Protocol I8B-MC-ITRN (a)

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 PRONTO-T2D

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PRONTO-T2D

[EudraCT number: 2015-005357-12]

LY900014

Study I8B-MC-ITRN is a Phase 3, prospective, randomized, double-blind, outpatient, multinational, multicenter, 2-group, parallel, active-controlled study in patients with type 2 diabetes comparing LY900014 to insulin lispro, both in combination with basal insulin.

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Protocol Electronically Signed and Approved by Lilly: 17 Feb 2017
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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 PRONTO-T2D

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 would shift 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 type 1 diabetes (T1D) and type 2 diabetes (T2D) in adults and children when given 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 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 degludec.

Objectives/Endpoints:

Objectives	Endpoints
Primary Objective	
1. To test the hypothesis that LY900014 is noninferior to insulin lispro on glycemic control (non-inferiority margin [NIM]=0.4% for hemoglobin A1c [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	1. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Multiplicity Adjusted Objectives	
2. To test the hypothesis that LY900014 is superior to insulin lispro in controlling 1-hour postprandial glucose (PPG) excursions, when administered as prandial insulin	2. 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
3. To test the hypothesis that LY900014 is superior to insulin lispro in controlling 2-hour PPG excursions when administered as prandial insulin	3. 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 test at Week 26

Objectives	Endpoints
4. To test the hypothesis that LY900014 is superior to insulin lispro on improving glycemic control (HbA1c) when administered as prandial insulin	4. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
5. To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	5. Rate (events/patient/100 years) of severe hypoglycemic events from baseline through Week 26
6. To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic postmeal hypoglycemia	6. 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
7. To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic hypoglycemia	7. 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
8. To compare LY900014 and insulin lispro with respect to 1,5-Anhydroglucitol (1,5-AG)	8. Change from baseline 1,5-AG values at Week 26
9. To compare LY900014 and insulin lispro with respect to 10-point self-monitored blood glucose (SMBG) profiles	9. Change from baseline 10-point SMBG values at week 26
10. To compare LY900014 and insulin lispro with respect to total, basal, and prandial insulin dose	10. Change from baseline in total, basal and prandial insulin doses and prandial/total insulin dose ratio at Week 26
11. To compare LY900014 and insulin lispro with respect to diabetes treatment satisfaction as measured by the Insulin Treatment Satisfaction Questionnaire (ITSQ)	11. Change from baseline ITSQ regimen inconvenience and lifestyle flexibility domain scores at Week 26
12. To compare LY900014 and insulin lispro with respect to the proportion of patients achieving HbA1c targets	12. The proportion of patients with HbA1c <7% and ≤6.5% at Week 26

Summary of Study Design:

Study I8B-MC-ITRN is a Phase 3, prospective, randomized, double-blind, outpatient, 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:

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.

All patients who complete the 4-week safety follow-up visit (Visit 801) and have treatment-emergent insulin lispro antibodies that have not returned to prespecified baseline range (Visit 2) will be asked to participate in follow-up to monitor insulin lispro antibody levels for up to 26 weeks after Visit 801.

Number of Patients:

Approximately 838 patients will be screened to achieve 670 randomized patients and 568 patients completing 26 weeks of treatment.

Statistical Analysis:

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

Efficacy analyses will be conducted on all randomized patients according to the treatment the patients are assigned. The analyses for the primary and multiplicity adjusted objectives will be performed for the efficacy estimand including data collected prior to permanent discontinuation of investigational product (IP) and for the ITT estimand (treatment regimen estimand) including all data collected regardless of IP use. 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.

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

CCI [redacted], the primary analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand that will include all data collected from randomization through Week 26, regardless of IP use. The reference will be all observed data from the randomized patients in the same treatment arm who discontinue IP and complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro from the analysis of covariance (ANCOVA) analysis of change from baseline to Week 26 in HbA1c using all randomized patients. The model for this analysis will include the effects of treatment and strata (pooled country, type of basal insulin, and number of prandial doses at entry), and the continuous covariate of baseline value.

If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis, the reference will be changed to include all observed data from all randomized patients in the same treatment arm who complete the study without missing data.

CCI [redacted], 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 measures (MMRM) analysis of change from baseline in HbA1c including data collected from all randomized patients prior to permanent discontinuation of IP through Week 26 (efficacy estimand). The model for this analysis will include the fixed class effects of treatment, strata (pooled country, type of basal insulin, and number of prandial doses at entry), visit, treatment-by-visit interaction, and the continuous, fixed covariate of baseline value.

For both primary analysis approaches, LY900014 will be declared noninferior to insulin lispro if the upper limit of the 2-sided 95% confidence interval (CI) for the LS mean difference in the change from baseline in HbA1c for LY900014 minus insulin lispro is below +0.4%. In addition, the 95% CI for the treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05.

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. The same graphical testing scheme will be applied for both the efficacy estimand and ITT estimand.

An analysis of covariance (ANCOVA) model with strata (pooled country, type of basal insulin, baseline HbA1c [≤8%, >8%], 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 either by MMRM or ANCOVA models. For categorical variables, Fisher's exact test or Pearson's chi-square 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), 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												
Telephone call for visit reminder or informing patient of completion in the study																			X	
Clinical Assessments																				
Patient demographics	X																			
Medical history and preexisting conditions	X																			
Physical exam/height	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[d]	X	X			X		X	X		X	X		X		X	X	X	X	X	X
Vital signs: blood pressure/pulse rate[e]	X	X			X		X	X		X	X		X		X	X	X	X	X	X
ECG (12-lead local)[f]	X																			
Diabetes and nutrition counseling[g]		X																		
Transfer to insulin lispro[h]		X																		
Transfer to allowed study basal insulin regimen[i]		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	
Basal and prandial insulin dose assessment[i]		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					
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	X	
Dispense eCOA and complete training[m]		X																		
Train on collecting 4-point and 10-point SMBG Profile[n]		X																		
Review 4-point SMBG profiles			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[n]						X	X			X		X		X			X			
Review 10-point SMBG profiles								X			X		X		X			X		X[o]
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			
Return of eCOA devices																			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[p]								X										X		
Urinalysis panel	X																			
Pregnancy test[q]	X							X												
Follicle-stimulating hormone test[r]	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
Pharmacogenetic samples								X												
Nonpharmacogenetic biomarker storage samples								X										X		X
Anti-insulin lispro antibodies		X						X		X	X				X			X	X[t]	X
Health outcomes questionnaire[u]																				
ITSQ		X						X										X		X
EQ-5D-5L		X						X										X		X
WPAI-GH		X						X										X		X

Schedule of Activities

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; eCOA = electronic clinical outcomes assessment; 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 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] Patients should be advised to remove their shoes and empty their pockets before the body weight is obtained.

[e] 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

[f] Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[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 insulin or premixed insulin.

[i] Patients will be transferred to insulin glargine U-100 once or twice daily or to degludec U-100 or U-200 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. Please also refer to 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] 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.

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

[p] MMTT can occur 0 to 4 days prior to the visit and patient must be fasting.

[q] Serum pregnancy test must be performed in women of childbearing potential at Visit 1 followed by a urine 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.

[r] 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.

[s] Pharmacogenetic sample can be collected at any other visit if not collected at Visit 8.

[t] Patients with treatment-emergent insulin lispro antibodies measured at Visit 801 that have not returned to prespecified baseline range (Visit 2), will be asked to undergo additional antibody monitoring as described in Appendix 8. This follow-up assessment also applies to any patient who discontinues study insulin treatment prior to the end of the planned treatment period who has a treatment-emergent antibody response that has not returned to baseline range by Visit 801. It is recommended that the first insulin lispro antibody follow-up visit (Visit 802) be scheduled for all study patients, regardless of treatment-emergent antibody status.

[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 SC 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.

3.2. Background

T2D 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. Only approximately 30% of insulin requiring diabetes patients are able to reach the goal HbA1c target of <7% (Stark Casagrande et al. 2013). Currently available rapid-acting insulin analogs continue to be 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.

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 persons 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, 16.3% of patients indicated that they inject 15 minutes prior to meals, 33% inject 1 to 14 minutes prior to meals, 38.6% inject at the time of the meal, and 12.1% inject after meals. 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.

HbA1c 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 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.

Please 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 (PAH).

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

4. Objectives and Endpoints

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

Table ITRN.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
1. 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	1. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Multiplicity Adjusted Objectives	
2. To test the hypothesis that LY900014 is superior to insulin lispro in controlling 1-hour PPG excursions, when administered as prandial insulin	2. 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
3. To test the hypothesis that LY900014 is superior to insulin lispro in controlling 2-hour PPG excursions when administered as prandial insulin	3. 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 test at Week 26
4. To test the hypothesis that LY900014 is superior to insulin lispro on improving glycemic control (HbA1c) when administered as prandial insulin	4. Difference between LY900014 and insulin lispro in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
5. To compare LY900014 and insulin lispro with respect to the rate of severe hypoglycemic events	5. Rate (events/patient/100 years) of severe hypoglycemic events from baseline through Week 26
6. To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic postmeal hypoglycemia	6. 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
7. To compare LY900014 and insulin lispro with respect to the incidence and rate of documented symptomatic hypoglycemia	7. 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
8. To compare LY900014 and insulin lispro with respect to 1,5-AG	8. Change from baseline 1,5-AG values at Week 26
9. To compare LY900014 and insulin lispro with respect to 10-point SMBG profiles	9. Change from baseline 10-point SMBG values at Week 26

Other Secondary Objectives (Continued)	
10. To compare LY900014 and insulin lispro with respect to total, basal, and prandial insulin dose	10. Change from baseline in total, basal and prandial insulin dose and prandial/total insulin dose ratio at Week 26
11. To compare LY900014 and insulin lispro with respect to diabetes treatment satisfaction as measured by the ITSQ	11. Change from baseline ITSQ regimen inconvenience and lifestyle flexibility domain scores at Week 26
12. To compare LY900014 and insulin lispro with respect to the proportion of patients achieving HbA1c targets	12. The proportion of patients with HbA1c <7% and ≤6.5% at Week 26
Tertiary/Exploratory Objectives	
13. To compare the safety of LY900014 relative to insulin lispro	13. Adverse events, vital signs, chemistry, and hematology laboratory measures
14. To compare the incidence of treatment-emergent anti-insulin lispro antibodies for LY900014 and insulin lispro	14. Incidence of treatment-emergent positive anti-insulin lispro antibodies
15. To compare LY900014 and insulin lispro with respect to quality of life as measured by the EQ-5D-5L	15. Change from baseline in EQ-5D-5L UK-population based health state index score and EQ-VAS score at Week 26
16. 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	16. Change from baseline in WPAI-GH item scores at Week 26
17. To compare LY900014 and insulin lispro with respect to changes in body weight	17. Change from baseline to Week 26 in weight (kg)
18. To compare LY900014 and insulin lispro with respect to the proportion of patients achieving improvement from baseline HbA1c targets	18. The proportion of patients with shifts in HbA1c to <8% and ≤9%, and >9% from baseline to Week 26
19. To compare LY900014 and insulin lispro with respect to glycemic variability	19. 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 = noninferiority 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-MC-ITRN (ITRN) is a Phase 3, prospective, double-blind, randomized, outpatient, 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. 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.

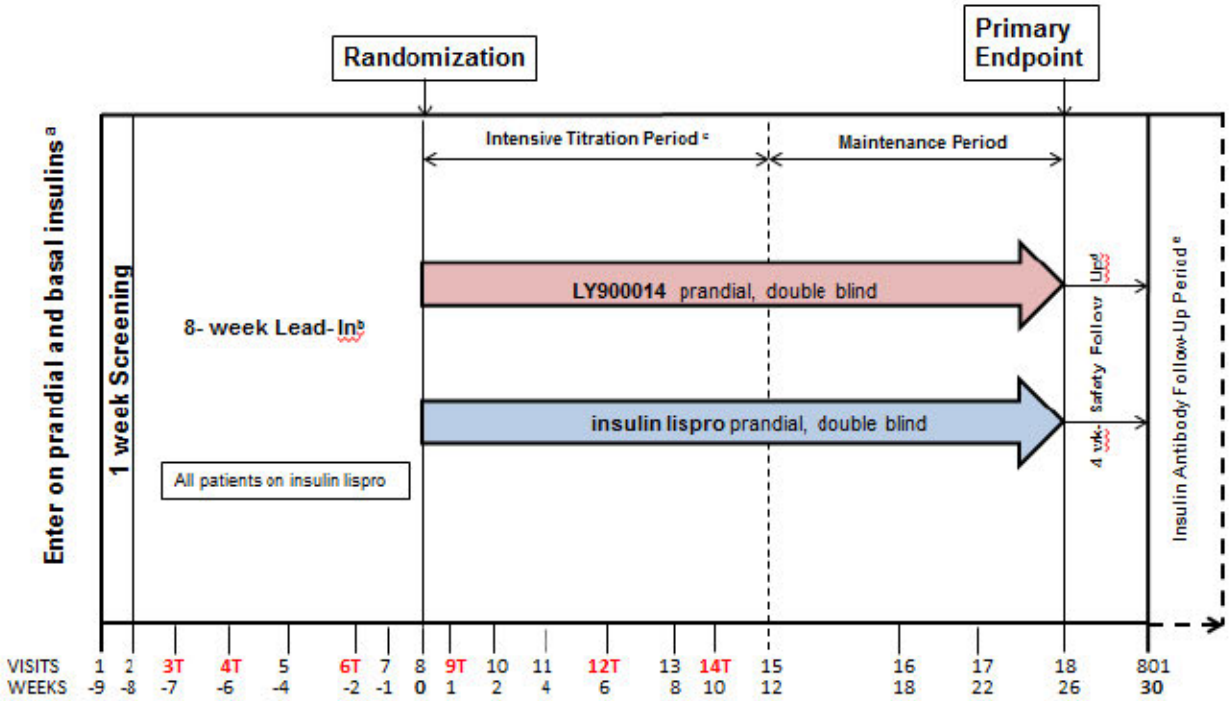
All patients who complete the 4-week safety follow-up visit (Visit 801) and have treatment-emergent insulin lispro antibodies that have not returned to the prespecified baseline range (Visit 2) will be asked to participate in follow-up to monitor insulin lispro antibody levels for up to 26 weeks after Visit 801 as described in Appendix 8.

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: a) basal insulin (insulin glargine U-100 or U-300, insulin degludec U-100 or U-200, 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 or twice daily or insulin degludec U-100 or U-200 once daily. Patients using basal insulin regimens other than insulin glargine U-100 or degludec U-100 or U-200 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 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 ITRN.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 an allowed study basal regimen of insulin glargine U-100 once or twice daily or insulin degludec U-100 or U-200 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.

e Eligible patients will have visits at approximately 3-month intervals for up to 26 weeks after Visit 801 for follow-up of insulin lispro antibody levels (see Appendix 8).

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

5.2. Number of Participants

Approximately 838 participants will be screened to achieve 670 randomized patients and 568 patients completing 26 weeks of treatment.

5.3. End of Study Definition

End of the study is the last scheduled procedure shown in the Insulin Lispro Antibody Follow-Up Assessment Schedule of Activities (Appendix 8) for the last patient.

5.3.1. Safety Follow-Up Period

Safety follow-up visit guidelines are as follows (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 Schedule of Activities.
- 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.
- For patients who finish Visit 18 without early discontinuation of IP, a safety follow-up visit should be completed 4 weeks after Visit 18.

All patients who complete the 4-week safety follow-up visit (Visit 801) and have treatment-emergent insulin lispro antibodies that have not returned to prespecified baseline range (Visit 2) will be asked to participate in follow-up to monitor insulin lispro antibody levels as described in Appendix 8. Patients participating in the antibody follow-up period will complete the study when insulin antibodies have returned to baseline range or when Visit 803 is completed, whichever occurs first.

5.4. Scientific Rationale for Study Design

Study ITRN 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 groups to allow comparison of LY900014 and insulin lispro when injected at the start of the meal.

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 ≤10.0% at screening. Prior to screening, patients may also be treated with up to 3 types of oral antihyperglycemic medications (OAMs) with stable dosing for 90 days prior to screening, 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 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 screening:

Type of Patient and Disease Characteristics

[1] Men or women diagnosed (clinically) with T2D, based on the World Health Organization (WHO) 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:

a) Basal insulin (insulin glargine U-100 [Basaglar/Abasaglar or LANTUS] or U-300, insulin detemir, insulin degludec U-100 or U-200, 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 insulin)

Or

b) 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

Doses of OAMs are required to have been stable for at least 90 days prior to screening. 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: 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 ≤10.0%, according to the central laboratory at the time of screening (Visit 1).

[6] Have a body mass index (BMI) of ≤45.0 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 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 urine pregnancy test is conducted at Visit 8.

[9] Have access to a telephone, or alternative means for close monitoring/communications, and have access to a reliable cellular signal for transmission of the electronic clinical outcomes assessment (eCOA) data

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

[11] Patient for whom 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.

[12] 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) Keep records in an eCOA as required by this protocol

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

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

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

[13] 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

[14] 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

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

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

[17] Have hypoglycemia unawareness as judged by the investigator

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

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

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

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

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

[23] Have 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

[24] Renal:

a) History of renal transplantation

b) Currently receiving renal dialysis

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

[25] 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 Gilberts Disease]) 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

[26] 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

[27] Having any hypersensitivity or allergy to any of the insulins or excipients used in this trial

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

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

[30] 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

[31] Have used thiazolidinediones, GLP-1 receptor agonist, or pramlintide within 90 days prior to screening

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

[33] Have used CSII within 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: liraglutide, lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion; or over-the-counter weight loss medications) 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 representative (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 ITRN.2 shows the treatment regimens.

Table ITRN.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 Labelling

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 1:1 ratio (double-blind LY900014 administered at meal time, double-blind insulin lispro administered at meal time). Stratification will be by country, HbA1c stratum (≤8.0%, >8.0% at Visit 7), and type of basal insulin during the lead-in period (glargine U-100 or degludec [U-100 or U-200]), and number of prandial doses at study entry (<3, ≥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 (AACE) (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 ITRN.3.

Table ITRN.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
Pre bedtime	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

7.2.1.2. Basal Insulin Therapy

At Visit 2, patients will be transferred to insulin glargine U-100 (Basaglar/Abasaglar or LANTUS) once or twice daily or to degludec U-100 or U-200 once daily if the patient enters the study on any other basal insulin regimen. 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 insulin glargine U-300 or 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 (please also refer to Section 7.2.1.4). 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 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. The patient may be transferred from once daily to twice daily insulin glargine dosing during the lead-in period if needed to reach the FBG target, and should continue the dosing frequency after randomization.

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. For patients treated with twice daily insulin glargine, the evening premeal SMBG level may be evaluated for assessment of the morning dose of insulin glargine.

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

Table ITRN.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 ITRN.5

Abbreviation: FBG = fasting blood glucose.

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

If Median (middle) 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]
80-109 mg/dL (4.4-6.1 mmol/L)	No adjustment
110-129 mg/dL (>6.1-7.2 mmol/L)	Increasing by 1-2 units
130-149 mg/dL (>7.2-8.3 mmol/L)	Increasing by 2-4 units
150-179 mg/dL (>8.3-9.9 mmol/L)	Increasing by 4-6 units
≥180 mg/dL (≥10.0 mmol/L)	Increasing by 6-8 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.

Source: Adapted from Bartley et al. 2008 and Bolli et al. 2009.

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 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 minimum 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 for a maximum of 2 prandial insulin adjustments per week. 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 ITRN.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 ITRN.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 (or middle) 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 ITRN.7.

Table ITRN.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 on the same date as Visit 18 or in 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 randomized to either LY900014 or insulin lispro. Additional guidance for diabetes therapy after the treatment period is provided in Section 7.8.2 and Appendix 8.

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 participants 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, and completion of patient eCOA. 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 ITRN.8.

Table ITRN.8. Concomitant Medications

Drug Class	Acute Use	Chronic Use	Safety Follow-up and Insulin Lispro Antibody Follow-Up Periods	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	No	No	Yes	
Premixed insulin or premixed insulin analog	No	No	Yes	
Insulin human inhalation powder (Afrezza®)	No	No	No	
Weight loss drugs (for example, prescription drugs: 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 topical, inhaled, intraocular, intra-articular, or intranasal preparations)	Yes	No	No	During the lead-in period, allow 1-time use for ≤7 consecutive days. During all other study periods, allow 1-time use ≤14 consecutive days.

Abbreviations: IV = intravenous; NPH = neutral protamine Hagedorn; SC = subcutaneous.

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**. Please also refer to Section 6.2, Exclusion Criterion [31] for criteria regarding thiazolidinediones, GLP-1 receptor agonists, and pramlintide. 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).

OAM 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.

Please also refer to Appendix 8 for information regarding the insulin lispro antibody follow-up assessment. 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 the 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 (including HbA1c) and safety data will be collected at scheduled visits. 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 may decide to stop 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 ITRN.8.
- If the patient has not taken IP for more than 14 consecutive days.

Discontinuation of the IP 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:

- ALT or AST >8X ULN.
- ALT or AST >5X ULN for more than 2 weeks.
- ALT or AST >3X ULN and TBL >2X ULN or prothrombin time >1.5X ULN.

- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- alkaline phosphatase (ALP) >3X ULN.
- ALP >2.5X ULN and TBL >2X ULN.
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.2. 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 identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with IP.

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.

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. Electronic Clinical Outcomes Assessment

The eCOA diary will collect all glucose data directly from the BG meters, thereby increasing the validity of measures reported by the patient and minimizing transcription errors in recording the measures. The use of e-diaries should also allow more complete and accurate capturing of hypoglycemia events, as well as more frequent and timely interactions between investigator and patients as the intensity of their individual diabetes management increases. The system will be used to collect prandial insulin doses (date, time, and actual dose taken) and the basal insulin dose, on the 3 days prior to study visits, on the days of 10-point SMBG profiles, and at other times as clinically indicated. Hypoglycemic events will be captured throughout the clinical study in eCOA along with date and time of the BG level if measured and hypoglycemia treatment and outcome data. Additionally, the eCOA system will incorporate study-specific reminders for patients to perform the 10-point SMBG profiles.

Physicians and designated clinical staff will have access to the eCOA portal (secure web-based site) with the ongoing near real-time updating of BG readings, insulin doses administered, and hypoglycemic events. Manual inspection of data will support at least weekly patient monitoring as an enhancement to standard of care for patient safety, as well as the potential for reaching an optimum efficacy outcome. Investigative staff will assess clinical data via the eCOA portal and recommend adjustments in basal and prandial insulin (also refer to Section 7.2.1).

An instruction manual will be provided to patients and investigative sites. Additional instruction and training will be provided to the investigative sites regarding data collection, review, retention and archival processes. In the event of eCOA malfunction or loss, the patient will be instructed to immediately contact the investigative site for instructions regarding replacement of the equipment.

9.1.4.2. Four-Point Self-Monitoring Blood Glucose

Patients should be instructed to measure a minimum of 4 SMBG readings daily (consists of fasting [pre morning meal], pre midday meal, pre evening meal, and pre bedtime), with additional readings as needed for glucose self-management. Site personnel may request additional SMBG monitoring from patients and/or assess SMBG values at other times (such as postprandial SMBG readings) 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.

9.1.4.3. Ten-Point Self-Monitoring Blood Glucose

Patients in both study groups should be instructed to perform 10-point SMBG profiles prior to 5 visits during the study (Visits 8, 11, 13, 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.

9.1.4.4. 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). 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 range of 71 to 180 mg/dL (3.9-10.0 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 the morning of the MMTT within the target FBG range, please 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 $\leq$70 mg/dL [3.9 mmol/L]) can be treated with 15 to 20 grams of carbohydrate. If a hypoglycemic episode requires more than approximately 20 grams of carbohydrate within 8 hours of the start of the MMTT or the patient experiences a severe hypoglycemic 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) (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 ITRN.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 ITRN.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	1 unit : 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

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 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, 15, 30, 60, 120, 180, and 240 minutes after the start of the meal.

9.1.4.5. Diabetes Education and Nutritional Counseling

Initial training at Visit 2 will include diabetes education and nutritional counseling including information on 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 informed consent form (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
- Considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.
- 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.

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 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 IP 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 $\leq$70 mg/dL (3.9 mmol/L) as hypoglycemia.

Hypoglycemia events will be collected in eCOA (Section 9.1.4.1). If a hypoglycemia event is suspected, the patient should record the BG value, any associated symptoms, and the treatment administered in eCOA. 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 eCOA and in consultation with the patient, see below and Section 9.2.1. All episodes of severe hypoglycemia must be reported as AEs via electronic data entry, and as SAEs.

Hypoglycemia will be described using the following definitions:

- **Documented hypoglycemia**
  - **Documented symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by BG of ≤70 mg/dL (3.9 mmol/L);
  - **Documented asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with a BG concentration of ≤70 mg/dL (3.9 mmol/L);
  - **Documented unspecified hypoglycemia:** an event during which BG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycemia were recorded;
- **Probable symptomatic hypoglycemia:** an event during which symptoms are indicative of hypoglycemia and which was presumably caused by BG ≤70 mg/dL (3.9 mmol/L) although no BG measurement was reported;
- **Severe hypoglycemia:** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the patient has an altered mental status and cannot assist in his/her own care, may be semiconscious or unconscious, or experience coma with or without seizures, and may require parenteral therapy. BG 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]).
- **Nocturnal hypoglycemia:** any hypoglycemic event (documented hypoglycemia or probable symptomatic hypoglycemia, including severe hypoglycemia) that occurs between bedtime and waking.
- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, that do not require the assistance of another person, are accompanied by BG >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold.
- **Overall hypoglycemia:** This category combines all cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia) excluding the events of relative hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category.

9.4.2. Severe Hypoglycemia

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, 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).

ECGs 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.

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

9.4.4. Vital Signs

For each patient, vital signs 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).

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.

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 4.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

9.7.1. Whole Blood Samples for Pharmacogenetic Research

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY900014 and to investigate genetic variants thought to play a role in T2D and related complications. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All pharmacogenetic samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

CCI [redacted]

CCI [redacted]

9.8. Biomarkers and Predictive or Other Analyses

CCI [redacted]

CCI [redacted]

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).

CCI [redacted]

[redacted]

Patients who complete the 4-week safety follow-up visit and have treatment-emergent anti-insulin lispro antibodies that have not returned to prespecified baseline range (Visit 2) will be asked to participate in follow-up to monitor antibody levels. Instructions for this follow-up assessment are provided in Appendix 8.

CCI [redacted]

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 670 patients will be randomized in order that 568 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 1:1 ratio to LY900014 and insulin lispro, both dosed 0 to 2 minutes before meals. Assuming a noninferiority margin (NIM) of 0.4%, no true difference between treatment groups, and an SD of 1.1%, 568 completers (284 in each group) will provide greater than 99% power to show noninferiority between LY900014 and insulin lispro using the upper limit of a 2-sided 95% confidence interval (CI) (LY900014 – insulin lispro). CCI [redacted]

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 statistical analysis plan (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 according to the treatment the patients are assigned. The analyses for the primary and multiplicity adjusted objectives will be performed for the efficacy estimand including data collected prior to permanent discontinuation of IP and for the ITT estimand including all data collected regardless of IP use (Section 10.3.3.1). Unless otherwise specified, the efficacy analyses for other secondary objectives and exploratory objectives will be performed for the efficacy estimand. 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. Countries in similar geographic regions with fewer than 10 patients, based on the all-randomized population, will be pooled to achieve a pooled country of at least 10 patients. All analyses using country in the model will use a pooled country, unless otherwise specified. The final pooling by country and geographic region will be finalized prior to data lock.

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 measures (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 (pooled 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 ($\leq$8%, >8%) 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. SAS PROC MIXED will be used to perform the analysis. 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 (pooled 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%, >8%) 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. LS 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 p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test or Pearson's chi-square 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 or Pearson's chi-square test for categorical data and an analysis of

variance (ANOVA) with treatment in the model for continuous data. 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 summarized and compared between treatment groups using Fisher's exact test.

The use of OAMs during the treatment period will be summarized by treatment group. In addition, the proportion of patients 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. There will be 2 primary analysis methods, each tested at the full significance level of 0.05.

CCI [redacted], the primary analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand (treatment regimen estimand) that will include all data collected from randomization through Week 26, regardless of IP use. The reference will be all observed data from the randomized patients in the same treatment group who discontinue IP and complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro from the ANCOVA analysis of change from baseline to Week 26 in HbA1c using all randomized patients as described in Section 10.3.1.

If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis, the reference will be changed to include all observed data from all randomized patients in the same treatment arm who complete the study without missing data.

CCI [redacted], 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 (efficacy estimand). The analysis model and selection of covariance structure is described in Section 10.3.1.

For both primary analysis approaches, LY900014 will be declared noninferior to insulin lispro 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%. In addition, the 95% CI for the treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05.

In addition to the primary objective, the superiority of LY900014 in controlling HbA1c compared to insulin lispro will also be assessed for each 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. Sensitivity Analyses for Missing Data

A missing-not-at-random (MNAR) based analysis will be performed for both the efficacy and ITT estimands to assess sensitivity to departures from the missing-at-random (MAR) assumption by repeatedly adjusting the imputations of missing data to provide a progressively more severe stress test (Ratitch et al 2013). The basic idea is to impute the missing values and add a value (delta) to the imputed values of the experimental group and perform an analysis for the primary endpoint on the delta-adjusted data set to see whether the conclusion of the primary analysis is overturned. If not, a larger delta is chosen and the process repeated until the primary result is overturned. If the delta required to overturn the primary result is not a plausible departure from MAR, then the primary result is robust to plausible departures from MAR. Imputation under the noninferiority null method, where delta equals the NIM, will be included as a special case of the progressive stress test.

For the ITT estimand, the reference group will be as described for the CCI primary analysis, and ANCOVA on the change from baseline to Week 26 in HbA1c will be used.

For the efficacy estimand, the reference group will be the insulin lispro treatment group. Imputation will be for all longitudinal visits.

10.3.3.1.2. 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 for the efficacy estimand 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. Analyses will be performed for both the efficacy estimand and ITT estimand as described in Section 10.3.3.1 using the same graphical testing scheme.

The graphical testing scheme will be described in the SAP. The study total alpha level (or study-wise type I error) is preset to be 5% for each estimand. The study total alpha level will be used for the primary objective in the initial step. The alpha level will be allocated to other key endpoints based on the weights in testing paths once the primary endpoint is successfully demonstrated. If 1 of the remaining hypotheses is successfully demonstrated with the preserved alpha level, its preserved alpha will be allocated to the remainder of the hypotheses by the weights in the paths. The iterative test procedure continues until none of the remaining hypotheses can be demonstrated with their preserved alphas or all hypotheses are demonstrated successful.

An ANCOVA model with strata (pooled country, type of basal insulin, number of prandial doses at entry, and baseline HbA1c [≤8%, >8%]), 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.

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

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 for the efficacy estimand.

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 AEs (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.

SAEs, AEs reported as reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the Medical MedDRA PT, sorted by decreasing frequency within the LY900014 treatment group. TEAEs 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 one 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. SAEs, AEs reported as reason for discontinuation from the study, and TEAEs will also be summarized for open-label insulin lispro during the lead-in period.

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 or Pearson's chi-square test will be used to compare treatment groups unless otherwise specified.

The analyses for assessing immunogenicity data will be described in the SAP after being agreed with the FDA on the threshold for determining treatment-emergent antibodies to insulin lispro.

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 EQ 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.

10.3.5.2. Subgroup Analyses

The following subgroups will be analyzed using the efficacy estimand to evaluate consistency of treatment effects on the primary efficacy measure if there are sufficient numbers of patients in each treatment by subgroup (for example, 10%):

- Age (<65, ≥65 years and <75, ≥75 years and <65, ≥65 to <75, ≥75 to <85, ≥85 years)
- HbA1c stratum (≤8.0%, >8.0%)
- Sex (male or female)
- BMI (<25, ≥25 kg/m^2 and <30, ≥30 kg/m^2 and <35, ≥35 kg/m^2)
- Duration of diabetes (using the median as the cut-off)
- Race
- Ethnicity
- Country
- Region
- Baseline 1-hour PPG excursion
- Baseline 1-hour PPG (PPG ≤180 mg/dL, >180 mg/dL)
- Baseline 2-hour PPG excursion
- Baseline 2-hour PPG (PPG ≤180 mg/dL, >180 mg/dL)
- Prandial insulin dosing plan (carbohydrate counting, pattern adjustment)
- Type of basal insulin during the lead-in period (glargine, degludec)
- Number of prandial doses at study entry (<3, ≥3)
- SGLT-2 inhibitor treatment

Analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 26) will be evaluated to assess the treatment by subgroup interaction. When analyzing HbA1c stratum (≤8.0%, >8.0%) as a subgroup, the baseline HbA1c will be not be included as a covariate to avoid confounding.

Additional subgroup analyses may also be performed.

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 and that does not necessarily have a causal relationship with this treatment. An adverse event 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
Product complaint	Product complaints are a customer's written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution.
CRP/CRS	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
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessment

eCRF	case report form
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	Food and Drug Administration
GCP	good clinical practice
GD	glucodynamic(s)
GRAS	Generally Recognized As Safe
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
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

MAR	missing at random
MDI	multiple daily injection
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measure
MMTT	mixed-meal tolerance test
NIM	noninferiority 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
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.
SC	subcutaneous
SD	standard deviation
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
TEADA	treatment-emergent anti-insulin lispro antibody

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]	**Stored Samples**
	Pharmacogenetic samples
	Nonpharmacogenetic biomarker samples

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 must be performed in women of childbearing potential at Visit 1 followed by a urine 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
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of 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 trial.

Appendix 3.1.2. Ethical Review

The investigator or an appropriate local representative must give assurance that the 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 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 GCP.

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

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

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 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 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.

Electronic clinical outcomes assessment (eCOA) measures (for example, a rating scale) or other data reported directly by the patient/patient (for example, daily dosing schedule, event diary) are entered into an eCOA instrument (for example, personal digital assistant), at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

If eCOA records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

CRF 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 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	**Alkaline phosphatase isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

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

CCI

[redacted]

Appendix 6. New York Heart Association Cardiac Disease Classification

CCI

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

Appendix 8. Insulin Lispro Antibody Follow-Up Assessment

Rationale for Insulin Lispro Antibody Follow Up Assessment

CCI [redacted]

Eligibility for Insulin Lispro Antibody Follow-Up Assessment

Any patient who develops a TEADA response that has not returned to the prespecified baseline range (based on Visit 2 sample) by the 4-week safety follow up visit (based on Visit 801 sample) will undergo additional anti-insulin lispro antibody monitoring. Study visits will continue at approximately 3 month intervals for a maximum of 6 months (approximately 26 weeks) after Visit 801 or until insulin lispro antibodies return to baseline range, whichever occurs sooner.

This follow-up assessment also includes any randomized patient who discontinues study insulin treatment prior to the end of the planned treatment period and has a TEADA response that has not returned to baseline range by Visit 801.

At Visit 801, it is recommended that the first insulin lispro antibody follow-up visit (Visit 802) be scheduled for all study patients, regardless of TEADA status. Visit 802 should occur no sooner than 13 weeks after Visit 801 to allow time to perform antibody testing on the Visit 801 sample. Insulin lispro antibody percent binding results will not be provided to sites. When insulin antibody results are available to determine whether the patient's insulin antibody levels have returned to baseline range, investigators will be notified and Visit 802 can be confirmed or cancelled as appropriate.

During the insulin lispro antibody follow-up period, investigators will be notified if insulin lispro antibodies for a given patient have returned to baseline range, at which time the patient's participation in the follow-up period should be stopped. In the exceptional circumstance that insulin antibody results are not available prior to the next scheduled follow-up visit, patients should be instructed to complete the visit as scheduled; however, the blood sample collected as part of the visit will only be analyzed if the insulin antibody results from the previous visit are still above baseline.

In any case, even where insulin antibodies persist, the insulin lispro antibody follow-up assessment is expected to last no longer than 30 weeks from the protocol-scheduled last treatment visit.

Patients should not participate in other clinical trials during the follow-up period.

Patients entering the protocol as part of a maximized extended enrollment addendum (I8B-MC-ITRN[1]) will not be included in the insulin lispro antibody follow-up assessment.

Procedures for Insulin Lispro Antibody Follow-Up Assessment

In order to reduce potential interference with antibody monitoring during this follow-up period, introduction of new insulin formulations should be avoided. Guidance for diabetes therapy during the insulin antibody follow-up period is provided in Section 7.8.2.

Blood samples for insulin lispro antibody and HbA1c measurements should be collected at approximately 3-month intervals for up to 26 weeks after Visit 801. All SAEs (including severe hypoglycemia) and all nonserious AEs should be reported. Vital signs, body weight, total daily prandial insulin dose, total daily basal insulin dose, and information on concomitant medications including OAMs will be collected at each insulin antibody follow-up visit as described in the Insulin Lispro Antibody Follow-Up Assessment Schedule of Activities (see chart below).

Schedule of Activities during Insulin Lispro Antibody Follow-Up Assessment

Study Period	Insulin Lispro Antibody Follow-Up Period		ED-IA Follow-Up
eCRF Visit Number	**802**	**803**	
Visit Window (days)	**±14**	**±14**	
Time on Study Relative to Last Treatment Dose Visit (weeks)	**17**	**30**	
Time on Study Relative to First Treatment Dose Visit (weeks)	**43**	**56**	
IWRS	X	X	X
Dispense glucose monitoring and ancillary supplies	X		
Telephone call for visit reminder or informing patient of completion in the study	X	X	
Return of unused diabetes medications and study supplies if required by local regulations	X	X	X
Concomitant medication (including OAMs)	X	X	X
Total daily prandial insulin dose	X	X	X
Total daily basal insulin dose	X	X	X
Vital signs	X	X	X
Body weight	X	X	X
Adverse events	X	X	X
Anti-insulin lispro antibodies	X	X	X[a]
HbA1c	X	X	X

Abbreviations: eCRF = electronic case report form; ED-IA = early discontinuation-insulin antibody; HbA1c = hemoglobin A1c; IWRS = interactive web response system; OAMs = oral antihyperglycemic medications.

[a] Insulin lispro antibody samples collected as part of the ED-IA follow-up visit will be analyzed only if the results from the previous visit are still above baseline.

Appendix 9. Protocol Amendment I8B-MC-ITRN (a) Summary 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 PRONTO-T2D

Overview

Protocol I8B-MC-ITRN 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 PRONTO-T2D has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I8B-MC-ITRN Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis	Updates to match main body	
Section 5.1 Overall Design and Figure ITRN.1.	Follow up for insulin lispro antibodies reduced from 48 to 26 weeks	CCI
[redacted] Period	Changed Visit 805 to 803	
Section 7.2.1.4 Study Prandial Insulin Therapy	Added text for initiation of study prandial insulin	Additional guidance for initiation of study prandial insulin at randomization
Section 7.2.1.5 Transitioning off Study Prandial Insulin Therapy	Modified	MMTT can be performed up to 4 days prior to Visit
Section 8.1.1 Permanent Discontinuation from Study Treatment	Clarified text	
Section 9.1.4.4. Mixed-Meal Tolerance Test	Added more instruction	In order to help patients to reach the desired fasting blood glucose range
Section 10.3.1 General Statistical Considerations	Updated ITT with imputation for primary endpoint Clarified the use of MMRM Clarified ANCOVA Clarified missing endpoints	CCI
10.3.3.1. Primary Analyses	Added more detail for submission and manuscript analysis plans	
10.3.3.1.1. Sensitivity Analyses for		

Section # and Name	Description of Change	Brief Rationale
Missing Data		CCI [redacted].
10.3.3.1.2. Additional Analyses for the Primary Endpoint		
10.3.3.2. Secondary Analyses		
10.3.5.2 Subgroup Analyses	Edits	
Appendix 8 Insulin Lispro Antibody Follow-Up Assessment	Edits to reduce the follow- up period from 1 year to 6 months	

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

1. Synopsis

Treatment Groups and Duration

All patients who complete the 4-week safety follow-up visit (Visit 801) and have treatment-emergent insulin lispro antibodies that have not returned to prespecified baseline range (Visit 2) will be asked to participate in follow-up to monitor insulin lispro antibody levels for up to ~~48~~ 26 weeks after Visit 801.

Statistical Analysis

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 be performed for the efficacy estimand including data collected prior to permanent discontinuation of investigational product (IP) and for the ITT estimand (treatment regimen estimand) including all data collected regardless of IP use.

CCI [redacted], the primary analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand that will include all data collected from randomization through Week 26, regardless of IP use. The reference will be all observed data from the randomized patients in the same treatment arm who discontinue IP and complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro from the ANCOVA analysis of change from baseline to Week 26 in HbA1c using all randomized patients. The model for this analysis will include the effects of treatment and strata (pooled country, type of basal insulin and number of prandial doses at entry), and the continuous covariate of baseline value.

If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis, the reference will be changed to include all observed data from all randomized patients in the same treatment arm who complete the study without missing data.

CCI [redacted], 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 (efficacy estimand). The model for this analysis will include the fixed class effects of treatment, strata (pooled

country, type of basal insulin, and number of prandial doses at entry), visit, treatment-by-visit interaction, and the continuous, fixed covariate of baseline value.

For both primary analysis approaches, LY900014 will be declared noninferior to insulin lispro 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%. In addition, the 95% CI for the treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05.

~~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 using all randomized patients. 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 noninferior to insulin lispro. In addition, the 95% CI for the treatment difference from the MMRM model will be compared to an alternative NIM of +0.3%. The model for this analysis will include the fixed class effects of treatment, strata (pooled 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. The same graphical testing scheme will be applied for both the efficacy estimand and ITT estimand.

5.1. Overall Design

All patients who complete the 4-week safety follow-up visit (Visit 801) and have treatment-emergent insulin lispro antibodies that have not returned to the prespecified baseline range (Visit 2) will be asked to participate in follow-up to monitor insulin lispro antibody levels for up to ~~48~~ 26 weeks after Visit 801 as described in Appendix 8.

Figure ITRN.2. Illustration of study design for Clinical Protocol I8B-MC-ITRN.

- Eligible patients will have visits at approximately 3-month intervals for up to ~~48~~ 26 weeks after Visit 801 for follow-up of insulin lispro antibody levels (see Appendix 8).

5.3.1. Safety Follow-Up Period

Patients participating in the antibody follow-up period will complete the study when insulin antibodies have returned to baseline range or when Visit ~~805~~ 803 is completed, whichever occurs first.

7.2.1.4. Study Prandial Insulin Therapy

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 ~~baseline MMTT~~ 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.

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 on same date as Visit 18 or in the evening the day prior to Visit 18 if the MMTT is performed prior to Visit 18 or at early discontinuation.

7.6 Treatment Compliance

Patients who, in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from IP or from the study.

8.1.1. Permanent Discontinuation from Study Treatment

- If the patient, for any reason, requires treatment with another therapeutic regimen ~~(including a change to the prescribed basal insulin injection time for insulin glargine U-100)~~ or therapeutic agent ~~(including addition of a second basal insulin injection)~~ 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.

9.1.4.4 Mixed-Meal Tolerance Test

~~Patients should arrive with no episodes of hypoglycemia (symptoms or BG ≤70 mg/dL [3.9 mmol/L]) during this fasting period.~~

Target FBG prior to the MMTT: Patients must have an FBG range of 71 to 180 mg/dL (3.9-10.0 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 the morning of the MMTT within the target FBG range, please 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 hypoglycemic episode requires more than approximately 20 grams of carbohydrate within 8 hours of the start of the MMTT or the patient experiences a severe hypoglycemic episode (as defined in Section 9.4.1 and 9.4.2), the patient should be instructed to notify the site and the MMTT must be rescheduled.

Insulin Injection:

~~Patients should inject basal insulin according to their usual schedule.~~

10.3.1 General Statistical Considerations

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 primary analysis method will be a~~A restricted maximum likelihood -based, mixed-effect model repeated measure (MMRM) analysis ~~using~~ will be used to analyze continuous longitudinal variables. ~~all~~ All the longitudinal observations at each scheduled postbaseline visit~~.~~ will be included in the analysis.

An analysis of covariance (ANCOVA) ~~model~~ will also be used to analyze continuous variables. The model for the change from baseline to the Week 26 HbA1c endpoint will include ~~with~~ treatment and strata (pooled country, type of basal insulin, and number of prandial doses at entry)~~, and treatment~~ as fixed effects and baseline as a covariate~~. will be conducted as supportive analyses~~. Unless otherwise stated, ~~Missing~~ missing endpoints will be imputed using the last-observation–carried-forward (LOCF) approach, using only postbaseline data.

10.3.3.1 Primary Analyses

There will be 2 primary analysis methods, each tested at the full significance level of 0.05.

CCI [redacted], the primary analysis method will use the copy reference approach to impute missing data based on multiple imputations with a pattern mixture model. This analysis is for the ITT estimand (treatment regimen estimand) that will include all data collected from randomization through Week 26, regardless of IP use. The reference will be all observed data from the randomized patients in the same treatment group who discontinue IP and complete the study without missing data. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and insulin lispro from the ANCOVA analysis of change from baseline to Week 26 in HbA1c using all randomized patients as described in Section 10.3.1

If there are only a limited number of patients in the reference group as described above that leads to a failure in performing the proposed multiple imputation analysis, the reference will be changed to include all observed data from all randomized patients in the same treatment arm who complete the study without missing data.

CCI [redacted], 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 (efficacy estimand). The analysis model and selection of covariance structure is described in Section 10.3.1.

For both primary analysis approaches, LY900014 will be declared noninferior to insulin lispro 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%. In addition, the 95% CI for the

treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05.

In addition to the primary objective, the superiority of LY900014 in controlling HbA1c compared to insulin lispro will also be assessed for each 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.

~~estimands to compare treatment groups for the analysis of the primary measure of change from baseline to Week 26 in HbA1c. One primary estimand will be an efficacy estimand that includes only data collected prior to permanent discontinuation of IP.~~ CCI [redacted] ~~. Both estimands will use the same primary analysis model, and each will be tested at the full significance level of 0.05.~~

~~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 using all randomized patients. 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. In addition, the 95% CI for the treatment difference from the MMRM model will be compared to an alternative NIM of +0.3%. The analysis model and selection of covariance structure is described in Section 10.3.1~~

10.3.3.1.1. Sensitivity Analyses for Missing Data

For the ITT estimand, the reference group will be as described for the CCI primary analysis, and ANCOVA on the change from baseline to Week 26 in HbA1c will be used. For the efficacy estimand, the reference group will be the insulin lispro treatment group. Imputation will be for all longitudinal visits.

10.3.3.1.2. Additional Analyses for the Primary Endpoint

The primary ~~analysis model,~~ 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 for the efficacy estimand 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.

~~In addition to the primary objective, the superiority of LY900014 in controlling HbA1c compared to insulin lispro will also be assessed with the same model using all randomized patients. If the p-value is less than the alpha level from the graphical approach allocated to this subjecthypothesis, LY900014 will be declared superior to insulin lispro.~~

10.3.3.2. Secondary Analyses

Analyses will be performed for both the efficacy estimand and ITT estimand as described in Section 10.3.3.1 using the same graphical testing scheme.

The graphical testing scheme will be described in the SAP. The study total alpha level (or study-wise type I error) is preset to be 5% for each estimand. The study total alpha level will be used for the primary objective in the initial step. The alpha level will be allocated to other key endpoints based on the weights in testing paths once the primary endpoint is successfully demonstrated. If 1 of the remaining hypotheses is successfully demonstrated with the preserved alpha level, its preserved alpha will be allocated to the remainder of the hypotheses by the weights in the paths. The iterative test procedure continues until none of the remaining hypotheses can be demonstrated with their preserved alphas or all hypotheses are demonstrated successful.

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.

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

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 for the efficacy estimand.

10.3.5.2. Subgroup Analyses

- Prandial insulin dosing plan (carbohydrate counting, ~~or fixed insulin dose~~pattern adjustment)
- Type of basal insulin during the lead-in period (glargine, ~~U 100,~~ degludec ~~U 100 or U 200~~)

Appendix 8

Eligibility for Insulin Lispro Antibody Follow-Up Assessment

Study visits will continue at approximately 3 month intervals for a maximum of ~~1 year~~6 months (approximately ~~48~~ 26 weeks) after Visit 801 or until insulin lispro antibodies return to baseline range, whichever occurs sooner.

Visit 802 should occur no sooner than ~~9~~ 13 weeks after Visit 801 to allow time to perform antibody testing on the Visit 801 sample.

In any case, even where insulin antibodies persist, the insulin lispro antibody follow-up assessment is expected to last no longer than ~~52~~ 30 weeks from the protocol-scheduled last treatment visit.

Procedures for Insulin Lispro Antibody Follow-Up Assessment

Blood samples for insulin lispro antibody and HbA1c measurements should be collected at approximately 3-month intervals for up to ~~48~~ 26 weeks after Visit 801.

Schedule of Activities during Insulin Lispro Antibody Follow-Up Assessment

Study Period	Insulin Lispro Antibody Follow-Up Period				ED-IA Follow-Up
eCRF Visit Number	802	803	~~804~~	~~805~~	
Visit Window (days)	~~±1~~14	±14	~~±14~~	~~±14~~	
Time on Study Relative to Last Treatment Dose Visit (weeks)	~~13~~17	~~26~~30	~~39~~	~~52~~	
Time on Study Relative to First Treatment Dose Visit (weeks)	~~39~~43	~~52~~56	~~65~~	~~78~~	
IWRS	X	X	~~X~~	~~X~~	X
Dispense glucose monitoring and ancillary supplies	X	~~X~~	~~X~~		
Telephone call for visit reminder or informing patient of completion in the study	X	X	~~X~~		
Return of unused diabetes medications and study supplies if required by local regulations	X	X	~~X~~	~~X~~	X
Clinical Assessments					
Concomitant medication (including OAMs)	X	X	~~X~~	~~X~~	X
Total daily prandial insulin dose	X	X	~~X~~	~~X~~	X
Total daily basal insulin dose	X	X	~~X~~	~~X~~	X
Vital signs	X	X	~~X~~	~~X~~	X
Body weight	X	X	~~X~~	~~X~~	X
Adverse events	X	X	~~X~~	~~X~~	X
Laboratory Assessments					
Anti-insulin lispro antibodies	X	X	~~X~~	~~X~~	X[a]
HbA1c	X	X	~~X~~	~~X~~	X

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