Protocol I8B-FH-ITSE

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro, Both in Combination with Insulin Glargine or Insulin Degludec in Adults with Type 2 Diabetes

NCT03952143

Approval Date: 27-Jun-2018

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LY900014

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Approval Date: 27-Jun-2018 GMT

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1. Synopsis

Title of Study:
A Prospective, Randomized, Double-Blind Comparison of LY900014 to Insulin Lispro, Both in Combination with Insulin Glargine or Insulin Degludec in Adults with Type 2 Diabetes

Rationale:
A prandial insulin with faster-onset and/or faster-offset characteristics might reduce glycemic excursions and the incidence of delayed postprandial hypoglycemia compared to currently available rapid-acting insulin analogs. Rapid-acting insulins, such as Humalog®, have been shown to have a more rapid onset of action compared to human insulin; however, the general consensus is that they are not rapid enough to match carbohydrate absorption, whether delivered by pump or syringe/pen injector, limiting efficacy. An ultra-rapid-acting prandial insulin that shifts the pharmacokinetic (PK) and glucodynamic profiles of insulin to provide an even faster onset of action, would better match carbohydrate absorption and allow for efficacious dosing immediately prior to meals or even after meals. Ultra-rapid insulin (URI) could be useful in the treatment of type 1 diabetes (T1D) and type 2 diabetes (T2D) in adults and children when delivered by multiple daily injections (MDI) or by continuous subcutaneous insulin infusion (CSII).

The aim of this study is to demonstrate that an ultra-rapid formulation of insulin lispro, LY900014, is non-inferior to insulin lispro on glycemic control as measured by change from baseline to Week 26 in hemoglobin A1c (HbA1c) in patients with T2D when administered in a double-blind manner as prandial insulin in combination with basal insulin glargine or degludec in accordance with local regulations.

Objectives/Endpoints:

Objectives	Endpoints
Primary Objective	
• To test the hypothesis that LY900014 is non-inferior to insulin lispro on glycemic control (non-inferiority margin [NIM]=0.4% for HbA1c) in patients with T2D, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec for 26 weeks	• Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Multiplicity Adjusted Objectives	
• To test the hypothesis that LY900014 is superior to insulin lispro in controlling 1-hour postprandial glucose (PPG) excursions, when administered as prandial insulin	• Difference between LY900014 and insulin lispro in the 1-hour PPG excursion (serum glucose measured 1 hour after the start of the meal minus fasting serum glucose) from a mixed-meal tolerance test (MMTT) at Week 26
• To test the hypothesis that LY900014 is superior to insulin lispro in controlling 2-hour PPG excursions when administered as prandial insulin	• Difference between LY900014 and insulin lispro in the 2-hour PPG excursion (serum glucose measured 2 hours after the start of the meal minus fasting serum glucose) from an MMTT at Week 26

Objectives	Endpoints
• To test the hypothesis that LY900014 is superior to insulin lispro on improving glycemic control (HbA1c) when administered as prandial insulin	• Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
• To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	• Rate (events/patient/100 years) of severe hypoglycemic events from baseline through Week 26
• To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic postmeal hypoglycemia	• Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic postmeal hypoglycemia within 1 and 2 hours after start of a meal from baseline through Week 26
• To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic hypoglycemia	• Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic hypoglycemic events from baseline through Week 26
• To compare LY900014 and insulin lispro with respect to 1,5-Anhydroglucitol (1,5-AG)	• Change from baseline in 1,5-AG values at Week 26
• To compare LY900014 and insulin lispro with respect to 10-point self-monitored blood glucose (SMBG) profiles	• Change from baseline in 10-point SMBG values at week 26
• To compare LY900014 and insulin lispro with respect to total, basal, and prandial insulin dose	• Change from baseline in total, basal and prandial insulin doses and prandial/total insulin dose ratio at Week 26
• To compare LY900014 and insulin lispro with respect to the proportion of patients achieving HbA1c targets	• The proportion of patients with HbA1c <7% and ≤6.5% at Week 26

Summary of Study Design:

Study I8B-FH-ITSE is a Phase 3, prospective, randomized, double-blind, multinational, multicenter, 2-group, parallel, active-controlled study conducted in patients with T2D currently treated with basal insulin in combination with at least 1 prandial insulin injection OR premixed insulin with at least 2 injections daily.

Treatment Groups and Duration:

Patients will be randomized to 1 of the 2 treatment groups in 2:1 ratio (LY900014:insulin lispro). The 2 treatment groups, LY900014 and insulin lispro, will be administered immediately (0-2 minutes) prior to each meal in a double-blind manner. The study includes a 1-week screening period and an 8-week lead-in period, followed by a 26-week treatment period and a 4-week safety follow-up period.

Number of Patients:

Approximately 705 patients will be screened to achieve 564 randomized patients and 480 patients completing 26 weeks of treatment. Approximately 450 Chinese patients will be randomized. The other 114 randomized patients are planned to be from other countries, which may include Mexico, Argentina, Brazil, India and Ukraine. The final participating countries and allocated patient numbers will be adjusted based on the actual condition.

Statistical Analysis:

The primary analysis is for the treatment period through Week 26.

Efficacy analyses will be conducted on all randomized patients using an intention-to-treat (ITT) approach according to the treatment the patients are assigned. The analyses for the primary and multiplicity adjusted objectives will include data collected prior to permanent discontinuation of investigational product (IP). When change from baseline is included as a response variable of analysis models, the patient will be included in the analysis only if a baseline and at least 1 post-baseline measurement are available. Selected efficacy analyses will also be conducted using the Per Protocol (PP) and Completer populations.

Safety analyses will be conducted on the Safety population. Analyses of AEs will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data collected prior to permanent discontinuation of IP. The second set of analyses will include all data collected during the course of the entire study including the follow-up visit, regardless of IP use. Analyses of hypoglycemia will use data collected prior to permanent discontinuation of IP, while analyses for post-treatment may be performed as needed. Analyses of safety laboratory measurements will be performed on all data during the planned treatment period regardless of IP use.

Baseline is defined as the last nonmissing measurement at or before the randomization visit (Visit 8), unless otherwise specified.

The primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro at Week 26 (Visit 18) from the mixed-effect model repeated measure (MMRM) analysis of change from baseline in HbA1c, including data collected from all randomized patients prior to permanent discontinuation of IP through Week 26. If the upper limit of the 2-sided 95% confidence interval (CI) for the least squares (LS) mean difference in the change from baseline in HbA1c for LY900014 minus insulin lispro is below +0.4%, LY900014 will be declared non-inferior to insulin lispro. The model for this analysis will include the fixed class effects of treatment, strata (country, type of basal insulin, and number of prandial doses at entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value.

A graphical approach (Bretz et al. 2011) for multiple comparisons will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the following multiplicity adjusted objectives: superiority of LY900014 compared with insulin lispro for 1-hour PPG excursion at Week 26, 2-hour PPG excursion at Week 26, and change from baseline to Week 26 in HbA1c.

An analysis of covariance (ANCOVA) model with strata (country, type of basal insulin, baseline HbA1c [$\leq$8.5%, >8.5%], and number of prandial doses at entry), and treatment as fixed effects and baseline as a covariate will be used to analyze the 1-hour and 2-hour PPG excursions. However, if the percentage of the patients with missing MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead. Analyses details will be documented in the statistical analysis plan (SAP).

Hypoglycemia rates will be summarized for periods of 30 days, 1 year, and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical

method. For each of the other categories of hypoglycemia, the number of hypoglycemia events during a specific period (rate) after randomization (for example, 0 to 12 weeks of treatment period) will be analyzed by using a negative binomial regression model. The model will include treatment and the baseline hypoglycemia rate (measured during lead-in) as a covariate. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days (or 30 days) will be included in the model to estimate the rate of hypoglycemia per year (or per 30 days). The proportion of patients with at least 1 hypoglycemic event in each category (incidence) during a specific period after randomization will be analyzed using a logistic regression model including treatment and baseline hypoglycemia rate value in the model.

Continuous safety variables, as well as the change from baseline for these variables, will be analyzed by MMRM or ANCOVA models. For categorical variables, Fisher's exact test will be used to compare treatment groups unless otherwise specified.

Change from baseline to last-observation-carried forward endpoints for the European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L), Insulin Treatment Satisfaction Questionnaire (ITSQ), and Work Productivity and Activity Impairment Questionnaire General Health (WPAI-GH) will be analyzed using ANCOVA models.

References:

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894-913.

Liu GF, Lu K, Mogg R, Mallick M, Mehrotra DV. Should baseline be a covariate or dependent variable in analyses of change from baseline in clinical trials? *Stat Med*. 2009;28(20):2509-2530.

Lu K. On efficiency of constrained longitudinal data analysis versus longitudinal analysis of covariance. *Biometrics*. 2010;66(3):891-896.

2. Schedule of Activities

Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period								Maintenance Period			Safety Follow-Up	ED
								Treatment Period												
eCRF Visit Number	**1**	**2**	**3[a]**	**4[a]**	**5**	**6[a]**	**7**	**8**	**9[a]**	**10**	**11**	**12[a]**	**13**	**14[a]**	**15**	**16**	**17**	**18**	**801**	**ED[b]**
Visit Window (± days)		**3**	**3**	**3**	**3**	**3**	**3**	**4**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Time on Study Relative to First Active Treatment Dose (weeks)	**-9**	**-8**	**-7**	**-6**	**-4**	**-2**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**18**	**22**	**26**	**30**	
Informed consent signed	X																			
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient eligibility review	X																			
Randomization[c]								X												
Clinical Assessments																				
Patient demographics	X																			
Medical history and preexisting conditions	X																			
Physical exam/height[d]	X																			
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs and product complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight[e]	X	X			X		X	X		X	X		X		X	X	X	X	X	X
Vital signs: blood pressure/pulse rate[f]	X	X			X		X	X		X	X		X		X	X	X	X	X	X
ECG (12-lead local)	X																			
Diabetes and nutrition counseling[g]		X																		
Transfer to insulin lispro[h]		X																		
Transfer to allowed study basal insulin regimen[i]		X																		
Basal and prandial insulin dose assessment[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Titrate basal insulin[j]		X	X	X	X	X	X													
Titrate prandial doses (as needed)[k]								X	X	X	X	X	X	X	X					

Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period								Maintenance Period			Safety Follow-Up	ED
								Treatment Period												
eCRF Visit Number	**1**	**2**	**3[a]**	**4[a]**	**5**	**6[a]**	**7**	**8**	**9[a]**	**10**	**11**	**12[a]**	**13**	**14[a]**	**15**	**16**	**17**	**18**	**801**	**ED[b]**
Visit Window (± days)		**3**	**3**	**3**	**3**	**3**	**3**	**4**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Time on Study Relative to First Active Treatment Dose (weeks)	**-9**	**-8**	**-7**	**-6**	**-4**	**-2**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**18**	**22**	**26**	**30**	
Ancillary Supplies/Diaries/IP																				
Dispense blood glucose meter, monitoring and ancillary supplies and complete training[l,m]		X						X		X	X		X		X	X	X	X		
Distribute study diary		X			X		X	X		X	X		X		X	X	X	X		
Diary use training[m]		X																		
Collect study diary and transfer diary data to eCRF (InForm)[n]					X		X	X		X	X		X		X	X	X	X	X	X
Train on collecting 4-point and 10-point SMBG Profile[n]		X																		
Review 4-point SMBG profiles[o]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Remind patient of 10-point SMBG requirements[p]						X	X							X			X			
Review 10-point SMBG profiles								X							X			X		X[q]
Review/discuss hypo data			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Dispense IP		X			X			X			X		X		X	X	X			
Patient returns used and unused study drug supplies					X			X			X		X		X	X	X	X		X
Drug accountability					X			X			X		X		X	X	X	X		X

Study Procedure	Study Screening	Lead-In Period						Intensive Titration Period								Maintenance Period			Safety Follow-Up	ED
								Treatment Period												
eCRF Visit Number	**1**	**2**	**3[a]**	**4[a]**	**5**	**6[a]**	**7**	**8**	**9[a]**	**10**	**11**	**12[a]**	**13**	**14[a]**	**15**	**16**	**17**	**18**	**801**	**ED[b]**
Visit Window (± days)		**3**	**3**	**3**	**3**	**3**	**3**	**4**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Time on Study Relative to First Active Treatment Dose (weeks)	**-9**	**-8**	**-7**	**-6**	**-4**	**-2**	**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**18**	**22**	**26**	**30**	
Laboratory Assessments																				
Patient fasts prior to visit		X						X										X		X
MMTT[r]								X										X		
Urinalysis panel	X																			
Pregnancy test[s]	X							X												
Follicle-stimulating hormone test[t]	X																			
Chemistry	X							X										X		X
Fasting serum glucose		X																		
Hematology	X							X										X		X
1,5-Anhydroglucitol								X			X				X			X		X
Hemoglobin A1c	X						X	X			X		X		X			X	X	X
Lipid profile								X										X		X
Anti-insulin lispro antibodies		X						X		X	X				X			X	X	X
Health outcomes questionnaires[u]																				
ITSQ		X						X										X		X
EQ-5D-5L		X						X										X		X
WPAI-GH		X						X										X		X

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; EQ-5D-5L = European Quality of Life – 5 Dimensions 5 Level; FBG = fasting blood glucose; hypo = hypoglycemia; IP = investigational product; ITSQ = Insulin Treatment Satisfaction Questionnaire; IWRS = interactive web response system; MMTT = mixed-meal tolerance test; SMBG = self-monitored blood glucose; WPAI-GH = Work Productivity and Activity Impairment Questionnaire General Health.

[a] Telephone visits are indicated by shaded columns. Activities include:

- Record visit in IWRS.
- Collect AEs and concomitant medications.
- Review blood glucose readings and study drug doses. Recommendations for basal or prandial insulin adjustments are provided, if necessary by the investigator or designee.
- Review hypoglycemic events.
- Provide reminders regarding scheduled visits, fasting, and SMBG profiles, as applicable.

[b] Patients who have been randomized will be asked to return for the ED visit in a fasting state unless patient is already fasting and at the site when the decision to discontinue is made. Patients who discontinue during the lead-in period prior to randomization, and who are not already at the site, will be asked to return for the ED in a nonfasting state and all activities should be completed except for laboratory tests and completing the questionnaires (ITSQ, EQ-5D-5L, and WPAI-GH).

[c] Randomization should occur after all Visit 8 procedures including MMTT. If MMTT is rescheduled post Visit 8, randomization should not occur until baseline MMTT is completed. The patient will administer their first dose of study insulin with the first meal after the MMTT has been completed and randomization has occurred.

[d] Physical examination shall be performed at Visit 1. It shall be performed at other visits if deemed necessary by the investigator.

[e] Patients should be advised to remove their shoes and empty their pockets before the body weight is obtained.

[f] Vital sign measurements must be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing. These measurements should be determined after patients have been seated quietly for at least 5 minutes in a chair with feet on the floor. The arm used for BP measurement should be supported at heart level

[g] Initial training at Visit 2 will include diabetes education and nutrition counseling. Appropriate site personnel will administer training and education using locally approved diabetes education/training materials and programs or by using other materials that may be provided by the Sponsor. Patients may be provided abbreviated training and education at visits following Visit 2 based upon patient needs.

[h] Only applies to patients treated with insulin glulisine, insulin aspart, regular human insulin, or premixed insulin.

[i] Patients will be transferred to insulin glargine U-100 once daily or to degludec U-100 once daily at Visit 2 if the patient enters the study on any other basal insulin regimen. Investigators will determine the appropriate basal insulin regimen for each patient. Basal insulin should be titrated during the 8-week lead-in period to the target FBG. Basal insulin dose may be adjusted if needed to facilitate optimal prandial insulin dosing during the intensive titration period (Weeks 0 to 12) or for safety reasons. Thereafter, during the maintenance period (Weeks 12 to 26), it is expected that adjustments to basal insulin doses would be for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

[j] Assessments of the basal insulin dose should be made at minimum weekly during the lead-in period, including Weeks -5 and -3. Assessment of the prandial insulin dose should be made at minimum weekly during the initial 12 weeks after randomization, including Weeks 3, 5, 7, 9, and 11. See also Sections 7.2.1.3 and 7.2.1.4.

[k] During the initial 12 weeks after randomization, the prandial insulin dose (either fixed insulin dose or insulin to carbohydrate ratio) and correction factor (as applicable) should be adjusted as necessary in order to meet the target SMBG levels. During the maintenance period (Weeks 12 to 26), it is expected that prandial insulin dose adjustments would be to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

[l] Glucose monitoring supplies will be dispensed at other visits, as needed.

[m] Training may be repeated at other visits, as needed.

[n] Study sites will retain study diaries.

[o] Patients should be encouraged to measure a minimum of 4 SMBG readings daily to satisfy dose titration. 4-point SMBG is required on three nonconsecutive days in the one week before each visit.

[p] Patients should be instructed to perform three 10-point SMBG profiles during a 2-week period. The 10-point SMBG profile is completed over a 1-day period, preferably on 3 nonconsecutive days (weekdays and weekends). Ten-point SMBG profiles should not be performed on the day of MMTT.

[q] Review of 10-point SMBG profiles at ED visit will take place only for patients randomized into the study.

[r] MMTT can occur 0 to 4 days prior to the visit and patient must be fasting. Time 0 of the MMTT will be when the patient starts to consume the meal. Serial venous blood samples to measure serum glucose will be taken at time -15, 0, 15, 30, 60, 120, 180, and 240 minutes after the start of the meal.

[s] Serum pregnancy test that is analyzed by central laboratory must be performed in women of childbearing potential at Visit 1 followed by a local urine or serum pregnancy test within 24 hours prior to IP exposure at randomization (Visit 8) and at other times at the investigator's discretion. When required per local regulations and/or institutional guidelines, local pregnancy testing will occur at mandatory times during the study treatment period, and the local pregnancy test must be kept at site.

[t] Follicle-stimulating hormone test must be performed at Visit 1 for a postmenopausal woman who is between 50 and 54 years of age (inclusive) with an intact uterus, not on hormone therapy, and who has had at least 6 months of spontaneous amenorrhea.

[u] Health outcomes questionnaires will be administered at the study sites based on the availability of appropriate translations. The questionnaires should be administered prior to other study procedures except at Visit 8 and Visit 18 when questionnaires may be administered following the start of the MMTT.

3. Introduction

3.1. Study Rationale

A prandial insulin with faster-onset and/or faster-offset characteristics might reduce glycemic excursions and decrease the incidence of delayed postprandial hypoglycemia compared to currently available rapid-acting insulin analogs. The insulin analog, insulin lispro (Humalog®), has been shown to be absorbed more quickly than regular human insulin (Humalog package insert, 2015). In healthy volunteers given subcutaneous (SC) doses of insulin lispro ranging from 0.1 to 0.4 U/kg, peak serum levels were seen 30 to 90 minutes after dosing. Rapid-acting insulins have been shown to have a more rapid onset of action compared to human insulin; however, the general consensus is that they are not rapid enough to match carbohydrate absorption and many patients are unable to achieve optimal glycemic control. An ultra-rapid-acting prandial insulin with pharmacokinetic (PK) and glucodynamic (GD) profiles that demonstrate faster absorption and onset of action, may better match carbohydrate absorption and lead to improved postprandial control. The time action profile of a rapid-acting insulin could be enhanced through the addition of excipients to an existing formulation to increase capillary blood flow and/or enhance vascular permeability. An ultra-rapid insulin (URI) would be useful in the treatment of type 1 diabetes (T1D) and type 2 diabetes (T2D) when delivered by multiple daily injections (MDI), by continuous subcutaneous insulin infusion (CSII), and in the development of closed loop insulin delivery systems.

The aim of this study is to demonstrate that an ultra-rapid formulation of insulin lispro, LY900014, is noninferior to insulin lispro on glycemic control as measured by change from baseline to Week 26 in hemoglobin A1c (HbA1c) in patients with T2D when administered in a double-blind manner as prandial insulin in combination with basal insulin glargine or degludec in accordance with local regulations. The study will expand the evaluation of the efficacy and safety of LY900014 to a broader race/ethnic spectrum of patients with T2D.

3.2. Background

Type 2 diabetes can remain asymptomatic for many years, and about 50% of people with T2D are undiagnosed (IDF [WWW]). The global prevalence of diabetes in 2015 among adults was estimated to be 9.0% or 415 million people, with greater than 90% of these cases being T2D (IDF [WWW]).

There have been many advances in the treatment of T2D in the last 20 years; however, reaching and maintaining glycemic goals remains challenging even under intensive insulin therapy regimens. Although estimates on the number of patients with diabetes not meeting targets vary, the values are consistently high. An analysis of NHANES data from 2007-2010 found that almost half of US adults with diabetes do not meet the HbA1c target of ≤7.0% (Ali et al. 2013). Another analysis of NHANES data showed that after improvements in glycemic control between 1999 and 2006, the HbA1c level plateaued through 2014 and the proportion of patients achieving HbA1c <7% has remained relatively unchanged between the two most recent waves of data (Carls et al. 2017). The UK National Diabetes Audit 2015–2016 reported that HbA1c levels were >7.5% in more than two thirds (70.8%) of people with T1D and in more than one third

(34.3%) of those with T2D (NHS 2017) Currently available rapid-acting insulin analogs are unable to match the kinetics of physiological postmeal insulin secretion, which is biphasic. Normal first-phase insulin response is a rapid but short-lived increase in secretion, which is then followed by a more slowly developing prolonged increase (Barrett et al. 2016). First phase insulin release prevents the rapid development of postprandial hyperglycemia, while second phase release of insulin ensures that glucose enters tissues in a steady, controlled manner throughout the late postprandial period. Thus, there remains a need to continue to develop formulations with a time action profile that more closely approximates that of endogenous insulin section.

Insulin lispro is indicated to be administrated within 15 minutes before a meal or immediately after a meal (Humalog package insert, 2015). Ideally, currently available rapid-acting insulin analogs should be injected 10 to 15 minutes prior to meal consumption in order to control postprandial glucose (PPG). However, many people inject their rapid-acting insulin at the time of the meal or after the meal. According to survey data from the T1D Exchange on the timing of prandial insulin injection, 21% of patients reported administering insulin several

minutes before meals, 44% immediately before meals, 10% during meals, and 24% after meals (Dayte et al. 2017).. Because patients often inject later than recommended, there is a greater mismatch between insulin action and postprandial blood glucose (BG) elevations. With postmeal dosing, the mismatch between the rise in BG and the onset of insulin action is even more pronounced. For the development of a URI, it will be important to understand the relationship between time action profile of the insulin, insulin injection timing, and meal timing in order to maximize improvements in postprandial glycemic control and minimize hypoglycemia risk. A URI with higher early insulin concentration and peak exposure, and shorter duration should improve early postprandial control and limit postmeal hyperglycemia, while reducing late postprandial hypoglycemia due to lower insulin exposure. Patients will administer Humalog at 0 to 2 minutes before the start of the meal to maintain the study blind.

Hemoglobin A1c provides an integrated measurement of both fasting and postprandial glycemic control and is the most reliable marker for overall glucose exposure. Elevation in HbA1c is the best predictor of diabetes complications. Control of both fasting and postprandial hyperglycemia is essential to reach HbA1c goals. The relative contribution of postprandial hyperglycemia is predominant with moderate to fairly well controlled HbA1c levels (Monnier et al. 2003).

A new pharmaceutical innovation that may allow more effective control of PPG levels is LY900014, a new formulation of insulin lispro developed as an ultra-rapid acting insulin with a faster onset of action and shorter duration of action compared to currently available rapid-acting insulin analogs. The changes in PK and GD characteristics are achieved by coformulating insulin lispro with treprostinil and ingredients Generally Recognized As Safe (GRAS) by the US Food and Drug Administration (FDA) as excipients.

LY900014 is a formulation of insulin lispro that contains the prostacyclin analog treprostinil, citrate, and other excipients. Treprostinil as an excipient enhances the absorption of insulin lispro by local vasodilatation rather than an as an active pharmaceutical ingredient that elicits a

systemic effect. Treprostinil is a prostacyclin analog administered either by inhalation (Tyvaso®), intravenous (IV) infusion, or continuous subcutaneous infusion (Remodulin®) for the treatment of symptomatic pulmonary arterial hypertension, and has been approved in the United States since 2002 (Remodulin package insert, 2014) and in Europe since 2005 (PMR [WWW]). Sodium citrate, an excipient that speeds insulin absorption, is also included in the formulation to further enhance the absorption of insulin lispro. Sodium citrate and the other excipients in the LY900014 formulation are listed in the FDA GRAS food additives database and in the FDA 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.

Refer to the Humalog local product labeling (for example, Humalog package insert, 2015; Humalog Summary of Product Characteristics, 2016) for more information regarding insulin lispro.

The Investigator's Brochure (IB) describes the clinical and nonclinical development of LY900014.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks of insulin lispro may be found in the country-specific product labeling (for example, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics).

Across all doses in the Eli Lilly and Company (Lilly) clinical studies that have evaluated treprostinil as a local vasodilator with or without insulin lispro, there was no clinically significant increase in those adverse events (AEs) associated with systemic absorption of treprostinil, as described in the Remodulin package insert (2014) (that is, headache, diarrhea, nausea, jaw pain, vasodilatation, rash, edema, anorexia, vomiting, asthenia, abdominal pain, and hypotension). The exposures of treprostinil in LY900014 for participants in upcoming and future clinical trials are expected to be much lower than those observed in the dose ranges previously explored with SC bolus administration of treprostinil and are expected to be substantially lower than those observed in the treatment of pulmonary artery hypertension. Treprostinil is unmeasureable in the serum after administration of LY900014 in doses expected to be used in the clinical setting.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated AEs of LY900014 can be found in the IB.

4. Objectives and Endpoints

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

Table ITSE.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
• To test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control (NIM=0.4% for HbA1c) in patients with T2D, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec for 26 weeks	• Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Multiplicity-Adjusted Objectives	
• To test the hypothesis that LY900014 is superior to insulin lispro in controlling 1-hour PPG excursions, when administered as prandial insulin	• Difference between LY900014 and insulin lispro in the 1-hour PPG excursion (serum glucose measured 1 hour after the start of the meal minus fasting serum glucose) from an MMTT at Week 26
• To test the hypothesis that LY900014 is superior to insulin lispro in controlling 2-hour PPG excursions when administered as prandial insulin	• Difference between LY900014 and insulin lispro in the 2-hour PPG excursion (serum glucose measured 2 hours after the start of the meal minus fasting serum glucose) from an MMTT at Week 26
• To test the hypothesis that LY900014 is superior to insulin lispro on improving glycemic control (HbA1c) when administered as prandial insulin	• Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
• To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	• Rate (events/patient/100 years) of severe hypoglycemic events from baseline through Week 26
• To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic postmeal hypoglycemia	• Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic postmeal hypoglycemia within 1 and 2 hours after start of a meal from baseline through Week 26
• To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic hypoglycemia	• Rate (events/patient/year and/or events/patient/30 days) and incidence (percent of patients with at least 1 event) of documented symptomatic hypoglycemic events from baseline through Week 26
• To compare LY900014 and insulin lispro with respect to 1,5-AG	• Change from baseline in 1,5-AG values at Week 26
• To compare LY900014 and insulin lispro with respect to 10-point SMBG profiles	• Change from baseline in 10-point SMBG values at Week 26
• To compare LY900014 and insulin lispro with respect to total, basal, and prandial insulin dose	• Change from baseline in total, basal and prandial insulin dose and prandial/total insulin dose ratio at Week 26

Objectives and Endpoints

Objectives	Endpoints
Other Secondary Objectives (Continued)	
• To compare LY900014 and insulin lispro with respect to the proportion of patients achieving HbA1c targets	• The proportion of patients with HbA1c <7% and ≤6.5% at Week 26
Tertiary/Exploratory Objectives	
• To compare the safety of LY900014 relative to insulin lispro	• Adverse events, vital signs, chemistry, and hematology laboratory measures
• To compare the incidence of treatment-emergent anti-insulin lispro antibodies for LY900014 and insulin lispro	• Incidence of treatment-emergent positive anti-insulin lispro antibodies
• To compare LY900014 and insulin lispro with respect to quality of life as measured by the EQ-5D-5L	• Change from baseline in EQ-5D-5L UK-population based health state index score and EQ-VAS score at Week 26
• To compare LY900014 and insulin lispro with respect to diabetes treatment satisfaction as measured by the ITSQ	• Change from baseline in ITSQ regimen inconvenience and lifestyle flexibility domain scores at Week 26
• To compare LY900014 and insulin lispro with respect to the impact that diabetes has on the ability to work and perform regular activities as measured by the WPAI-GH	• Change from baseline in WPAI-GH item scores at Week 26
• To compare LY900014 and insulin lispro with respect to changes in body weight	• Change from baseline to Week 26 in weight (kg)
• To compare LY900014 and insulin lispro with respect to glycemic variability	• Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 10-point SMBG profiles

Abbreviations: 1,5-AG = 1,5-Anhydroglucitol; EQ-5D-5L = European Quality of Life – 5 Dimensions 5 Level; EQ-VAS = EuroQol visual analog scale; HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire; MMTT = mixed-meal tolerance test; NIM = non-inferiority margin; PPG = postprandial glucose; SMBG = self-monitored blood glucose; T2D = type 2 diabetes; WPAI-GH = Work Productivity and Activity Impairment Questionnaire General Health.

5. Study Design

5.1. Overall Design

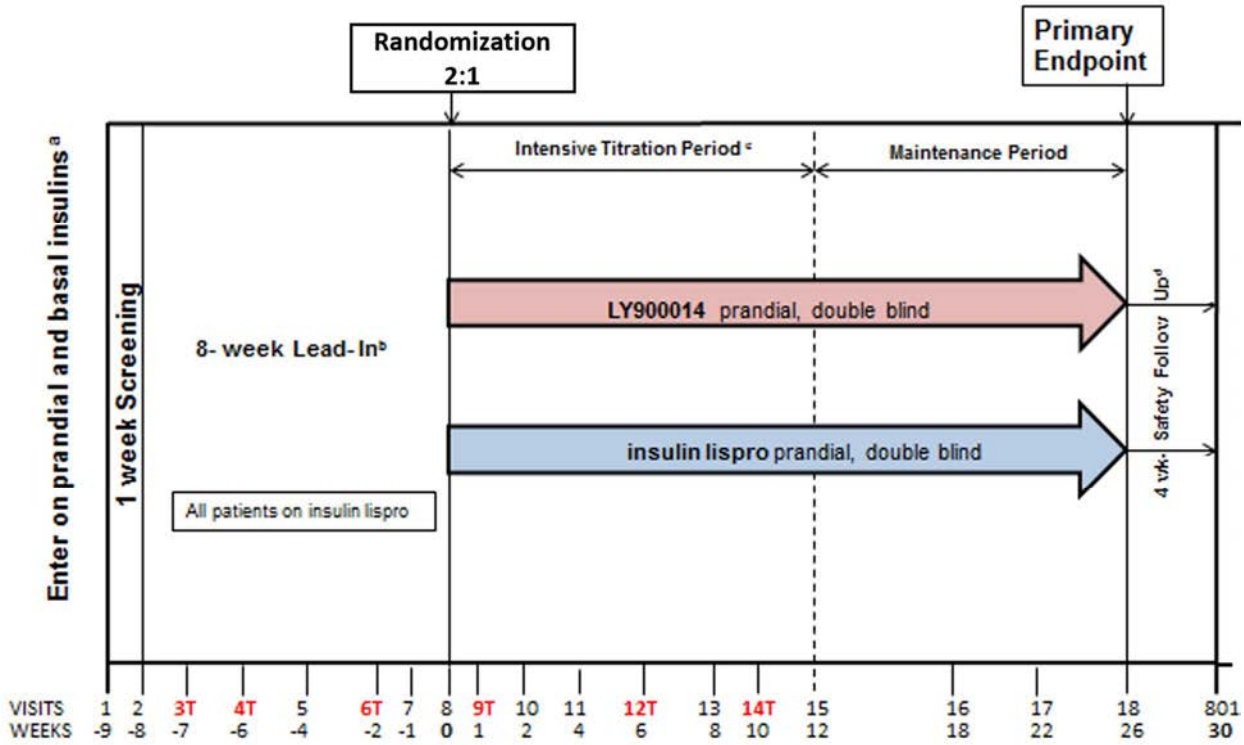
Study I8B-FH-ITSE (ITSE) is a Phase 3, prospective, double-blind, randomized, multinational, multicenter, 2-group, parallel, active-controlled study conducted in patients with T2D currently treated with basal insulin in combination with at least 1 prandial insulin injection OR premixed insulin with at least 2 injections daily. Patients will be randomized to 1 of the 2 treatment groups in 2:1 ratio (LY900014: insulin lispro). Each of the treatment therapies, LY900014 and insulin lispro, will be administered immediately (0-2 minutes) prior to each meal in a double-blind manner. The study is designed to demonstrate noninferiority of LY900014 when compared with insulin lispro in change from baseline to Week 26 in HbA1c, when both are administered at the start of the meal. The study includes a 1-week screening period and an 8-week lead-in period, followed by a 26-week treatment period, and a 4-week safety follow-up period.

The purpose of the lead-in period (prior to randomization) will be to titrate basal insulin, obtain preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates. Patients treated with either a) basal insulin (insulin glargine U-100, insulin degludec U-100, insulin detemir or neutral protamine Hagedorn [NPH] insulin) in combination with at least 1 prandial injection of bolus insulin or b) at least 2 injections of premixed insulin will be eligible for inclusion in the trial.

Patients should use the same study basal insulin regimen throughout the trial, with allowed regimens as follows: insulin glargine U-100 (Basaglar/Abasaglar or LANTUS) once daily or insulin degludec U-100 once daily in accordance with local regulation. Patients using basal insulin regimens other than insulin glargine U-100 or degludec U-100 will be transferred at Visit 2 to an allowed study basal insulin regimen, which will be chosen by the investigator. Basal insulin will be titrated during the 8-week lead-in period using a titration algorithm to allow the patient to reach the target fasting blood glucose (FBG) by the end of this period.

Patients treated with insulin aspart, insulin glulisine, regular human insulin, or premixed insulin will be transferred to insulin lispro at Visit 2, so that all patients will be treated with insulin lispro throughout the lead-in period. Patients treated with 1 to 2 prandial injections a day or premixed insulin prior to study entry will transition to 3 injections a day of prandial insulin lispro at the beginning of the lead-in period. At Visit 8, patients will be randomized to either LY900014 or insulin lispro at each meal. During the initial 12 weeks after randomization (intensive titration period), prandial insulin doses should be titrated as necessary in order to meet the target self-monitored blood glucose (SMBG) levels. Basal insulin may be titrated as needed to facilitate optimal prandial dosing or for safety reasons such as hypoglycemia or unacceptable hyperglycemia. Thereafter, during the maintenance period (Weeks 12-26 of treatment), it is expected that adjustments to prandial and basal insulin doses would be to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

Figure ITSE.1 illustrates the study design.



Abbreviations: T = telephone visit; wk = week.

a At Visit 2, patients treated with insulin aspart, insulin glulisine, regular insulin, or premixed insulin will be transferred to insulin lispro. At Visit 2, patients treated with a basal insulin regimen other than insulin glargine U-100 or insulin degludec will be transferred to insulin glargine U-100 once daily or insulin degludec U-100 once daily. At Visit 8, patients will be randomized to either insulin lispro or LY900014 and continue their basal insulin regimen.

b Titrate basal insulin.

c Titrate prandial insulin (insulin lispro or LY900014).

d Patients will discontinue study insulins at Week 26.

Figure ITSE.1. Illustration of study design for Clinical Protocol I8B-FH-ITSE.

5.2. Number of Participants

Approximately 705 patients will be screened to achieve 564 randomized patients and 480 patients completing 26 weeks of treatment. Approximately 450 Chinese patients will be randomized. The other 114 randomized patients are planned to be from other countries, which may include Mexico, Argentina, Brazil, India and Ukraine . The final participating countries and allocated patient numbers will be adjusted based on the actual condition.

5.3. End of Study Definition

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

5.3.1. Safety Follow-Up Period

Safety follow-up visit guidelines are as follows (see Section 2):

- For patients who discontinue from the study early during the lead-in period (prior to randomization), only an early discontinuation visit should be completed.
- For patients who discontinue from investigational product (IP) early but remain in the study, all remaining visits should be completed per the Schedule of Activities (Section 2).
- For patients who discontinue from the study early (regardless of whether they discontinue IP at the same time or have discontinued IP at an earlier visit), an early discontinuation visit followed by the safety follow-up visit (Visit 801) should be completed as per the Schedule of Activities (Section 2).
- For patients who finish Visit 18 without early discontinuation of IP, a safety follow-up visit should be completed 4 weeks after Visit 18.

5.4. Scientific Rationale for Study Design

Study ITSE is a Phase 3 study to evaluate LY900014 compared to insulin lispro each in combination with basal insulin glargine or degludec in patients with T2D. The trial has 2 double-blind treatment groups, to allow comparison of LY900014 and insulin lispro when injected at the start of the meal. The 2:1 randomization ratio is to meet the regulatory requirement of China SDA.

The study is designed to compare HbA1c lowering as the primary endpoint, a measure of glycemic control accepted by health care providers and regulatory authorities as a validated measure of glycemic control over time and as the best marker for the development and progression of diabetes complications. The lead-in period consists of 8 weeks to allow for optimization of basal insulin dosing. The 26-week treatment period consists of a 12-week intensive titration period to optimize prandial insulin dosing followed by a 14-week maintenance period to ensure that the primary endpoint HbA1c reflects glycemic control on the patient's insulin regimen.

5.5. Justification for Dose

LY900014 will have the same insulin lispro concentration (100 U/mL) as that of commercially available Humalog. The addition of treprostinil to the insulin lispro formulation does not modify the physical, chemical, or biological integrity of insulin lispro. The dosage of basal and prandial insulins used in this study should be determined based on the individual needs of each patient.

6. Study Population

This study will include patients who have been diagnosed with T2D and are being treated with: basal insulin in combination with at least 1 prandial injection of bolus insulin or at least 2 injections of premixed insulin for at least 90 days (Inclusion Criterion [3]), and have an HbA1c value of ≥7.0 and ≤11.0% at screening. Prior to screening, patients may also be treated with up to 3 types of oral antihyperglycemic medications (OAMs) as specified in Inclusion Criterion [4].

Patients must give written informed consent (approved by Lilly or its designee and the ethical review board [ERB] governing the site) before being allowed to participate in the study and before any screening assessments are performed.

Study investigator(s) will review the patient's records and/or history and screening test results/measurements to determine if the patient meets all inclusion criteria and no exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the patient begins the lead-in period.

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screen:

Type of Patient and Disease Characteristics

[1] Men or women diagnosed (clinically) with T2D, based on the World Health Organization classification (Appendix 5) for at least 1 year prior to screening

Patient Characteristics

[2] Are at least 18 years of age

[3] Have been treated for at least 90 days prior to screening with one of insulin regimens:

(3a) Basal insulin (insulin glargine U-100, insulin detemir, insulin degludec U-100, or NPH insulin) in combination with at least 1 prandial injection of bolus insulin (insulin lispro U-100 or U-200, insulin aspart, insulin glulisine, or regular human insulin) in accordance with local regulations

Or

(3b) Premixed analog or human insulin regimens with any basal and bolus insulin combination injected at least twice daily

[4] Patients may be treated with up to 3 of the following OAMs in accordance with local regulations.:

- Metformin
- Dipeptidyl peptidase-4 (DPP-4) inhibitor

- Sodium glucose cotransporter 2 (SGLT2) inhibitor
- Sulfonylurea
- Meglitinide
- Alpha-glucoside inhibitor

Combination medications (2 or more medications in 1 pill) should be counted as the number of individual components.

During the study lead-in and treatment periods, patients may continue the use of up to 2 of the following OAMs in accordance with local regulations: metformin, SGLT2 inhibitor. Other prestudy OAMs will be discontinued at the beginning of the lead-in period. Please also refer to management of OAMs in Section 7.7.1.

[5] Have an HbA1c value between ≥7.0 and ≤11.0%, according to the central laboratory at the time of screening (Visit 1).

[6] Have a body mass index (BMI) of ≤35.0 kg/m^2 at screening (Visit 1).

[7] Male patients:

a) No male contraception required except in compliance with specific local government study requirements.

[8] Female patients:

a) Women not of childbearing potential may participate and include those who are:

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

Or

ii) postmenopausal – defined as either

(1) a woman 50 to 54 years of age (inclusive) with an intact uterus, not on hormone therapy who has had either

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

Or

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

Or

(2) a woman 55 years of age or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea;

Or

(3) a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

b) Women of childbearing potential participating:

i) Cannot be pregnant or intend to become pregnant,

ii) Cannot be breastfeeding (including the use of a breast pump),

iii) Must remain abstinent or use 1 highly effective method of contraception or a combination of 2 effective methods of contraception for the entirety of the study (Appendix 7),

iv) Test negative for pregnancy at the time of screening (Visit 1). Note: a local urine or serum pregnancy test is conducted at Visit 8.

[9] Have refrigeration in the home or have ready access to refrigeration for storage of insulin therapy

[10] Is a patient who the investigator has determined can be randomized and maintain the treatment regimens based on their previous medical history including insulin dosing regimens, hypoglycemic episodes, and glycemic control.

[11] Capable of, willing, and desirous to do the following:

a) Inject insulin with the use of an insulin injection device (insulin pen) according to included directions

b) Perform self-BG monitoring including 10-point SMBG on designated days

c) Participate in two 4-hour mixed-meal tolerance tests (MMTTs) and consume a standardized meal for the tests

d) Follow a suggested algorithm for basal and prandial insulin dose adjustment as agreed upon with the investigator

e) Comply with the use of the study insulin and scheduled visits

f) Complete patient diary and questionnaire

[12] Considered healthy (apart from T2D) upon completion of medical history, physical examination, vital signs, electrocardiogram (ECG), and analysis of laboratory safety variables, as judged by the investigator

Informed Consent

[13] Have given written informed consent to participate in this study in accordance with local regulations.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

[14] Have any other condition (including known drug or alcohol abuse, psychiatric disorder including eating disorder) that precludes the patient from following and completing the protocol

[15] Have been diagnosed, at any time, with T1D or Latent Autoimmune Diabetes in Adults

[16] Have hypoglycemia unawareness as judged by the investigator

[17] Have had any episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) within the 6 months prior to screening

[18] Have had 1 or more episodes of diabetic ketoacidosis or hyperglycemic hyperosmolar state within the 6 months prior to screening

[19] Have a known diagnosis of secondary diabetes (for example, diabetes caused by hemochromatosis, acromegaly, chronic pancreatitis, or pancreatectomy)

[20] Excessive insulin resistance defined as having received a total daily dose of insulin >2.0 U/kg at the time of screening

[21] Have a history of or are being evaluated for bariatric surgery including Roux-en-Y gastric bypass surgery, gastric banding, and/or gastric sleeve

[22] Have clinically significant cardiovascular disease, within the last 6 months prior to screening, defined as stroke, decompensated heart failure New York Heart Association class III or IV (Appendix 6), myocardial infarction, unstable angina pectoris or coronary arterial bypass graft

[23] Renal:

a) History of renal transplantation

b) Currently receiving renal dialysis

c) Serum creatinine >2.0 mg/dL (177 μmol/L) at screening

[24] Hepatic: Have obvious clinical signs or symptoms of liver disease (for example, acute or chronic hepatitis or cirrhosis), or elevated liver enzyme measurements as indicated below at screening:

a) Total bilirubin level (TBL) ≥2X the upper limit of normal (ULN [with the exception of Gilbert's syndrome]) as defined by the central laboratory,

Or

b) Alanine aminotransferase (ALT) ≥3X ULN as defined by the central laboratory,

Or

c) Aspartate aminotransferase (AST) ≥3X ULN as defined by the central laboratory

[25] Malignancy: Have active or untreated malignancy, have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years, or are at an increased risk for developing cancer or a recurrence of cancer in the opinion of the investigator

[26] Have any hypersensitivity or allergy to any of the insulins or excipients used in this trial

[27] Have hypersensitivity or allergy to the ingredients in the standardized test meal (for example, nut allergy)

[28] Hematologic: Have had a blood transfusion or severe blood loss within 90 days prior to screening or have known hemoglobinopathy, hemolytic anemia, or any other traits of hemoglobin abnormalities known to interfere with measurement of HbA1c

[29] Have presence of clinically significant gastrointestinal disease (for example, clinically active gastroparesis associated with wide glucose fluctuations) in the investigator's opinion

Prior/Concomitant Therapy

[30] Have used thiazolidinediones, glucagon-like peptide 1 (GLP-1) receptor agonist, or pramlintide within 90 days prior to screening

[31] Have used insulin human inhalation powder (Afrezza®) within 90 days prior to screening

[32] Are currently taking traditional medicine (herbal medicine or patent medicine) with known/specified content of anti-hyperglycemic effects within 90 days prior to screening.

[33] Have used CSII for more than 14 dayswithin 90 days prior to screening

[34] Glucocorticoid therapy: receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (including IV, intramuscular, SC, or oral, but excluding topical, intraocular, intranasal, intra-articular and inhaled preparations) or have received such therapy within 8 weeks immediately prior to screening with the exception of replacement therapy for adrenal insufficiency

[35] Have used any weight loss drugs (for example: prescription drugs such as liraglutide, lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion; over-the-counter weight loss medications; traditional/herbal medicine with known weight loss effects) within 90 days prior to screening

Prior/Concurrent Clinical Trial Experience

[36] Are currently enrolled in any other clinical trial involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study

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

[38] Have previously completed or withdrawn from this study after having signed the informed consent form (ICF) or any other study investigating LY900014 after receiving at least 1 dose of the IP

Other Exclusions

[39] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[40] Are Lilly employees or representatives (including employees, temporary contract workers, or designees responsible for the conduct of the study)

[41] Are unable and/or unwilling to provide informed consent, to make themselves available for the duration of the study, or to abide by study procedures

6.3. Lifestyle Restrictions

- Patients should be instructed not to donate blood or blood products during the study.
- Patients should be instructed to avoid major changes in dietary intake or physical activity during the 3 days prior to MMTT.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Retests are also not allowed, except for cases when results are not available from the original sample.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY900014 and insulin lispro administered subcutaneously 0 to 2 minutes prior to the start of the meal for 26 weeks. Table ITSE.2 shows the treatment regimens.

Table ITSE.2. Treatment Regimens

Regimen	Dose Strength	Dose Administration	Route of Administration	Timing of Dose Administration
LY900014	100 U/mL	Individualized dosing	Subcutaneous	0 to 2 minutes before start of the meal
Insulin lispro	100 U/mL	Individualized dosing	Subcutaneous	0 to 2 minutes before start of the meal

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the IP to the patient
- explaining requirements for recording insulin doses to the patient
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- at the end of the study returning all used and unused IP to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labeling

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

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

During the lead-in period, 100 U/mL insulin lispro will be provided using open-label prefilled pens.

7.1.2. Medical Devices

The medical devices provided for use in the study are prefilled pens. LY900014 prefilled pens are new investigational combination products.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 8. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Patients will be randomized to 1 of the 2 treatment groups in 2:1 ratio (double-blind LY900014 administered at meal time:double-blind insulin lispro administered at meal time). Stratification will be by country (China vs. Other), HbA1c stratum (≤8.5% vs. >8.5% at Visit 7), and type of basal insulin during the lead-in period (glargine U-100 vs. degludec U-100), and number of prandial doses at study entry (<3 vs. ≥3).

The IWRS will be used to assign all IP during the study, including insulin lispro during the lead-in period. The IWRS will be used to assign prefilled pens containing double-blind IP to each patient randomized to the 2 blinded study groups. Site personnel will confirm that they have located the correct prefilled pens by entering a confirmation number found on the prefilled pen into the IWRS.

7.2.1. Selection and Timing of Doses

7.2.1.1. Target Glucose Values for Titration of Insulin Therapy

The overall glycemic control goals for all patients enrolled in the study are similar to those recommended by the American Association of Clinical Endocrinologists (Bailey et al. 2016). Fasting, prandial, postprandial, and bedtime glucose target values used to reach the SMBG goals and for determination of titration in insulin therapy are listed in Table ITSE.3.

Table ITSE.3. Target Glucose Values for Adjustment of Insulin Therapy

Time of Target Blood Glucose Measurement	Self-Monitored Blood Glucose (SMBG) Target (Range)
Fasting or Pre morning meal	Target: 100 mg/dL or 5.6 mmol/L Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
Pre midday meal	Target: 100 mg/dL or 5.6 mmol/L Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
Pre evening meal	Target: 100 mg/dL or 5.6 mmol/L Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
Prebedtime	Range: 90 to 130 mg/dL or 5.0 to 7.2 mmol/L
1-2 hour postprandial	Target: <140 mg/dL or 7.8 mmol/L

Note: Every effort should be made to reach the targets while avoiding hypoglycemia.

7.2.1.2. Basal Insulin Therapy

At Visit 2, patients will be transferred to insulin glargine U-100 (Basaglar/Abasaglar or LANTUS) once daily or to degludec U-100 once daily in accordance with local regulations if the patient enters the study on any other basal insulin regimen. For patients treated with basal and 3 or more prandial injections a day, the initial basal insulin dose may be unit-for-unit of the prestudy basal insulin regimen or 80% of the prior basal insulin daily dose if the patient was previously treated with twice-daily NPH insulin.

At Visit 2, patients treated with 1 to 2 prandial insulin injections a day or premixed insulin will be transferred to an allowed study basal insulin and to insulin lispro (see Section 7.2.1.4). Patients transitioning from regular human insulin or human insulin mixtures should be reminded about the importance of injecting insulin lispro immediately prior to meals. The total daily insulin dose will be divided between basal and bolus insulin doses at the discretion of the investigator. The initial basal insulin dose may be approximately 40% to 60% of the total daily dose. The initial prandial insulin dose may be approximately 40% to 60% of the total daily dose. The distribution for use across the 3 main meals is at the discretion of the investigator. The basal insulin dose may be influenced by other clinical circumstances and safety considerations known to the investigator; thus, the prescribed basal insulin dose during the study lead-in and treatment period is determined by, and the responsibility of, the investigator.

Patients should use the same study basal insulin regimen throughout the trial. The study basal insulin can be dosed at any time during the day and should be taken at approximately the same time of day throughout the course of the study.

7.2.1.3. Basal Insulin Titration

During the 8-week lead-in period, basal insulin dose adjustments should be determined by the investigator in discussion with the patient based on SMBG and hypoglycemia data. Basal insulin should be titrated to reach the FBG target of 100 mg/dL (5.6 mmol/L). Decreases to the basal insulin dose may be made at any time during the study based upon the judgment of the investigator (for example, in response to hypoglycemia).

Every effort should be made to reach the FBG target during the lead-in period to allow adequate time for prandial insulin dose adjustments during the titration period; however, basal insulin dose may be adjusted if needed to facilitate optimal prandial insulin dosing during the intensive titration period (Weeks 0 to 12) or for safety reasons. Thereafter, during the maintenance period (Weeks 12 to 26), it is expected that adjustments to basal insulin doses would be to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

Assessments of the basal insulin dose should be made at minimum weekly intervals during the lead-in period and thereafter at each study visit and as clinically indicated. Additional discussion between visits may be required to enable the patient to reach the FBG target. The basal insulin dose may be adjusted every 3 to 4 days (twice per week) when appropriate, based on the patient's glycemic needs and SMBG levels. Investigators may use discretion and provide direction for patients to adjust the basal insulin dose.

Hypoglycemia events can be assessed over the previous week, as shown in Table ITSE.4. After the hypoglycemia assessment, the median FBG value from the 3 previous corresponding FBG values can be used for basal insulin adjustment, as shown in Table ITSE.5.

Table ITSE.4. Basal Insulin Hypoglycemia Assessment

Hypoglycemic Events in the Previous Week	Basal Insulin Change
2 or more nocturnal hypoglycemia events occur or 1 severe hypoglycemia event occurs at any time of the day	Decrease the basal insulin dose to the previous lower dose (or by 10% if this is first dose)
1 nocturnal hypoglycemia event occurs	Do not increase basal insulin dose. Consider decrease in basal insulin dose if clinically indicated
No nocturnal events occur	Titrate the basal insulin dose based upon Table ITSE.5

Table ITSE.5. Summary of Basal Insulin Adjustments after Hypoglycemia Assessment

If Median FBG from the 3 Previous FBG Values is:	Adjust the Basal Insulin Dose by:
<80 mg/dL (<4.4 mmol/L)	Decreasing dose to previous lower dose[a]
80-100 mg/dL (4.4-5.6 mmol/L)	No adjustment
101-139 mg/dL (5.7-7.7 mmol/L)	Increasing by 0-2 units
140-179 mg/dL (7.8-9.9mmol/L)	Increasing by 4units
≥180 mg/dL (≥10.0 mmol/L)	Increasing by 6 units

Abbreviation: FBG = fasting blood glucose

[a] If there is no previous dose because this was the first assigned dose, then the basal dose should be decreased by 10% in consultation with the investigator.

Sources: Adapted from Bartley et al. 2008; Bolli et al. 2009; Tinahones et al. 2014.

7.2.1.4. Study Prandial Insulin Therapy

At Visit 2, insulin lispro will be dispensed to all patients for use throughout the lead-in period. Patients treated with 3 or more prandial injections a day of insulin aspart, insulin glulisine, or regular human insulin will be transferred to insulin lispro (unit for unit). At Visit 2, patients treated with 1 to 2 prandial insulin injections a day or premixed insulin will transition to 3 injections of prandial insulin with 3 main meals a day. The total daily insulin dose will be divided between basal and bolus insulin doses at the discretion of the investigator. The initial basal insulin dose may be approximately 40% to 60% of the total daily dose. The initial prandial insulin dose may be approximately 40% to 60% of the total daily dose.

The initial distribution of prandial insulin may be equal (33% of total daily prandial dose prior to each meal). Otherwise, the investigator, in consultation with the patient, may alter the percentage of prandial insulin prescribed at each meal as clinically indicated such as by the patient's history of prandial insulin administration, SMBG levels, and meal pattern. The prandial insulin dose may be adjusted during the lead-in as clinically indicated. Modifications in the calculation of the prandial insulin dose may also be influenced by other clinical circumstances and safety considerations known to the investigator; thus, the prescribed prandial insulin dose

during the study lead-in and treatment period is determined by, and the responsibility of, the investigator.

At Visit 8, patients will be randomized to either LY900014 or insulin lispro, and will administer their first blinded study prandial insulin dose with the next meal following the randomization visit. The total daily bolus insulin dose of LY900014 or insulin lispro may be initiated unit for unit. Consideration can be made to reduce the initial total daily bolus insulin dose (including correction factor if applicable) by approximately 10% to 20%, such as for patients with fairly well-controlled HbA1c or SMBG levels. Study prandial insulin will be administered 0-2 minutes prior to the start of each meal (pre morning meal, pre midday meal, and pre evening meal). Patients should have 3 doses of prandial insulin per day and eat 3 main meals per day (morning, midday, and evening) on a regular basis.

This study will use 2 possible plans for determining prandial insulin dosing including:

- Pattern adjustment: The patient is prescribed a fixed dose or dose range of insulin for each meal. The fixed dose or dose range of insulin may be individualized for each meal.
- Carbohydrate counting: If the patient performed carbohydrate counting for prandial insulin dosing (insulin to carbohydrate ratio plan) prior to study enrollment, this plan may be continued during the study. The prandial insulin dose is based upon the patient estimated carbohydrate content of the meal (as unit insulin per grams carbohydrate).

The patient should maintain the same prandial insulin dosing plan throughout the study. Correction factor (for example, 1 unit of insulin per glucose [mg/dL or mmol/L] above target goal) may be implemented with either prandial insulin dosing plan. Decreases to the prandial insulin dose may be made at any time during the study based upon the judgment of the investigator (for example, in response to hypoglycemia).

For patients who are carbohydrate counting, the insulin to carbohydrate ratio and correction factor should be assessed and adjusted as needed at minimum weekly in order to meet the study target SMBG levels during the initial 12 weeks after randomization (the intensive titration period). The insulin to carbohydrate ratio may be adjusted every 3 to 4 days (twice per week) when appropriate, based on the patient's glycemic needs and SMBG levels. Postprandial SMBG levels from 10-point SMBG profiles should also be evaluated for optimization of prandial insulin dosing. Additional postprandial SMBG levels may be performed as clinically indicated. During the maintenance period (Weeks 12 to 26), it is expected that prandial insulin dose adjustments would be to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

For patients who are using the pattern adjustment plan, the prandial insulin dose and correction factor should be assessed and adjusted as needed, at least weekly, in order to meet the study target SMBG levels during the initial 12 weeks after randomization (the intensive titration period). The prandial insulin dose may be adjusted every 3 to 4 days (twice per week) when

appropriate, based on the patient's glycemic needs and SMBG levels. In addition to the minimum weekly investigator dose assessment, investigators may use discretion and provide direction for patients to adjust prandial insulin dosing per week. Prandial insulin dose adjustments more than twice per week will not constitute a protocol violation. Postprandial SMBG levels from 10-point SMBG profiles should also be evaluated for optimization of prandial insulin dosing. Additional postprandial SMBG levels may be performed as clinically indicated. During the maintenance period (Weeks 12 to 26), it is expected that prandial insulin dose adjustments would be to maintain glycemic control or for safety reasons, such as hypoglycemia or unacceptable hyperglycemia.

In the pattern adjustment plan, assessment of the prandial insulin dose includes review of the previous 3 days of SMBG levels for the corresponding meal or bedtime (Table ITSE.6). *For example, if assessing the need to adjust the fasting (pre morning meal) prandial insulin dose, review the preceding 3 pre midday meal SMBG levels.*

Table ITSE.6. Prandial Insulin Doses and Corresponding Self Monitored Blood Glucose Values Pattern Adjustment Plan

Prandial Insulin Dose Assessed	Corresponding SMBG Value for Review
Fasting or morning premeal	3 previous midday premeal SMBG values
Midday premeal	3 previous evening premeal SMBG values
Evening premeal	3 previous bedtime SMBG values

Abbreviation: SMBG = self-monitored blood glucose.

The median value from premeal glucose readings from the 3 previous days is chosen as the "adjustment value" and the change in dose (either increase or decrease) is based upon this value Table ITSE.7.

Table ITSE.7. LY900014 or Insulin Lispro Adjustment Algorithm Pattern Adjustment Plan

If Meal Time Dose of Insulin Lispro is:	Median SMBG Value Below Target Range	Median SMBG Value at Target Range[a]	Median SMBG Value Above Target Range
≤10 units	Decrease by 1 unit	No change	Increase by 1 unit
11-19 units	Decrease by 1-2 units	No change	Increase by 1-2 units
≥20 units	Decrease by 2-3 units	No change	Increase by 2-3 units

Abbreviation: SMBG = self-monitored blood glucose.

[a] Median SMBG value at target range OR experienced 1 unexplained hypoglycemic event (≤70 mg/dL [3.9 mmol/L]) or signs/ symptoms consistent with hypoglycemia noted.

Target Range: Premeal: 80 to <110 mg/dL (4.4 to 6.1 mmol/L)
Bedtime: 90 to 130 mg/dL (5.0 to 7.2 mmol/L)
1-2 hour postprandial: <140 mg/dL (7.8 mmol/L).

Source: Adapted from Bergenstal et al. 2008.

For either prandial insulin dosing plan, the investigator may determine the appropriate correction factor for the patient to administer when premeal SMBG are above target based on clinical

judgment, taking into account the patient's clinical history with previous/current insulin regimen and recent glucose profiles. Alternatively, the correction factor may initially be calculated as follows:

correction factor = 1800/total daily insulin dose = estimated decrease in SMBG (mg/dL) level per unit of prandial insulin administered or

correction factor = 100/total daily insulin dose = estimated decrease in SMBG (mmol/L) level per unit of prandial insulin administered

7.2.1.5. Transitioning off Study Prandial Insulin Therapy

Patients will take their last prandial dose of study insulin (LY900014 or insulin lispro) at Visit 18 with the MMTT if performed the same date as Visit 18 or the evening the day prior to Visit 18 if the MMTT is performed prior to Visit 18 or at early discontinuation.

No special instructions for transition to nonstudy prandial insulin are necessary for patients who were using basal bolus therapy prior to study entry. After completion of study treatment, these patients will restart the prandial insulin therapy used prior to study entry, or may transition to a rapid-acting insulin analog other than insulin lispro if the patient was treated with regular human insulin prestudy.

Patients who were using premixed insulins or premixed insulin analogs prior to study entry may choose to stay on basal bolus regimen at the discretion of the investigator. However, patients who were not using insulin lispro prior to entry should NOT use insulin lispro during the safety follow-up period.

7.3. Blinding

This is a double-blind study. The treatment groups, LY900014 and insulin lispro, will be administered immediately (0-2 minutes) prior to each meal in a double-blind manner. Investigators, patients, and study site personnel will be blinded to assigned dosing regimens throughout the study.

To preserve the blinding of the study, the Lilly study team will remain blinded throughout the study; only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. Unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from IP and should remain in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is

warranted, the investigator should make every effort to contact the Lilly clinical research physician (CRP/CRS) prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Dosage Modification

See Section 7.2.1.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive IP and only authorized site staff may supply or administer study treatment. All study treatments should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

In-use insulins should be maintained at room temperature, and refrigerated material should be warmed to near room temperature before injection. In-use insulin must not be used after 28 days.

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 investigator or designee will assess compliance of the patient at each visit, based on a review of the patient's glycemic control, adherence to the visit and treatment schedule. Patients who are deemed noncompliant will receive additional diabetes education and training, as required, and the importance of compliance with the protocol will be reinforced. Patients who, in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from IP or from the study. No specific study data will be collected for analysis of treatment compliance.

7.7. Concomitant Therapy

Guidance on restrictions for concomitant therapies is provided in Table ITSE.8.

Table ITSE.8. Concomitant Medications

Drug Class	Acute Use	Chronic Use	Safety Follow-up Period	Conditions for Use
Sulfonylurea, meglitinide, DPP-4 inhibitor, alpha-glucoside inhibitor	No	No	Yes	
Thiazolidinedione, glucagon like peptide-1 receptor agonist	No	No	No	
NPH insulin, insulin glargine U-300, insulin detemir, insuln degludec U-200	No	No	Yes	May be used in emergencies for up to 14 consecutive days
Regular human insulin	No	No	Yes	May be used in emergencies for up to 14 consecutive days
Premixed insulin or premixed insulin analog	No	No	Yes[a]	May be used in emergencies for up to 14 consecutive days
Insulin human inhalation powder (Afrezza®)	No	No	No	
Weight loss drugs (for example: prescription drugs such as liraglutide, lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion; or over-the-counter weight loss medications)	No	No	Yes	
Systemic glucocorticosteroid (including IV, intramuscular, SC, or oral) but excluding non-systemic glucocorticosteroid (including topical, inhaled, intraocular, intra-articular, or intranasal preparations)	Yes	No	No	During the lead-in period, allow 1-time use for ≤14 consecutive days. During all other study periods, allow 1-time use a total of ≤21 consecutive days.

Abbreviations: DPP-4 = dipeptidyl peptidase-4; IV = intravenous; NPH = neutral protamine Hagedorn; SC = subcutaneous.

[a] Patients who were using premixed insulins prior to study entry may choose to stay on basal bolus regimen. However, patients who were not on lispro product prior to entry should NOT use lispro product during the follow-up period

7.7.1. Management of Oral Antihyperglycemic Medications

During the study lead-in and treatment periods, patients may continue the use of up to **2 of the following OAMs**: **metformin, SGLT2 inhibitor in accordance with local regulations**. Please also refer to Exclusion Criterion [30] for criteria regarding thiazolidinediones, GLP-1 receptor agonists, and pramlintide (Section 6.2). Other prestudy OAMs including sulfonylurea,

meglitinide, DPP-4 inhibitor, and alpha-glucosidase inhibitor agents will be discontinued at the beginning of the lead-in period (Visit 2).

Oral antihyperglycemic medication dosing is to remain stable during study lead-in and treatment, except with the development of contraindications or for safety reasons. During study lead-in and treatment, all glycemic management is to be conducted by adjustment of basal and prandial insulin doses. In emergency situations, it may be necessary for patients to change their dose of OAM and/or be treated with a nonstudy insulin. This will be allowed for up to 14 consecutive days (Section 8.1.2).

7.8. Treatment after the End of the Study

7.8.1. Continued Access

LY900014 will not be made available after conclusion of the study to patients. Rapid-acting insulin analogs and regular human insulin are available in all countries for use as prandial insulin.

7.8.2. Special Treatment Considerations

After discontinuation of IP at the end of the treatment period or earlier, randomized patients should restart the prandial insulin used prior to study entry or transition to a rapid-acting insulin analog other than insulin lispro if the patient was not treated with insulin lispro prestudy. Patients may continue treatment with the basal insulin used during the study or return to their prestudy basal insulin at investigator discretion.

During this follow-up period, OAMs used during the study treatment period should be continued and other prestudy OAMs may be considered at investigator discretion as appropriate.

Investigators should provide patients with appropriate guidance for glucose monitoring and insulin dose adjustment throughout the follow-up period in order to maintain glycemic control.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

In the event that a patient is discontinued from the study treatment, the investigator should encourage the patient to remain in the study for continued safety monitoring.

Lilly recognizes the importance of complete data collection. This study includes elements to minimize missing data. Randomized patients who are discontinued from IP before study completion are encouraged to remain in the study for continued monitoring. For patients who remain in the study after early discontinuation of IP, both efficacy (except MMTT) and safety data will be collected at scheduled visits. MMTT assessment will NOT be performed for these patients. The difference between stopping IP and discontinuing the study will be explained to patients as part of the informed consent, and patients will be encouraged to continue in the study even if they stop study drug. In addition, study site investigators will be trained on the importance of complete data collection, with additional re-education of sites and patients as necessary.

8.1.1. Permanent Discontinuation from Study Treatment

Patients will be discontinued from the IP in the following circumstances:

- The investigator may decide that the patient should stop IP. If this decision is made because of an AE, SAE, or a clinically significant laboratory value, the study drug is discontinued for that patient and appropriate measures are to be taken. Lilly or its designee is to be alerted.
- The patient requests to discontinue IP.
- If the patient becomes pregnant.
- If an investigator, study site personnel performing assessments, or patient is unblinded, the patient must discontinue IP.
- If the patient, for any reason, requires treatment with another therapeutic regimen or therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from IP should occur prior to introduction of the new agent.
- Use of prohibited concomitant medication (see Table ITSE.8).
- If the patient has not taken IP for more than 14 consecutive days.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via CRF.

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

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

Patients discontinuing from the investigational product prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

During the study, patients who temporarily discontinue the IP may be able to resume IP based on the following scenario:

Patient has not taken IP for 14 consecutive days or less:

- If the treatment regimen restarts within 14 days of when the patient initially stopped taking IP, patient may continue in the study and begin treatment again with IP. During this time, nonstudy insulins may have been used. If the patient decides to continue in the study, no early termination procedures will be completed. Patients will continue study visits through the safety follow-up.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- The investigator decides that the patient should be discontinued from the study
- The patient requests to be discontinued from the study
- The patient discontinues insulin lispro or study-allowed basal insulin regimen for >14 consecutive days in the lead-in period.

Patients who discontinue the study early, but after randomization, will have early discontinuation procedures performed as shown in the Schedule of Activities (Section 2).

Patients who discontinue during the lead-in period will not need to fast, have laboratory samples drawn, or complete questionnaires, but will have all other early discontinuation procedures performed.

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

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

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

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy measure is the change from baseline to Week 26 in HbA1c.

9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be collected at the times shown in the Schedule of Activities (Section 2).

- Fasting and PPG collected during the MMTT
    - 1-hour and 2-hour PPG excursions: serum glucose measured 1 hour and 2 hours after the start of a meal minus fasting serum glucose
    - Incremental areas under the serum glucose concentration-time curve from 0 to 30 minutes, 0 to 1 hour, 0 to 2 hours, 0 to 3 hours, and 0 to 4 hours after a meal; maximum serum glucose after a meal
    - Glucose variability measured by the coefficient of variation and standard deviation (SD)
- 1,5-Anhydroglucitol (1,5-AG)
- SMBG 10-point profiles (fasting, 1-hour post morning meal, 2-hours post morning meal, pre midday meal, 1-hour post midday meal, 2-hours post midday meal, pre evening meal, 1-hour post evening meal, 2-hours post evening meal, and bedtime)
    - 1-hour and 2-hour PPG excursions
    - Within- and between-day glucose variability measured by the coefficient of variation and SD
- Proportion of patients with HbA1c $\leq$6.5% and <7.0%
- Prandial, basal, and total insulin dose (units and units/kg), and prandial/total insulin ratio.

9.1.3. Appropriateness of Assessments

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to diabetes.

9.1.4. Study Procedures

The following procedures will be performed at the times shown in the Schedule of Activities (Section 2).

9.1.4.1. Four-Point Self-Monitoring Blood Glucose

Patients should be encouraged to measure a minimum of 4 SMBG readings daily to facilitate dose titration (consists of fasting [pre morning meal], pre midday meal, pre evening meal, and pre bedtime), with additional readings as needed for glucose self-management. 4-point SMBG is required on three nonconsecutive days in the one week before each visit. Site personnel may request additional SMBG monitoring from patients and/or assess SMBG values at other times (such as postprandial SMBG measurements) to make clinical management decisions. Missing values in 4-point SMBG profiles will not be considered protocol deviations unless, in the opinion of the investigator, they are excessive and reflect noncompliance with the protocol.

9.1.4.2. Ten-Point Self-Monitoring Blood Glucose

Patients in both study arms should be instructed to perform 10-point SMBG profiles prior to 3 visits during the study (Visits 8, 15, and 18). Three 10-point profiles should be done during the 2 weeks prior to each visit. Each 10-point profile during this 2-week time interval should be completed over a 1-day period, preferably on 3 nonconsecutive days (weekdays and weekends), as per the Schedule of Activities (Section 2). The 10-point profile consists of 10 SMBG measurements on the same day at premeal, 1-hour, and 2-hours after the start of the morning, midday, and evening meals, and at bedtime. The 10-point SMBG profile is inclusive of the daily 4-point SMBG readings. Patients should be encouraged to eat a morning, midday, and evening meal on the days that the 10-point SMBG is monitored. Premeal measurements should be taken before the patient begins eating the meal. Patients may eat a snack and cover with bolus insulin if that is their usual practice. Missing values in 10-point SMBG profiles will not be considered protocol deviations unless, in the opinion of the investigator, they are excessive and reflect noncompliance with the protocol.

9.1.4.3. Mixed-Meal Tolerance Test

A 4-hour MMTT will be performed in all patients at baseline (Week 0, Visit 8) and at the end of primary treatment period (Week 26, Visit 18). For patients who remain in the study after early discontinuation of IP, MMTT assessment will NOT be performed. Patients will be instructed to fast for at least 8 hours prior to the administration of the MMTT at the study site. The MMTT can occur 0 to 4 days prior to the visit. The MMTT can be rescheduled up to 2 times within the visit window, ideally at 24-hour intervals, if the patient does not meet the target FBG. It is preferred for the rescheduled MMTT to occur as close to the visit date as possible.

Target FBG prior to the MMTT: Patients must have an FBG in the range of 71 to 180 mg/dL (3.9 to 10.0 mmol/L) prior to starting the MMTT. If the glucose is outside of this range, the MMTT should be rescheduled.

In order to increase the likelihood of having patients arrive on the morning of the MMTT within the target FBG range, note the following:

- Patients should be instructed to avoid major changes in dietary intake or physical activity during the 3 days prior to the MMTT.
- Patients should be instructed to inject basal insulin according to their usual schedule.
- Patients should not administer correction doses with insulin lispro or LY900014 within 4 hours of the start of the MMTT.

During the 8-hour fasting period and up to 2 hours prior to the start of the MMTT, episodes of non-severe hypoglycemia (symptoms or BG ≤70 mg/dL [3.9 mmol/L]) can be treated with 15 to 20 grams of carbohydrate. If a hypoglycemia episode requires more than approximately 20 grams of carbohydrate within 8 hours of the start of the MMTT or the patient experiences a severe hypoglycemia episode (as defined in Sections 9.4.1 and 9.4.2), the patient should be instructed to notify the site and the MMTT must be rescheduled.

Test Meal: The MMTT meal will consist of a standardized liquid nutrition shake(s) (approximately total energy 700 kcal and 100 grams of carbohydrates, such as Ensure Plus®, Abbott Nutrition), Patients are expected to consume the meal within 15 minutes. Patients should consume the same test meal for both the baseline and end of primary treatment period MMTT, if possible.

Insulin Injection: During the Visit 8 MMTT, all patients will have insulin lispro injected 0 to 2 minutes before the start of the meal. During the Visit 18 MMTT, patients will have their blinded study insulin, either LY900014 or insulin lispro, injected 0 to 2 minutes before the start of the meal. The prandial insulin dose administered during the MMTT will be individualized for each patient.

- If the patient uses the carbohydrate counting prandial dosing plan, the morning meal insulin to carbohydrate ratio will be used to calculate the prandial insulin dose for the MMTT.
- If the patient does not use carbohydrate counting, the prandial insulin dose for the MMTT will be calculated based on the average total daily insulin dose for the 3 days prior to the MMTT per Table ITSE.9.
- Modifications in the calculation of the insulin dose may also be influenced by other clinical circumstances and safety considerations known to the investigator; thus the MMTT prandial insulin dose is determined by, and the responsibility of, the investigator.

Table ITSE.9. Insulin to Carbohydrate Ratio for the MMTT Prandial Insulin Dose

Average Total (Basal+Bolus) Insulin Dose (units) in the Last 3 Days	Insulin to Carbohydrate Ratio (1 unit per number of grams carbohydrate)
8-11 units	1unit : 50 grams
12-14	1:40
15-18	1:30
19-21	1:25
22-27	1:20
28-35	1:15
36-45	1:12
46-55	1:10
56-65	1:8
66-80	1:6
81-120	1:5
>120	1:4

Abbreviation: MMTT = mixed-meal tolerance test.
Source: Scheiner [WWW].

Hypoglycemia during the MMTT: If the patient has signs or symptoms of hypoglycemia during the MMTT, BG should be measured with a glucometer. If the patient's BG is ≤70 mg/dL (3.9 mmol/L), the patient should receive 15 grams of rapidly absorbable carbohydrate. The patient's BG should be retested in 15 minutes or as clinically indicated and, if it remains ≤70 mg/dL (3.9 mmol/L), treatment with another 15 grams of carbohydrate should be given until BG is >70 mg/dL (3.9 mmol/L). Sample collection should continue per the schedule if possible.

Sample Collection: Time 0 of the MMTT will be when the patient starts to consume the meal. Serial venous blood samples to measure serum glucose will be taken at time -15, 0 (immediately before the start of the meal), 15, 30, 60, 120, 180, and 240 minutes after the start of the meal.

9.1.4.4. Diabetes Education and Nutritional Counseling

Initial training at Visit 2 will include diabetes education and nutrition counseling, as well as hypoglycemia recognition and management Appropriate site personnel will administer training and education using locally approved diabetes education/training materials and programs or by using other materials that may be provided by the sponsor. Patients may be provided abbreviated training and education at visits following Visit 2 based upon patient needs.

9.2. Adverse Events

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

The investigator is responsible for the appropriate medical care of patients 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 IP or the study, or that caused the patient to discontinue the IP before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and/or IP, via electronic data entry.

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

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

The investigator answers yes/no when making this assessment.

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

If a patient's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry, clarifying, if possible, the circumstances leading to any dosage modifications or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency

room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- When a condition related to the prefilled pen necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.
- Severe hypoglycemia events: episodes of severe hypoglycemia as determined by the investigator according to the definition provided in Sections 9.4.1 and 9.4.2 must be reported as SAEs

Although all AEs occurring after signing the ICF are recorded in the case report form (CRF), SAE reporting begins after the patient has signed the ICF and has received IP. However, if an SAE occurs after signing the ICF, but prior to receiving IP, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic adverse event should have additional data collected using the CRF.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

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

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP and/or drug delivery system so that the situation can be assessed.

- Complaints must be reported by site staff within 24 hours of notification to the clinical site/study personnel, or within 24 hours of study/site personnel becoming aware of a product issue, regardless of the availability of the complaint sample.
- Retain the IP under appropriate storage conditions, if available or when obtained, until instructed to return it to Lilly.
- Product complaints for non-Lilly Products (including concomitant drugs) that do not have a Lilly Product Batch or Control number, are reported directly to the manufacturer per product label.
- Follow the instructions outlined in the Product Complaint Form for other reporting requirements.

9.3. Treatment of Overdose

Excess insulin administration may result in hypoglycemia. Refer to the IB for LY900014 and product label for insulin lispro.

9.4. Safety

9.4.1. Hypoglycemia

Patients are encouraged to perform SMBG whenever hypoglycemia may be suspected, either by symptoms experienced or perceived increased risk as related to dietary intake, physical activity, or inadvertent or atypical insulin dosing. All patients will be instructed to treat a BG ≤70 mg/dL (3.9 mmol/L) as hypoglycemia.

Hypoglycemia events will be collected in the patient diaries provided by the sponsor via the investigator. If a hypoglycemia event is suspected, the patient should record the BG value, any associated symptoms, and the treatment administered in patient diaries. The patient should contact the site as necessary. Reports of hypoglycemia will be classified by the investigator as "severe" or "not severe" based upon data collected in patient diaries and in consultation with the patient, see below and Section 9.2.1. All episodes of severe hypoglycemia must be collected as AEs via electronic data entry, and reported as SAEs.

Hypoglycemia will be described using the following definitions:

Documented Glucose Alert Level, BG ⩽70 mg/dL (3.9 mmol/L)

- **Documented symptomatic hypoglycemia:** with typical symptoms of hypoglycemia.
- **Documented asymptomatic hypoglycemia:** without typical symptoms of hypoglycemia.
- **Documented unspecified hypoglycemia**: with no information about symptoms of

hypoglycemia available.

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

- **Documented symptomatic hypoglycemia**
- **Documented asymptomatic hypoglycemia**
- **Documented unspecified hypoglycemia**

Severe hypoglycemia

- **Severe hypoglycemia (in adults):** Patients had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG ⩽70 mg/dL [3.9 mmol/L]).

Other hypoglycemia:

- **Nocturnal hypoglycemia:** Any documented hypoglycemic event (including severe hypoglycemia) that occurs between bedtime and waking.
- **Relative hypoglycemia:** An event during which typical symptoms of hypoglycemia occur, that does not require the assistance of another person and is accompanied by BG >70 mg/dL (3.9 mmol/L).
- **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia were present, but BG measurement was not reported.
- **Overall hypoglycemia:** This optional category combines most cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). It does not include relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in the category of overall hypoglycemia.

9.4.2. Severe Hypoglycemia

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined in Section 9.4.1, is made by the investigator based upon the medical need of the patient to have required assistance and is not predicated on the report of a patient simply having received assistance.

9.4.3. Electrocardiograms

For each patient, ECGs should be performed at Visit 1 according to the study specific requirements described in the Schedule of Activities (Section 2).

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

Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

9.4.4. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities (Section 2) including the study specific requirements.

9.4.5. Laboratory Tests

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

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of IP should be reported to Lilly or its designee as an AE via electronic data entry .

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine 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 and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the CRF 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 discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

Not applicable.

9.8. Biomarkers and Predictive or Other Analyses

9.8.1. Samples for Immunogenicity Testing

Blood samples for immunogenicity testing will be collected to determine antibody production against insulin lispro as specified in the Schedule of Activities (Section 2).

9.9. Health Economics

The self-reported questionnaires will be administered according to the Schedule of Activities (Section 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

9.9.1. EQ-5D-5L

The European Quality of Life – 5 Dimensions 5 Level (EQ-5D-5L; van Reenen and Janssen [WWW]) is a patient-rated questionnaire used to evaluate health status. The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). This part of the EQ-5D can be used to generate a health state index score, which is often used to compute quality-adjusted life years for utilization in health economic analyses. The health state index score is calculated based on the responses to the 5 dimensions, providing a single value on a scale from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility. The second part of the questionnaire consists of a visual analog scale (VAS) on which the patient rates their perceived health state from 0 (worst imaginable health state/the worst health you can imagine) to 100 (best imaginable health state/the best health you can imagine).

9.9.2. Insulin Treatment Satisfaction Questionnaire

The Insulin Treatment Satisfaction Questionnaire (ITSQ; Anderson et al. 2004) is a validated instrument containing 22 items that assesses treatment satisfaction for persons with diabetes on insulin. Items are measured on a 7-point Likert-type scale, where lower scores reflect better outcomes. In addition to an overall score, the items that make up the 5 domains of satisfaction are categorized as:

- Inconvenience of Regimen (5 items)
- Lifestyle Flexibility (3 items)
- Glycemic Control (3 items)
- Hypoglycemic Control (5 items)
- Insulin Delivery Device Satisfaction (6 items).

All individual patient-domain scores will be calculated as the mean of nonmissing items in the domain if <20% of the items within the relevant domain are missing; otherwise, the domain score will be missing. The domain scores will be transformed to a scale of 0 to 100 (derived as 100*[7-raw score]/6). An overall score is calculated as the mean of the nonmissing transformed domain score and only calculated when all 5 domain scores are nonmissing. A higher score indicates better treatment satisfaction.

9.9.3. Work Productivity and Activity Impairment Questionnaire General Health

The Work Productivity and Activity Impairment Questionnaire General Health (WPAI-GH; Reilly et al. 1993) consists of 6 questions to determine employment status, hours missed from work because of problems associated with diabetes, hours missed from work for other reasons, hours actually worked, the degree to which diabetes affected work productivity while at work,

and the degree to which diabetes affected activities outside of work. Four scores are derived: percentage of absenteeism, percentage of presenteeism (reduced productivity while at work), an overall work impairment score that combines absenteeism and presenteeism, and percentage of impairment in activities performed outside of work. Greater scores indicate greater impairment and less productivity.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 564 patients will be randomized in order that 480 patients complete the study through the primary endpoint at Week 26.

The primary objective of this study is to test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control as measured by change from baseline to Week 26 in HbA1c in patients with T2D when administered in a double-blind manner as prandial insulin in combination with basal insulin glargine or insulin degludec and OAM.

Patients will be randomized in a 2:1 ratio to LY900014 and insulin lispro, both dosed 0 to 2 minutes before meals. Assuming a non-inferiority margin (NIM) of 0.4%, no true difference between treatment arms, and an SD of 1.1%, 480 completers (320 in the LY900014 group and 160 in the insulin lispro group) will provide 96% power to show noninferiority between LY900014 and insulin lispro using the upper limit of a 2-sided 95% confidence interval (CI; LY900014 – insulin lispro). Assuming a 15% dropout rate for 26 weeks, approximately 564 patients will need to be randomized.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All patients who sign informed consent.
Enrolled	All patients who receive at least 1 dose of open-label insulin lispro in the 8-week lead-in period.
Randomized	All patients who are randomly assigned to study treatment at Visit 8. Treatment group will be defined on the basis of the treatment the patients are assigned.
Safety	All randomized patients who receive at least 1 dose of the randomly assigned IP.
Completer	Patients included in the randomized population who have completed Week 26 of study treatment without permanent discontinuation of IP.
Per Protocol	Patients included in the randomized population who have completed Week 26 of study treatment without permanent discontinuation of IP and without significant protocol deviations through Week 26 that would significantly impact the primary objective. Treatment group will be defined on the basis of the treatment the patients actually receive.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. 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 SAP or the clinical study report (CSR). Additional exploratory analyses of data will be conducted as deemed appropriate.

The primary analysis is for the treatment period through Week 26.

Efficacy analyses will be conducted on all randomized patients using an intention-to-treat (ITT) approach according to the treatment the patients are assigned. Efficacy analyses, including the analyses for the primary and multiplicity adjusted objectives, will be performed, including data collected prior to permanent discontinuation of IP. When change from baseline is included as a response variable of analysis models, the patient will be included in the analysis only if a baseline and at least 1 postbaseline measurement are available. Selected efficacy analyses will also be conducted using the Per Protocol (PP) and Completer populations.

Safety analyses will be conducted on the Safety population. Analyses of AEs will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data collected prior to permanent discontinuation of IP. The second set of analyses will include all data collected during the course of the entire study including the follow-up visit, regardless of IP use. Analyses of hypoglycemia will use data collected prior to permanent discontinuation of IP; while analyses for post-treatment may be performed as needed. Analyses of safety laboratory measurements will be performed on all data during the planned treatment period regardless of IP use.

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. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

A graphical approach for multiple comparisons (Bretz et al. 2011) will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and multiplicity adjusted objectives.

Baseline is defined as the last nonmissing measurement at or before the randomization visit (Visit 8) unless otherwise specified.

A restricted maximum likelihood-based, mixed-effect model repeated measure (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment, strata (country, type of basal insulin, and number of prandial doses at entry), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. For analyses of variables other than HbA1c, the HbA1c stratum (≤8.5%, >8.5%) will be included in the model. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on least squares (LS) means and Type III tests. If this analysis fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Compound symmetry with heterogeneous variances
- Toeplitz
- Autoregressive
- Compound symmetry without heterogeneous variances

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

An analysis of covariance (ANCOVA) will also be used to analyze continuous variables. The model for the change from baseline to the Week 26 HbA1c endpoint will include treatment and strata (country, type of basal insulin, and number of prandial doses at entry) as fixed effects and baseline as a covariate. Unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward (LOCF) approach, using only postbaseline data. For analyses of variables other than HbA1c, the HbA1c stratum (≤8.5%, >8.5%) will be included in the model.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least squares means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the nominal p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test will be used for treatment comparisons.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided. Frequency counts and percentages of all patients entered, enrolled, randomized, completing, and/or discontinuing from the study will be presented for each treatment group. Reasons for discontinuation from study treatment and from the study during the treatment period will be summarized and compared between treatment groups using Fisher's exact tests. Reasons for discontinuation from the study during the lead-in and follow-up periods will be summarized.

10.3.2.2. Patient Characteristics

Standard baseline characteristics of age, sex, ethnicity, race, height, weight, and BMI will be summarized for all randomized patients. Summary statistics will include sample size, mean, SD, median, minimum, and maximum for continuous measures and sample size, frequency, and percent for categorical measures. Comparisons between treatment groups will be performed using Fisher's exact test for categorical data and an analysis of variance (ANOVA) with treatment in the model for continuous data. With no multiplicity control, nominal p-values from such comparisons should be interpreted as a descriptive measure. Baseline diabetes characteristics will be summarized in a similar manner.

Medical history and AEs at baseline will be summarized by preferred term (PT) within system organ class (SOC), and comparison between treatment groups will be performed using Fisher's exact test.

10.3.2.3. Concomitant Therapy

The type of insulin therapy at study entry and at baseline will be compared between treatment groups using Fisher's exact tests. The dose of basal and bolus insulin therapy during the lead-in period will be compared between treatment groups using an ANOVA with treatment in the model.

Concomitant medications used during the treatment period will be descriptively summarized.

The use of OAMs during the treatment period will be summarized by treatment group. In addition, the proportion of subjects on OAMs at baseline will be summarized.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control (NIM=0.4% for HbA1c) in patients with T2D, when administered as prandial insulin (0-2 minutes prior to the meal), in combination with basal insulin for 26 weeks.

The primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro at Week 26 (Visit 18) from the MMRM analysis of change from baseline in HbA1c, including data collected from all randomized patients prior to permanent discontinuation of IP through Week 26. If the upper limit of the 2-sided 95% CI for the LS mean difference in the change from baseline in HbA1c for LY900014 minus insulin lispro is below +0.4%, LY900014 will be declared noninferior to insulin lispro. The analysis model and selection of covariance structure is described in Section 10.3.1.

In addition to the primary objective, the superiority of LY900014 in controlling HbA1c compared to insulin lispro will also be assessed with the analysis approach described above. If the p-value is less than the alpha level from the graphical approach allocated to the superiority hypothesis, LY900014 will be declared superior to insulin lispro.

10.3.3.1.1. Additional Analyses for the Primary Endpoint

The primary MMRM analysis model will be repeated using the PP and Completer populations to check the sensitivity of the analysis. If the conclusion differs from that of all randomized patients, the data and analyses will be further investigated.

A secondary analysis model will be an ANCOVA for HbA1c change from baseline to Week 26 (Visit 18), using the model described in Section 10.3.1. Missing endpoints will be imputed using the LOCF approach using postbaseline data only.

10.3.3.2. Secondary Analyses

A graphical approach for multiple comparisons will be used to strongly control the overall Type I error (2-sided alpha level of 0.05) for testing the treatment effect for the primary and the following multiplicity adjusted objectives: superiority of LY900014 compared with insulin lispro for 1-hour PPG excursion at Week 26, 2-hour PPG excursion at Week 26, and change from baseline to Week 26 in HbA1c. The graphical testing scheme will be described in the SAP.

An ANCOVA model with strata (country, type of basal insulin, number of prandial doses at entry, and baseline HbA1c [≤8.5%, >8.5%]), and treatment as fixed effects and baseline as a covariate will be used to analyze the 1-hour and 2-hour PPG excursions. However, if the percentage of the patients with missing MMTT data at baseline is higher than 15%, a constrained longitudinal data analysis model (Liu et al. 2009; Lu 2010) will be used instead. Analyses details will be documented in the SAP.

Superiority in change from baseline in HbA1c for LY900014 compared with insulin lispro will be determined from the analysis approaches outlined in Section 10.3.3.1.

Hemoglobin A1c and change from baseline in HbA1c at all time points will be analyzed by the same MMRM model used for the primary analysis..

Additional continuous secondary efficacy variables, as well as the change from baseline for these variables, will be analyzed either by the MMRM or ANCOVA models described in Section 10.3.1.

Treatment comparisons for the proportion of patients with HbA1c <7.0% and ≤6.5% will be analyzed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c by visit interaction, and treatment by visit interaction. An unstructured covariance structure will be used. As a sensitivity analysis, the proportion of patients with HbA1c <7.0% and ≤6.5% at Week 26 (Visit 18), imputed using LOCF, will be compared using a logistic regression model including treatment and baseline HbA1c value in the model.

Actual and change from baseline in basal, prandial, and total dose, as well as the prandial/total insulin dose ratio, will be analyzed by the MMRM models described in Section 10.3.1.

10.3.3.3. Tertiary/Exploratory Analyses

Continuous variables and the change from baseline for these variables will be analyzed either by the MMRM or ANCOVA models described in Section 10.3.1. Categorical variables will be analyzed either by model (for example, logistic regression) or by Fisher's exact test or Pearson's chi-square test. Analysis details for the tertiary endpoints will be described in the SAP.

10.3.4. Safety Analyses

Safety measures will include AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro.

Events that are newly reported after the first dose of IP or reported to worsen in severity from baseline will be considered treatment-emergent adverse events (TEAEs). The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity.

Serious adverse events, AEs reported as reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the MedDRA PT, sorted by decreasing frequency within the LY900014 treatment group. Treatment-emergent adverse events will also be summarized by PT sorted by decreasing frequency within SOC for all TEAEs and TEAEs by maximum severity. For events that are specific to 1 sex, the denominator and computation of the percentage will include only patients from the given sex. The number and proportion of patients with at least 1 event for each type of event will be summarized and compared between treatment groups using Fisher's exact test. Serious adverse events, AEs reported as reason for discontinuation from the IP or study, and TEAEs will also be summarized for open-label insulin lispro during the lead-in period. Symptoms solicited by questionnaires will not be considered spontaneous AEs for analysis.

Hypoglycemia rates will be summarized for periods of 30 days, 1 year, and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical method (details will be described in the SAP). For each of other categories of hypoglycemia, the number of hypoglycemia events during a specific period (rate) after randomization (for example, 0-12 weeks of treatment period) will be analyzed by using a negative binomial regression model. The model will include treatment and the baseline hypoglycemia rate (measured during lead-in) as a covariate. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days (or 30 days) will be included in the model to estimate the rate of hypoglycemia per year (or per 30 days). The proportion of patients with at least 1 hypoglycemic event in each category (incidence) during a specific period after randomization will be analyzed using a logistic regression model including treatment and baseline hypoglycemia rate value in the model.

Continuous safety variables, as well as the change from baseline for these variables, will be analyzed either by MMRM or ANCOVA models. For categorical variables, Fisher's exact test will be used to compare treatment groups unless otherwise specified.

The analyses for assessing immunogenicity data will be described in the SAP.

10.3.5. Other Analyses

10.3.5.1. Health Economics

Summary statistics, including number of patients and proportion of categorical outcomes (5 levels) for the 5 dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) of the EQ-5D-5L will be provided by visit and by treatment. The change from baseline to LOCF endpoint (Week 26, Visit 18) in the EQ-5D-5L UK population-based health state index score and EuroQol VAS score will be analyzed using the ANCOVA model described in Section 10.3.1.

For the ITSQ, the change from baseline to LOCF endpoint while on treatment in each domain transformed score (inconvenience, lifestyle, hypoglycemic control, glycemic control, delivery system) and overall transformed score will be analyzed using the ANCOVA model described in Section 10.3.1.

For the WPAI-GH, the change from baseline to LOCF endpoint in each score (absenteeism, presenteeism, work productivity loss, and activity impairment) will be analyzed using the ANCOVA model described in Section 10.3.1.

10.3.6. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
1,5-AG	1,5-Anhydroglucitol
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BG	blood glucose
blinding/masking	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
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
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.
CSII	continuous subcutaneous insulin infusion
CSR	clinical study report
DPP-4	dipeptidyl peptidase-4

ECG	electrocardiogram
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	European Quality of Life – 5 Dimensions 5 Level
ERB	ethical review board
FBG	fasting blood glucose
FDA	US Food and Drug Administration
GCP	good clinical practice
GD	glucodynamic(s)
GLP-1	glucagon-like peptide 1
GRAS	Generally Recognized As Safe
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
IP	investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITSQ	Insulin Treatment Satisfaction Questionnaire
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
LLT	lowest level term
LOCF	last-observation-carried-forward
LS	least squares

MDI	multiple daily injection(s)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measure
MMTT	mixed-meal tolerance test
NIM	Non-inferiority margin
NPH	neutral protamine Hagedorn
OAM	oral antihyperglycemic medication
PK	pharmacokinetic(s)
PP	per protocol
PPG	postprandial glucose
PT	preferred term
RBA	radio ligand-binding assay
SAE	serious adverse event
SAP	statistical analysis plan
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.
SD	standard deviation
SGLT2	sodium glucose cotransporter 2
SMBG	self-monitored blood glucose
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
T1D	type 1 diabetes
T2D	type 2 diabetes
TBL	total bilirubin level

TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
URI	ultra-rapid insulin
VAS	visual analog scale
WPAI-GH	Work Productivity and Activity Impairment Questionnaire General Health

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry (Serum Concentrations of):**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils, segmented	Aspartate aminotransferase (AST)
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Uric acid
Basophils	Calcium
Platelets	Chloride
	Magnesium
Urinalysis	Total protein
Specific gravity	Glucose
pH	Albumin
Protein	Creatine kinase (CK)
Glucose	
Ketones	Serum glucose, fasting
Blood	1,5-Anhydroglucitol
Urine leukocyte esterase	HbA1c
Bilirubin	
Nitrite	**Lipid Panel**
	LDL[d]
Serology	HDL
Anti-insulin lispro antibodies	Total cholesterol
	Triglycerides
Pregnancy Test (females only)[b]	
Follicle-Stimulating Hormone[c]	

Abbreviations: HDL = high-density lipoproteins; IP = investigational product; LDL = low-density lipoproteins; RBC = red blood cells; WBC = white blood cells.

a All laboratory tests will be assayed by a Lilly-designated central laboratory, unless otherwise noted.

b Serum pregnancy test that is analyzed by central laboratory must be performed in women of childbearing potential at Visit 1 followed by a local urine or serum pregnancy test within 24 hours prior to IP exposure and at other times at the investigator's discretion. When required per local regulations and/or institutional guidelines, local pregnancy testing will occur at mandatory times during the study treatment period.

c Follicle-stimulating hormone test must be performed at Visit 1 for a postmenopausal woman who is between 50 and 54 years of age (inclusive) with an intact uterus, not on hormone therapy, and who has had at least 6 months of spontaneous amenorrhea.

d This value will be calculated. If triglycerides >400 mg/dL, then direct LDL will be assayed.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in 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 or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product (IP).
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Eli Lilly and Company (Lilly) before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on good clinical practice (GCP).

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- ICF
- .other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

Appendix 3.1.4. Investigator Information

Physicians with a specialty in endocrinology or primary care physicians specializing in endocrinology or internal medicine will participate as investigators in this clinical trial.

Appendix 3.1.5. 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.

Appendix 3.1.6. Final Report Signature

The CSR coordinating investigator will sign the final clinical study report (CSR) for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An investigator will be selected by the Lilly study team to serve as the CSR coordinating investigator. The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. 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
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (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 use standard computer edits to detect errors in data collection
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, 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 original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Some or all of a patient's data will be directly entered into the eCRF at the time that the information is obtained. In instances where direct data entry is not used, the site will maintain source documentation in the trial files, and the patient's data will be transcribed into the eCRF. Paper documentation provided by the patient will serve as the source document, including a study drug administration log and an event-medication diary, that will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I8B-MC-ITSD is described in Clinical Trial Agreement.

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 the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
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
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
CPK	

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

a Assayed by Lilly-designated or local laboratory (if test results are required urgently to manage patient care).

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

Appendix 5. World Health Organization Classification for Diabetes

Type 1 Diabetes Mellitus: Type 1 diabetes is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia, but also to prevent spontaneous ketosis and death (Bennett 1991; Alberti and Zimmet 1998).

Type 2 Diabetes Mellitus: Type 2 Diabetes (T2D), although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, and weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in T2D, but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) because of acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with T2D later progress to a state of absolute insulin deficiency (Bennett 1991; Alberti and Zimmet 1998).

References:

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Appendix 6. New York Heart Association Cardiac Disease Classification

Functional Capacity

Class I

Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II

Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III

Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV

Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

1994 Revisions to Classification of Functional Capacity and Objective Assessment of Patients with Diseases of the Heart

www.americanheart.org.

Appendix 7. Classification of Contraceptive Methods

Women of child-bearing potential must use either 1 highly effective method of contraception or a combination of 2 effective methods of contraception. The patient may choose to use a double-barrier method of contraception (see chart below).

- Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

Methods of Contraception

Highly Effective Methods of Contraception	**Effective Methods of Contraception (must use combination of 2 methods)**
• Combined oral contraceptive pill and mini-pill • NuvaRing® • Implantable contraceptives • Injectable contraceptives (such as Depo-Provera®) • Intrauterine device (such as Mirena® and ParaGard®) • Contraceptive patch – ONLY women <198 lb or 90 kg • Total abstinence • Vasectomy	• Male condom with spermicide • Female condom with spermicide • Diaphragm with spermicide • Cervical sponge • Cervical cap with spermicide

Leo Document ID = 34659eb5-4293-4899-bf3e-2a53e9030a7b

Approver: PPD
Approval Date & Time: 27-Jun-2018 01:36:06 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 27-Jun-2018 01:36:06 GMT
Signature meaning: Approved