 95% CIs for the ratios will be calculated using Fieller's theorem (Chow and Liu 2009).

Log-transformed AUCs, $C_{max}$ for insulin lispro/aspart may be evaluated to estimate geometric means, ratios of geometric means and their corresponding 95% CIs using the same mixed-effect model as PK time parameters.

Statistical significance will be achieved when the p-value for a test is less than 0.05. The primary comparison will be of LY900014 to Humalog. The following comparison will also be performed. No multiplicity test adjustment will be made for these comparisons.

- LY900014 versus FIASP
- LY900014 versus NovoRapid
- Humalog versus NovoRapid

## *10.3.3. Pharmacodynamic Analyses*

### 10.3.3.1. Pharmacodynamic Parameter Estimation

Patients who receive at least 1 dose of study drug and have evaluable PD data will be included in the analysis set for the PD analyses.

Data will be analysed for the patients during each MMTT. The change from baseline values (the average of -30, -15 and 0 minutes represented as the 0-hour time point following the start of the MMTT) for each patient will be calculated. The ΔAUC[0-1h], area under the baseline subtracted glucose concentration versus time curve from time 0 to 2 hours post-meal (ΔAUC[0-2h] and area under the baseline subtracted glucose concentration versus time curve from time 0 to 5 hours post-meal (ΔAUC[0-5h]) will be calculated. In addition, the change from baseline maximum glucose observed during the 5 hours post-meal and change from baseline 1 hour glucose and 2 hour glucose after the start of the meal will be calculated. Other partial ΔAUCs may be calculated, as deemed appropriate.

In addition, a graphical comparison of the "normal" glucose response following the MMTT from healthy subjects to the glucose response following administration of these insulin analogues (LY900014, Humalog, FIASP or NovoRapid) in patients with T1DM will be presented.

Parameters will be individually calculated for each patient and presented by summary statistics.

### 10.3.3.2. Pharmacodynamic Statistical Inference

Patients who did not complete the entire meal or had significant changes in nutrient consumption of the standardised test meal or dose changes during the MMTTs will be excluded from all the statistical analysis of the PD parameters.

Summary statistics (including number of patients, mean, standard deviation or standard error, minimum and maximum) will be presented by treatment. All PD parameters (including ΔAUCs, glucose changes from baseline and time parameters) on the original scale (not log transformed) will be analysed using a statistical model that includes treatment, sequence and period as fixed

effects and patient within sequence as a random effect. The p-value on the difference between LSmeans will be used to determine statistical significance and the corresponding 95% CIs for the LSmean ratios from Fieller's theorem will be presented.

Statistical significance will be achieved when the p-value for a test is less than 0.05. The primary comparison will be of LY900014 to Humalog. The following comparison will also be performed.

- LY900014 versus FIASP
- LY900014 versus NovoRapid
- Humalog versus NovoRapid

No multiplicity adjustment will be done for the above pair comparisons.

### *10.3.4. Interim Analyses*

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

# 11. References

AMIS database. 13 June 2006. DIMDI (Deutsches Institut für medizinische Dokumentation und Information. Available at: https://www.dimdi.de/dynamic/de/db/recherche/index.htm. Accessed: November 07, 2017.

Chow SC, Liu JP. Design and analysis of bioavailability and bioequivalence studies. 3rd ed. Florida: Taylor and Francis Group, LLC; 2009:88-90.

FIASP [Summary of Product Characteristics]. DK-2880 Bagsværd, Denmark: Novo Nordisk A/S; 2017.

Humalog [package insert]. Indianapolis, IN: Eli Lilly and Company; 2017.

[IHSG] International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40(1):155-157.

NovoRapid [Summary of Product Characteristics]. DK-2880 Bagsværd, Denmark: Novo Nordisk A/S; 2017.

CCI

# Appendix 1. Abbreviations and Definitions

| Term | Definition |
|---|---|
| **AE** | adverse event: Any untoward medical occurrence in a patient or clinical investigation patient 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 0 to 30 minutes |
| **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.<br><br>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received. |
| **BMI** | body mass index |
| **CI** | confidence interval |
| **$C_{max}$** | maximum observed drug concentration |
| **complaint** | A complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| **compliance** | Adherence to all the study-related requirements, good clinical practice (GCP) requirements and the applicable regulatory requirements. |
| **confirmation** | A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results. |
| **CP** | clinical pharmacologist |
| **CRF** | case report form |
| **CRP** | clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer. |
| **CRU** | clinical research unit |

| | |
|---|---|
| **ΔAUC** | area under the baseline subtracted glucose concentration versus time curve from time 0 to 1 hour |
| **early 50% $t_{max}$** | time to early half-maximal drug concentration |
| **ECG** | Electrocardiogram |
| **eCRF** | electronic case report form |
| **enrol** | The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment. |
| **enter** | Patients entered into a study are those who sign the informed consent form directly. |
| **ERB** | ethical review board |
| **FDA** | Food and Drug Administration |
| **FSH** | follicle-stimulating hormone |
| **GCP** | good clinical practice |
| **GFR** | glomerular filtration rate |
| **HbA1c** | glycated haemoglobin |
| **HIV** | human immunodeficiency virus |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **informed consent** | A process by which a patient 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 patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form. |
| **investigational product** | A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the 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(ly) |
| **late 50% $t_{max}$** | time to late half-maximal drug concentration |
| **LSmeans** | least-squares means |

| | |
|---|---|
| **MDI** | multiple daily injection |
| **MMTT** | mixed meal tolerance test |
| **non-investigational product** | A product that is not being tested or used as a reference in the clinical study, but is provided to patients and used in accordance with the protocol, such as concomitant or rescue/escape medication for preventative, diagnostic or therapeutic reasons, medication to ensure adequate medical care and/or products used to induce a physiological response. |
| **OGTT** | oral glucose tolerance test |
| **NPH** | neutral protamine Hagedorn |
| **PAH** | pulmonary arterial hypertension |
| **PD** | pharmacodynamics(s) |
| **PG** | plasma glucose |
| **PK** | pharmacokinetic(s) |
| **randomise** | The process of assigning patients to an experimental group on a random basis. |
| **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. |
| **SMPG** | self-monitored plasma glucose |
| **SUSAR** | suspected unexpected serious adverse reaction |
| **T1DM** | type 1 diabetes mellitus |
| **T2DM** | type 2 diabetes mellitus |
| **TBL** | total bilirubin level |
| **$T_{max}$** | time to maximum observed drug concentration |
| **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 |
| **ULN** | upper limit of normal |

# Appendix 2. Clinical Laboratory Tests

## Safety Laboratory Tests

| | |
|---|---|
| Haematology[a] | Clinical Chemistry[a] |
| Haematocrit | Sodium |
| Haemoglobin | Potassium |
| Erythrocyte count (RBC) | Bicarbonate |
| Mean cell volume | Chloride |
| Mean cell haemoglobin | Calcium |
| Mean cell haemoglobin concentration | Phosphorus |
| Leucocytes (WBC) | HbA1c[b] |
| Platelets | Glucose[c] |
| Absolute counts of: | Blood urea nitrogen (BUN) |
| Neutrophils | Uric acid |
| Lymphocytes | Total cholesterol |
| Monocytes | Total protein |
| Eosinophils | Albumin |
| Basophils | Total bilirubin |
| | Alkaline phosphatase (ALP) |
| Urinalysis | Aspartate aminotransferase (AST) |
| Specific gravity | Alanine aminotransferase (ALT) |
| pH | Creatinine |
| Protein | Gamma-glutamyl transferase (GGT) |
| Glucose | C-peptide[b] |
| Ketones | |
| Bilirubin | Breath ethanol testing[d] |
| Urobilinogen | Urine drug screen[b,d] |
| Blood | Hepatitis B surface antigen[b] |
| Nitrite | Hepatitis C antibody[b] |
| Leucocytes | HIV[b] |
| Microscopy[e] | Pregnancy test[f] |
| | FSH[b] |
| | International normalised ratio (INR)[b] |
| | Partial thromboplastin time (PTT)[b] |

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

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

b Performed at screening.

c Fasting at screening, dose-finding assessment visit and Day 1 of Period 1 and at the follow-up visit.

d Will be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.

e If clinically indicated, per investigator's discretion.

f Females only: serum pregnancy test at screening and urine pregnancy test are performed as indicated in the Schedule of Activities.

# Appendix 3. Study Governance, Regulatory and Ethical Considerations

## *Informed Consent*

The investigator is responsible for

- ensuring that the patient/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 patient/subject. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient/subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant and retaining a copy on file.

## *Recruitment*

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

## *Ethical Review*

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

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

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

- the current IB or Patient Information Leaflet, Package Insert or Summary of Product Characteristics 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, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

## *Final Report Signature*

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

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

## *Data Quality Assurance*

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records and clinical notes. If requested, the investigator will provide the sponsor,

applicable regulatory agencies and applicable ERBs with direct access to the original source documents.

## *Data Collection Tools/Source Data*

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

## *Data Protection*

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

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

## *Study and Site Closure*

## *Discontinuation of Study Sites*

Study site participation may be discontinued if Lilly or its designee, the investigator or the ERB of the study site judges it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and GCP.

## *Discontinuation of the Study*

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

# Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with 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[a]** |
| AST | **Alkaline Phosphatase Isoenzymes[a]** |
| GGT | **Anti-smooth Muscle Antibody (or Anti-actin** |
| CPK | **Antibody)[a]** |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international 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-ITSL Sampling Summary for Patients**

| Purpose | Blood Volume per Sample (mL) | Number of Blood Samples | Total Volume (mL) |
|---|---|---|---|
| Screening | 11 | 1 | 11 |
| Clinical laboratory tests[a] | 9 | 3 | 27 |
| Dose-finding assessment | 0.2 | 15 | 3 |
| Blood glucose sampling (run-in) | 0.2 | 13 samples x 4 periods = 52 | 10.4 |
| Blood glucose sampling (MMTT) | 0.2 | 24 samples x 4 periods = 96 | 19.2 |
| Pharmacokinetics | 3 | 25 samples x 4 periods = 100 | 300 |
| Total | | | 370.6 |
| Total for clinical purposes [rounded up to the nearest 10 mL] | | | 380 |

Abbreviation: MMTT = mixed meal tolerance test.

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

**Protocol I8B-MC-ITSL Sampling Summary for Healthy Subjects**

| Purpose | Blood Volume per Sample (mL) | Number of Blood Samples | Total Volume (mL) |
|---|---|---|---|
| Screening[a] | 11 | 1 | 11 |
| OGTT | 2 | 3 | 6 |
| Blood glucose sampling (MMTT) | 0.2 | 24 | 4.8 |
| Endogenous insulin | 3 | 25 | 75 |
| Total | | | 96.8 |
| Total for clinical purposes [rounded up to the nearest 10 mL] | | | 100 |

Abbreviations: MMTT = mixed meal tolerance test; OGTT = oral glucose tolerance test.

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

# Appendix 6. Oral Glucose Tolerance Test

Oral glucose tolerance test (OGTT) will be performed as a screening test in healthy subjects (see Section 2).

The OGTT is a 2-hour test that checks the PG levels before and 2 hours after the subject consumes a 75 g glucose beverage (for example, ACCU-CHEK® Dextro® O.G-T).

To be tested, subjects must be on a stable diet, at a stable weight, with a stable level of exercise, and without acute illness or recent hospitalisation. The subject has to fast overnight for at least 8 hours, and should take nothing by mouth except water. No medication, caffeine or tobacco consumption is allowed until the completion of the test. The subject is given a 75 g glucose beverage that should be consumed in 5 minutes or less. Three blood samples are collected to measure PG levels: before ingestion of the glucose beverage and at 1 hour and 2 hours after the start of ingestion of the glucose beverage.

# Appendix 7. Protocol Amendment I8B-MC-ITSL(a) Summary
# A Mixed Meal Tolerance Test Study to Evaluate the Pharmacokinetics and Pharmacodynamics of LY900014 Compared to Humalog Following a Single Dose in Adults with Type 1 Diabetes

## Overview

Protocol I8B-MC-ITSL, A Mixed Meal Tolerance Test Study to Evaluate the Pharmacokinetics and Pharmacodynamics of LY900014 Compared to Humalog Following a Single Dose in Adults with Type 1 Diabetes, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- It was clarified in the protocol that the lead-in period would be 7 to 14 days prior to dose-finding assessment, instead of at least 14 days prior to dose-finding assessment.

# Revised Protocol Sections

| | |
|---|---|
| **Note:** | All deletions have been identified by ~~strikethroughs~~.<br>All additions have been identified by the use of underscore. |

## 1. Protocol Synopsis

**Treatment Arms and Planned Duration for an Individual Patient with T1DM:**

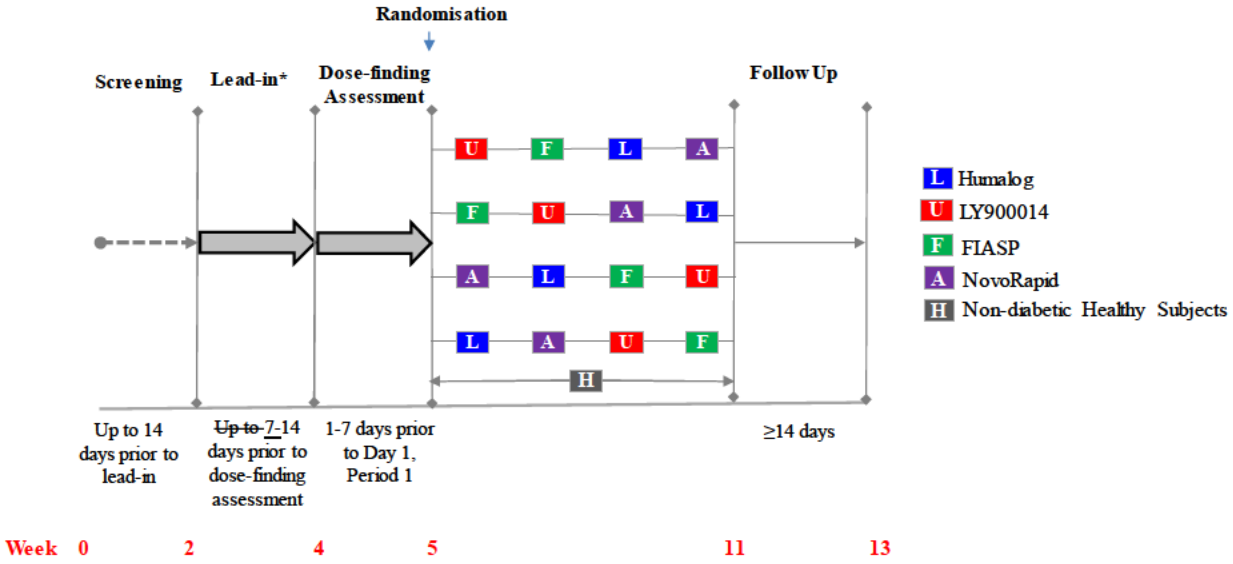
Patients will be screened over a 14-day period prior to start of a~~n approximate~~ 7- to 14-day lead-in (insulin transition) period.

## 2. Schedule of Activities

**Study Schedule Protocol I8B-MC-ITSL for Patients with T1DM**

| | Screening | Lead-In | Dose-Finding Assessment | Study Period (Periods 1 to 4) | | Follow-up/Early Discontinuation | Comments |
|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 14 days prior to lead-in** | **~~Up to~~7-14 days prior to dose-finding assessment** | **1-7 days prior to Period 1, Day 1** | **Day -1** | **Day 1** | **≥14 days after discharge** | |

## 5.1 Overall Design




Abbreviation: MMTT = mixed meal tolerance test.
*Lead-in period ~~up to~~7 to 14 days prior to dose-finding assessment to enable transition to insulin glargine; patients continue use of insulin glargine and usual prandial insulin analogues throughout the study during lead-in and between MMTT assessments.
Dose-finding MMTT with Humalog is performed between 1 and 7 days prior to MMTT in Period 1.
4-period crossover: the 4 MMTT assessments may occur on successive days, but all should be completed within 6 weeks.
Intravenous glucose insulin infusion is provided from 7 hours to 30 minutes prior to MMTT to achieve a stable baseline glucose target in the patients with type 1 diabetes mellitus.
Single MMTT is performed in non-diabetic healthy subject cohort; no lead-in period is required.

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

### 5.1.1 Patients with T1DM

……

Eligible patients who have fulfilled the entry criteria and completed all screening procedures will return to the CRU ~~at least~~7 to 14 days prior to the dose-finding assessment visit to begin a lead-in (insulin transition) period. When patients visit the CRU to begin the lead-in period, patients will receive and review instructions on general diabetes education including measurement of self-monitored plasma glucose (SMPG), and on the insulin transition (see Section 9.4.7).

#### 5.1.1.1 Lead-in and Insulin Transition

After completing all screening procedures according to the Schedule of Activities (Section 2), patients will return to the CRU for the lead-in visit and receive instructions on the insulin transition. The lead-in CRU visit is to take place 7 to 14 days prior to the dose-finding

assessment. At the lead-in CRU visit, patients will transition from their current regimen of basal insulin to the CRU-provided insulin glargine according to the following guidance:

- ~~At least~~ 7 to 14 days prior to their admission to the CRU for the dose-finding assessment, patients will switch from neutral protamine Hagedorn (NPH) insulin, insulin detemir, insulin degludec or insulin glargine to the CRU-provided once-daily evening dose of insulin glargine. The starting dose will be at the investigator's discretion using patients' current insulin regimen as the reference.