Protocol I8B-MC-ITSW(a)

A Study of LY900014 in Participants with Type 2 Diabetes using Continuous Glucose Monitoring

NCT04605991

Approval Date: 13-Jul-2020

Title Page

Protocol Title: A Study of LY900014 in Participants with Type 2 Diabetes using Continuous Glucose Monitoring

Protocol Number: I8B-MC-ITSW

Amendment Number: (a)

Compound: LY900014

Study Phase: 3b

Short Title: PRONTO-Time in Range

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number

IND: 127210

Approval Date: Protocol Electronically Signed and Approved by Lilly: 21 April 2020 GMT
Protocol Amendment (a) Electronically Signed and Approved on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol I8B-MC-ITSW	21-Apr-2020

Amendment [a]

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Addition of language to align with Lilly guidance	Clarification of inclusion criteria for females regarding pregnancy, breastfeeding, and contraceptive guidance
5.2 Exclusion Criteria	Renumbering of exclusion criteria	Renumbering was completed to align with Lilly guidance
8.2.5. Hypoglycemia	Addition of language to align with classifications	Clarification of standard classifications for hypoglycemia
10.1.1. Regulatory and Ethical Considerations	Addition of language to align with Lilly template	Clarification of regulatory information for investigator sites
10.2. Appendix 2: Clinical Laboratory Tests	Complement laboratory testing updated	Complement laboratory tests were updated to align with current evaluations
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Addition of language to align with Lilly guidance	Clarification of contraceptive guidance
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Study of LY900014 in Participants with Type 2 Diabetes using Continuous Glucose Monitoring

Short Title: PRONTO-Time in Range

Rationale: The aim of this study is to evaluate time in range (70-180 mg/dL [3.9-10.0 mmol/L]) from continuous glucose monitoring (CGM) with LY900014 treatment in a basal-bolus multiple daily injection (MDI) regimen in combination with insulin glargine U-100 in participants with type 2 diabetes (T2D).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate time glucose values from continuous glucose monitoring (CGM) are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period with LY900014 treatment	• Percentage of time with CGM glucose values between 70-180 mg/dL (3.9-10.0 mmol/L) (both inclusive) during daytime period with 14 days of CGM use at Week 12 compared with baseline
Gated Secondary	
• To evaluate HbA1c	• HbA1c change from baseline to Week 12
• To evaluate time glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the 24-hour period with LY900014 treatment	• Percentage of time with CGM glucose values between 70-180 mg/dL (3.9-10.0 mmol/L) (both inclusive) during the 24-hour period with 14 days of CGM use at Week 12 compared with baseline
Other Secondary	
• To evaluate time in hypoglycemic glucose ranges, obtained from CGM use	• Percentage of time with CGM glucose values <54 mg/dL (<3.0 mmol/L) during daytime and 24-hour periods with 14 days of CGM use at Week 12 compared with baseline
• To evaluate time in hyperglycemic glucose ranges, obtained from CGM use	• Percentage of time with sensor glucose values >180 mg/dL (>10.0 mmol/L) and >250 mg/dL (>13.9 mmol/L), during

	daytime and 24-hour periods with 14 days of CGM use at Week 12 compared with baseline
• To evaluate postprandial incremental AUCs, obtained from CGM use	• Postprandial incremental $AUC_{0\text{-}1\ hour}$ and incremental $AUC_{0\text{-}2\ hour}$ at Week 12 compared with baseline
• To evaluate proportion of participants achieving HbA1c targets	• The proportion of participants with HbA1c <7% and ≤6.5% at Week 12
• To evaluate bolus, basal, and total daily insulin dose	• Bolus, basal, and total insulin doses and bolus/total insulin ratio at Week 12 compared with baseline
• To evaluate severe hypoglycemia	• Incidence of severe hypoglycemia events from baseline to Week 12
• To evaluate insulin treatment satisfaction regarding glycemic control as measured by the ITSQ	• Change from baseline in ITSQ glycemic control domain scores at Week 12

Abbreviations: AUC = area under the curve; HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire.

Overall Design

Study I8B-MC-ITSW (ITSW) is a Phase 3b, prospective, open-label, outpatient, multicenter, single-treatment-group study conducted in participants with T2D currently treated with a basal-bolus analog MDI regimen. Participants will use unblinded CGM (Freestyle Libre 14-day system) for diabetes management and glucose data collection during the study. The study is designed to evaluate the time sensor glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) with 12 weeks of LY900014 treatment.

LY900014 will be injected immediately (0-2 minutes) prior to each meal in combination with insulin glargine U-100 as basal insulin. Basal-bolus insulin doses will be titrated to achieve protocol glucose targets during the study.

Disclosure Statement: This is a single group treatment study.

Number of Participants:

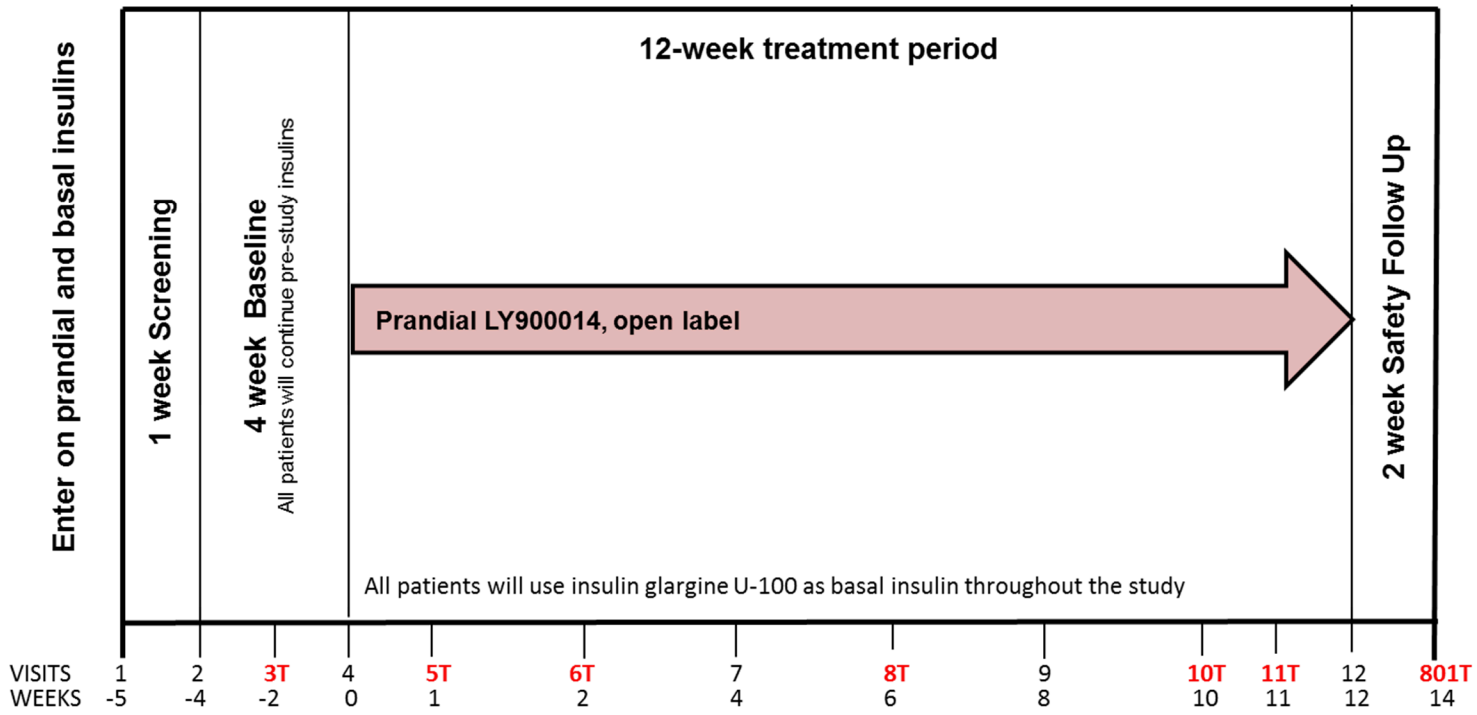
Approximately 167 participants will be assigned to treatment such that approximately 150 evaluable participants complete the study.

Intervention Groups and Duration:

The study includes screening, 4-week baseline, 12-week treatment, and 2-week posttreatment follow-up periods. Participants will continue treatment with prestudy insulins during the 4-week baseline period.

Data Monitoring Committee: No

1.2. Schema



T=Telephone visits

1.3. Schedule of Activities (SoA)

	Screen	Baseline		Treatment Period										ED
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**801**	**ED**
Visit Window (± days)		**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	
Time (weeks)	**-5**	**-4**	**-2**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**11**	**12**	**14**	
Telephone visits are indicated by shaded columns. Telephone visits can become office visits if needed. Site documentation will serve as the source for telephone visits.														
Informed Consent Signed	X													
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant eligibility review	X													
Treatment assignment				X										
Note: Treatment assignment should occur after completion of all Visit-4 procedures. Participants who have been assigned treatment will be asked to return for the ED visit.														
Clinical Assessments														
Participant demographics	X													
Medical history and preexisting conditions	X													
Physical exam/height	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and product complaints	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X		X			X		X			X		X
Vital signs, blood pressure and heart rate	X	X		X			X		X			X		X
Note: Vital sign measurements should be determined after participants have been seated quietly for at least 5 minutes in a chair with feet on the floor. The arm used for blood pressure measurement should be supported at heart level.														
ECG (12-lead; local)	X													
Note: Participants must be supine for approximately 5-10 minutes before ECG collection and remain supine, but awake, during ECG collection.														
Diabetes, hypoglycemia and nutrition counseling		X												
Note: 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. Participants may be provided abbreviated training and education at visits following Visit 2 as appropriate.														
Basal and prandial insulin dose assessments		X	X	X	X	X	X	X	X	X	X	X	X	X

	Screen	Baseline		Treatment Period										ED
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**801**	**ED**
Visit Window (± days)		**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	
Time (weeks)	**-5**	**-4**	**-2**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**11**	**12**	**14**	
Telephone visits are indicated by shaded columns. Telephone visits can become office visits if needed. Site documentation will serve as the source for telephone visits.														
Supplies and IP														
Dispense CGM system, CGM reader, and mobile device with preloaded CGM application and complete training		X												
Note: Participants may be provided additional training at visits following Visit 2 as appropriate.														
Dispense study supplies		X		X			X		X					
Review/discuss CGM data and hypoglycemia events			X	X	X	X	X	X	X	X	X	X		X
Upload CGM data to study vendor portal				X			X		X			X		X
Train on use of study paper diary for collection of insulin dose data		X												
Dispense study diary		X		X			X		X					
Remind participant of study diary requirements		X	X	X	X	X	X	X	X	X	X			
Collect/review study diary and transfer insulin dose data to eCRF				X			X		X			X		X
Dispense LY900014 and Basaglar®				X			X		X					
Participant returns unused study drug supplies							X		X			X		X
Return study mobile device and CGM reader												X		X
Drug accountability				X			X		X			X		X
Laboratory Assessments (no fasting required)														
HbA1c	X			X			X		X			X		X
Chemistry panel	X													
Hematology	X													
Serum pregnancy test (in WOCBP)	X													
Urine pregnancy test				X										
Note: Urine pregnancy test must be performed within 24 hours prior to IP exposure at randomization (Visit 4) and at other times at the investigator's discretion.														
Follicle-stimulating hormone test	X													

	Screen	Baseline		Treatment Period										ED
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**801**	**ED**
Visit Window (± days)		**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**7**	
Time (weeks)	**-5**	**-4**	**-2**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**11**	**12**	**14**	
Telephone visits are indicated by shaded columns. Telephone visits can become office visits if needed. Site documentation will serve as the source for telephone visits.														
Note: Follicle-stimulating hormone test must be performed at Visit 1 for women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had cessation of menses for at least 1 year without an alternative medical cause.														
Health Outcomes Questionnaires (to be completed on paper by study participants and data will be transferred by sites to the eCRF)														
Insulin Treatment Satisfaction Questionnaire (ITSQ)		X		X								X		X
Diabetes-Specific Attitudes about Technology Use (DSAT)		X		X								X		X
Study mealtime insulin experience question												X		X

Abbreviations: CGM = continuous glucose monitoring; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; HbA1c = hemoglobin A1c; IP = investigational product; IWRS = interactive web-response system; WOCBP = women of childbearing potential.

2. Introduction

2.1. Study Rationale

Hemoglobin A1c (HbA1c) is widely accepted by health care providers and regulatory authorities as the best marker for the development of long-term diabetes complications. As a valid measure of glycemic control over time, HbA1c reflects average glucose over the previous 2 to 3 months. The role of HbA1c in clinical management should not be undervalued, however it does not provide information about acute glycemic excursions of hypoglycemia or hyperglycemia or about the degree of glucose variability. Measures in addition to HbA1c such as time in target glucose range as well as other CGM parameters are becoming increasingly important in diabetes clinical care and in patients' daily diabetes management and should be evaluated in conjunction with HbA1c.

Study ITSW will evaluate glycemic control improvement assessed by HbA1c and will provide new CGM data, including time in range in adults with T2D treated with LY900014 in a basal-bolus MDI regimen with insulin glargine U-100. Study ITSW will also allow assessment of 24-hour glucose profiles and further evaluation of postprandial glucose (PPG) excursions. Unblinded CGM will be used for daily diabetes management and glucose data collection. Basal-bolus insulin doses will be titrated to achieve protocol glucose targets during the study.

2.2. Background

There have been many advances in the treatment of T2D in the last 20 years; however, reaching and maintaining glycemic goals remains challenging even with intensive insulin therapy regimens. Large surveys of people with Type 1 diabetes (T1D) and T2D have indicated that time in target glucose range is an important parameter to patients to improve diabetes management and mindset (Runge et al. 2018). Time in range is also a quantitative measure that evaluates treatment efficacy (Runge et al. 2018). Thus, there is a need to consider the patients' daily glycemia in addition to the 2- to 3-month average, as measured by HbA1c.

Currently available, rapid-acting insulin analogs continue to be unable to match the kinetics of physiological postmeal insulin secretion. LY900014 is 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, and it will more closely mimic endogenous insulin action in healthy subjects. These changes in pharmacokinetic (PK) and pharmacodynamic (PD) characteristics are achieved by coformulating insulin lispro with 2 enabling excipients, treprostinil and citrate.

The efficacy and safety profiles of LY900014 in patients with T1D and T2D have been evaluated in 2 randomized, active-controlled, multicenter, multinational, Phase 3, MDI clinical trials: Studies I8B-MC-ITRM and I8B-MC-ITRN.

Studies ITRM (patients with T1D) and ITRN (patients with T2D) studied MDI injections of LY900014 and Humalog®, both in combination with insulin glargine or insulin degludec. The primary endpoint in Studies ITRM and ITRN was HbA1c change from baseline to Week 26,

with multiplicity-adjusted objectives for 1- and 2-hour PPG excursions with standardized meal tests.

In Studies ITRM and ITRN, the primary objective of noninferiority for the change from baseline to Week 26 for HbA1c was confirmed for LY900014 compared with Humalog (when administered 0-2 minutes before a meal) as the upper limit of the 95% confidence interval (CI) for the difference in change in HbA1c was less than the prespecified noninferiority margin of 0.4%. In Study ITRM in patients with T1D, the mean HbA1c at Week 26 was 7.21% for LY900014 and 7.34% for Humalog. In Study ITRN in patients with T2D, the mean HbA1c at Week 26 was 6.92% for LY900014 and 6.86% for Humalog.

LY900014 was superior to Humalog in lowering 1- and 2-hour PPG excursions during standardized meal test with dosing 0 to 2 minutes before a meal. At Week 26, mean PPG excursions were statistically significantly lower in the LY900014 group than in the Humalog group at all time points from 15 minutes to 4 hours in Study ITRM and from 30 minutes to 4 hours in Study ITRN.

In Study ITRM, blinded CGM was performed in a subgroup of patients with T1D (total n=269). The results from the CGM substudy reflect and support key observations from the main study. Results showed that improvements in PPG control observed in patients in the mealtime LY900014 versus Humalog group (with dosing 0-2 minutes before a meal) were also associated with an increased time spent in target glucose range (both 71-180 mg/dL [3.9-10.0 mmol/L] and 71-140 mg/dL [3.9-7.8 mmol/L]) during the daytime period, which is the period when prandial insulins are typically used.

Since Study ITRN did not include a CGM addendum in patients with T2D, Study ITSW will provide new CGM data in that population including time in range, assessment of 24-hour glucose profiles, and further evaluation of PPG excursions.

A detailed description of the chemistry, pharmacology, efficacy, and safety of LY900014 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LY900014 may be found in the IB.

Participants may experience the benefit of improved glycemic control with basal-bolus insulin dose treatment, dose titration, and use of unblinded CGM.

Considering the measures to minimize risk to participants participating in this study, the potential risks identified in association with LY900014 are justified by the anticipated benefits that may be afforded to participants with diabetes.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate time glucose values from continuous glucose monitoring (CGM) are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period with LY900014 treatment	• Percentage of time with CGM glucose values between 70-180 mg/dL (3.9-10.0 mmol/L) (both inclusive) during daytime period with 14 days of CGM use at Week 12 compared with baseline
Gated Secondary	
• To evaluate HbA1c	• HbA1c change from baseline to Week 12
• To evaluate time glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the 24-hour period with LY900014 treatment	• Percentage of time with CGM glucose values between 70-180 mg/dL (3.9-10.0 mmol/L) (both inclusive) during the 24-hour period with 14 days of CGM use at Week 12 compared with baseline
Other Secondary	
• To evaluate time in hypoglycemic glucose ranges, obtained from CGM use	• Percentage of time with CGM glucose values <54 mg/dL (<3.0 mmol/L) during daytime and 24-hour periods with 14 days of CGM use at Week 12 compared with baseline
• To evaluate time in hyperglycemic glucose ranges, obtained from CGM use	• Percentage of time with sensor glucose values >180 mg/dL (>10.0 mmol/L) and >250 mg/dL (>13.9 mmol/L), during daytime and 24-hour periods with 14 days of CGM use at Week 12 compared with baseline

Objectives	Endpoints
• To evaluate postprandial incremental AUCs, obtained from CGM use	• Postprandial incremental $AUC_{0\text{-}1\ hour}$ and incremental $AUC_{0\text{-}2\ hour}$ at Week 12 compared with baseline
• To evaluate proportion of participants achieving HbA1c targets	• The proportion of participants with HbA1c <7% and ≤6.5% at Week 12
• To evaluate bolus, basal, and total daily insulin dose	• Bolus, basal, and total insulin doses and bolus/total insulin ratio at Week 12 compared with baseline
• To evaluate severe hypoglycemia	• Incidence of severe hypoglycemia events from baseline to Week 12
• To evaluate insulin treatment satisfaction regarding glycemic control as measured by the ITSQ	• Change from baseline in ITSQ glycemic control domain scores at Week 12
Tertiary/Exploratory	
• To evaluate proportion of participants achieving CGM-based glycemic targets	• The proportion of participants with percentage of time in target CGM glucose range (70-180 mg/dL [3.9-10.0 mmol/L]) >70%, time in hypoglycemia (<54 mg/dl [<3.0 mmol/L]) <1%, and time in hyperglycemia (>250 mg/dL [>13.9 mmol/L]) <5% with 14 days of CGM use at Week 12
• To evaluate glucose profiles, obtained from CGM use	• Average glucose for a 24-hour period from each 14-day CGM session at Week 12 compared with baseline
• To evaluate glucose variability, obtained from CGM use	• CV with 14 days of CGM use at Week 12 compared with baseline
• To evaluate insulin treatment satisfaction as measured by the ITSQ	• Change from baseline in ITSQ total and domain scores (except glycemic control domain) at Week 12

Objectives	Endpoints
• To characterize participants' willingness to incorporate LY900014 into diabetes management routine	• Distribution of responses to study mealtime insulin experience question at Week 12
• To evaluate attitudes towards diabetes technology use as measured by the DSAT	• Change from baseline in DSAT total score at Week 12

Abbreviations: AUC = area under the curve; CV = coefficient of variation; DSAT = Diabetes-Specific Attitudes about Technology Use scale; HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire.

4. Study Design

4.1. Overall Design

Study ITSW is a Phase 3b, prospective, open-label, outpatient, multicenter, single-treatment-group study conducted in participants with T2D currently treated with a basal-bolus analog MDI regimen. Participants will use unblinded CGM (Freestyle Libre 14-day system) for diabetes management and glucose data collection during the study. The study is designed to evaluate the time sensor glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) with 12 weeks of LY900014 treatment.

LY900014 will be injected immediately (0-2 minutes) prior to each meal in combination with insulin glargine U-100 (Basaglar®) as basal insulin. Basal-bolus insulin doses will be titrated to achieve protocol glucose targets during the study.

4.2. Scientific Rationale for Study Design

Study ITSW is a Phase 3b, single-treatment-group study conducted in participants with T2D currently treated with a basal-bolus analog MDI regimen. Study ITSW is designed to provide new CGM data (including time in range) in adults with T2D treated with LY900014 in a basal-bolus MDI regimen. Unblinded CGM will be used for daily diabetes management and glucose data collection. Time in range and HbA1c will be evaluated for change from baseline to endpoint. Additional CGM parameters including time in hypoglycemia, time in hyperglycemia, 24-hour glucose profiles, and PPG excursions will also be evaluated.

4.2.1. Participant Input into Study Design

The sponsor involved participants in the design of this study by engaging participants in simulations and other face-to-face or virtual collaborative events. The insights gained from these events were used to ensure that the study design is supportive of the well-being of the study participants and that the study procedures can be implemented effectively at the investigative sites.

4.3. Justification for Dose

LY900014 will have the same insulin lispro concentration (100 U/mL) as that of commercially available Humalog. The dosage of basal and prandial insulins used in this study should be determined based on the individual needs of each participant.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SoA) for the last participant in the trial globally.

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

Age and Sex

2. Participant must be at least 18 years of age at the time of signing the informed consent.
3. Male or Female
    a. Male: no contraception required.
    b. Female: A female participant is eligible to participate if she is not pregnant, intending to become pregnant, or breastfeeding, and at least one of the following conditions applies:
        - Is not a woman of childbearing potential (see Appendix 4, Section 10.4)
            OR
        - Is a woman of childbearing potential (WOCBP) and must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of two effective methods of contraception for the entirety of the study. Contraception requirements for participants are provided in Appendix 4 (Section 10.4).
        - A WOCBP must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy text within 24 hours prior to exposure to investigational product (IP) at Visit 4.

Type of Participant and Disease Characteristics

4. Participants diagnosed (clinically) with type 2 diabetes mellitus for at least 1 year prior to screening
5. Have been treated with basal-bolus MDI therapy for at least 90 days prior to screening including:
    a. Basal insulin glargine U-100, in combination with bolus insulin analog (insulin lispro, insulin aspart, or insulin glulisine) with meals
    b. Participant must have been treated with the same type of allowed bolus insulin analog for at least 30 days prior to screening.
6. Participants may be treated with up to 3 of the following OAMs for T2D in accordance with local regulations:

a. Metformin
b. Dipeptidyl peptidase-4 (DPP-4) inhibitor
c. sodium glucose cotransporter 2 (SGLT2) inhibitor
d. oral glucagon-like peptide 1 (GLP-1) agonist

Doses of oral antihyperglycemic medications (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.

7. Participants may be treated with injectable GLP-1 receptor agonist for T2D in accordance with local regulations. The GLP-1 receptor agonist dose is required to have been stable for at least 90 days prior to screening.
8. Have an HbA1c value ≥7.5% and ≤10% according to the central laboratory at screening

Weight

9. Body mass index (BMI) ≤40.0 kg/m^2 at screening (Visit 1).

Other Inclusions

10. Have access to a telephone, or alternative means for close monitoring/communications
11. Have refrigeration in the home or have ready access to refrigeration for storage of insulin therapy
12. Have a regular wake/sleep schedule (awake/work during the day and sleep during the night)
13. Willing to use the CGM device (Freestyle Libre) supplied for this study for glucose monitoring, diabetes management, and data collection per protocol
    Note: If participants were using CGM prior to screening, participants may not use their own personal CGM device during the study baseline and treatment periods.
14. Capable of, willing, and desirous to do the following during the study:
    a. Adhere to a basal-bolus insulin MDI regimen and use of the study provided prandial and basal insulins according to injection instructions and protocol
    b. Follow a general daily pattern of administering prandial insulin doses with 3 main meals per day (morning, midday, and evening)
    c. Able to read and understand the language(s) available for devices and application used in the study
    d. Use study-provided mobile device and associated medical application and comply with study requirements as required by this protocol
    e. Comply with scheduled visits and study requirements

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

15. Have been diagnosed at any time with type 1 diabetes mellitus or latent autoimmune diabetes in adults

16. Have had any episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) within 6 months prior to screening
17. Have had any episode of hyperglycemic hyperosmolar state or diabetic ketoacidosis within 6 months prior to screening
18. Have hypoglycemia unawareness as judged by the investigator
19. Have excessive insulin resistance, defined as having received a total daily dose of insulin >2.0 U/kg at the time of screening
20. Have cardiovascular disease within 6 months prior to screening, defined as stroke, decompensated heart failure (New York Heart Association Class III or IV), myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft
21. Renal:
    a. History of renal transplantation
    b. Currently receiving renal dialysis
    c. Serum creatinine >2.0 mg/dL (177 μmol/L) at screening as measured by the central laboratory
22. Hepatic: Have obvious clinical signs or symptoms of liver disease (excluding nonalcoholic fatty liver disease), acute or chronic hepatitis, cirrhosis, or elevated liver enzyme measurements as indicated below at screening (Visit 1):
    a. Total bilirubin level (TBL) ≥2× the upper limit of normal (ULN) (except for Gilbert's syndrome) as defined by the central laboratory, or
    b. Alanine aminotransferase (ALT) ≥3× ULN as defined by the central laboratory, or
    c. Aspartate aminotransferase (AST) ≥3× ULN as defined by the central laboratory
23. 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
24. Have any hypersensitivity or allergy to any of the insulins or excipients used in this trial
25. Hematologic: Have had a blood transfusion or severe blood loss within 90 days prior to screening (Visit 1) or have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or any other traits known to interfere with the measurement of HbA1c
26. Have presence of clinically significant gastrointestinal disease (for example, clinically active gastroparesis associated with wide glucose fluctuations) in the investigator's opinion
27. Have a history of or are being evaluated for bariatric surgery including Roux-en-Y gastric bypass surgery, gastric banding, and/or gastric sleeve
28. Have any other condition (including known drug or alcohol abuse, or psychiatric disorder including eating disorder) that precludes the participant from following and completing the protocol

Prior/Concomitant Therapy

29. Have used thiazolidinedione, sulfonylurea, pramlintide, or any other oral or injectable medication intended for the treatment of T2D other than as specified in Inclusion criteria [6, 7] within 90 days prior to screening

30. Have been on an insulin treatment regimen that includes Fiasp®, LY900014, degludec, detemir, neutral protamine Hagedorn insulin, regular human insulin, any premixed insulin, insulin human inhalation powder (Afrezza®) or any insulin therapy other than as specified in Inclusion criterion [5] within 90 days prior to screening
31. Have used continuous subcutaneous (SC) insulin infusion therapy within the 90 days prior to screening
32. Glucocorticoid therapy: Receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (including intravenous, intramuscular, SC, or oral, but excluding topical, intraocular, intranasal, intraarticular, and inhaled preparations) or have received such therapy within 8 weeks immediately prior to screening (Visit 1), with the exception of replacement therapy for adrenal insufficiency
33. Have used any weight loss drugs (for example, prescription drugs: lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion; or over-the-counter weight loss medications) within 90 days prior to screening

Prior/Concurrent Clinical Study Experience

34. Are currently enrolled in any other clinical trial involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
35. 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
36. Have previously completed or withdrawn from this study or any other study investigating LY900014 after receiving at least 1 dose of the IP

Other Exclusions

37. 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
38. Are Lilly employees or representatives (including employees, temporary contract workers, or designees responsible for the conduct of the study)
39. 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

5.3. Lifestyle Considerations

During the study, participants must avoid:

1. Donating blood or blood products
2. Major changes in diet or exercise

5.4. 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 in which results are not available from the original sample.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6. Study Intervention

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to a study participant according to the study protocol.

6.1. Study Interventions

Intervention Name	LY900014
Type	Drug
Dose Formulation	Solution
Unit Dose Strength(s)	100 U/mL in 3 mL cartridge
Dosage Level(s)	Individualized dosing
Route of Administration	Subcutaneous
Packaging and Labeling	LY900014 will be provided in prefilled pens. Each pen will be labeled as required per country requirement.
Sourcing	Provided centrally by the sponsor, subsidiary, or designee

6.1.1. Medical Devices

1. The Lilly manufactured medical devices provided for use in this study are:
    a. the LY900014 prefilled pen, and
    b. the insulin glargine U-100 (Basaglar) prefilled pen.
2. Instructions for use for each of the prefilled pens will be provided.
3. The FreeStyle Libre is a marketed, non-Lilly, medical device for CGM. It will also be provided to study participants.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, 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.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.
5. 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.
6. In-use insulin should be maintained at room temperature. In-use insulin must not be used after 28 days.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single arm study.

6.4. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by reviewing the participant's glycemic control, adherence to the visit and treatment schedule, use of the study CGM system, adjustment of prandial insulin doses as appropriate, and completion of study diaries. Compliance will be documented in the source documents and the electronic case report form (eCRF).

Participants who are deemed noncompliant will receive additional diabetes education and training, as required, and the importance of compliance with the protocol will be reinforced. Participants who, in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from the study.

6.5. Concomitant Therapy

The following concomitant therapies will not be allowed during the study:

- any oral or injectable medication intended for the treatment of diabetes mellitus other than study insulins and those specified in Section 6.5.1. Exception: short-term use of nonstudy insulins is permissible as outlined in Section 7.1.1.
- chronic (lasting longer than 7 consecutive days) systemic glucocorticoid therapy excluding topical, intraocular, intranasal, inhaled, or intraarticular preparations.
- Weight loss drugs (for example, prescription drugs: lorcaserin, orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion; or over-the-counter weight loss medications)

6.5.1. Management of Oral Antihyperglycemic Medications and Injectable GLP-1 Agonist

During the study baseline and treatment periods, participants may **continue** the use of:

- up to 3 of the following OAMs for the treatment of T2D: metformin, SGLT2 inhibitor, DPP-4 inhibitor, oral GLP-1 agonist and/or

- an injectable GLP-1 agonist for the treatment of T2D

Please note that participants must have entered the study on these agents with stable dosing for 90 days prior to screening (Section 5.1, Inclusion Criteria [5,6,7]). Please also refer to Section 5.2, Exclusion Criteria [29,30].

Oral antihyperglycemic medications and GLP-1 dosing should remain stable during the study baseline and treatment periods, except with the development of contraindications or for safety reasons. During the study, all glycemic management is to be conducted by adjustment of basal and prandial insulin doses.

6.6. Dose Modification

6.6.1. Target Glucose Values for Titration of Insulin Therapy

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

Time of Target Glucose Measurement	Glucose Target (Range)
Fasting or Premorning meal	Target: 100 mg/dL or 5.6 mmol/L Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
Premidday meal	Target: 100 mg/dL or 5.6 mmol/L Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
Preevening meal	Target: 100 mg/dL or 5.6 mmol/L Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
Prebedtime	Range: 80 to <110 mg/dL or 4.4 to 6.1 mmol/L
1-2 hour or peak postprandial	Target: <140 mg/dL or 7.8 mmol/L

6.6.2. Basal Insulin Therapy and Titration

Participants must have been treated with basal insulin glargine U-100 prior to entering the study. Participants will continue their prestudy basal and prandial insulin therapy during the baseline period from Visit 2 to 4. The allowed basal insulin regimen during the study baseline and treatment periods is insulin glargine U-100 once or twice daily. The same dosing frequency should be maintained during the study.

The initial dose of basal insulin provided by the sponsor (insulin glargine U-100) at Visit 4 may be unit-for-unit. 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 treatment period is determined by, and the responsibility of, the investigator.

The study basal insulin can be dosed at any time during the day and should be dosed at approximately the same time of day during study treatment. If there is a safety concern such as hypoglycemia, the dose timing of basal insulin may be changed per investigator discretion.

At all clinic and telephone visits during the 12-week treatment period, basal insulin dose should be reviewed and adjusted by the investigator, in discussion with the participant, based on CGM and hypoglycemia data. Twenty-four-hour glucose profiles from CGM should be evaluated for optimization of basal insulin dosing. Additional discussion between visits may be required to enable the participant to reach the glucose targets. Investigators may use discretion and provide direction for participants to adjust the basal insulin dose. Basal insulin should be titrated to reach the protocol target glucose values during the treatment period. 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). The participant should contact the site with any questions or concerns regarding insulin dosing.

Recommendations for basal insulin dose adjustment are described below. Hypoglycemia events can first be assessed over the previous week as described in the table below.

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 as described below.

After the hypoglycemia assessment, the fasting glucose CGM pattern over the previous 3 days can be used for basal insulin adjustment as described in the table below.

If fasting glucose CGM pattern 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

Abbreviations: CGM = continuous glucose monitoring.

[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.

6.6.3. Study Prandial Insulin Therapy and Titration

Participants will continue their prestudy basal and prandial insulin therapy during the baseline period from Visits 2 to 4. At Visit 4, participants will start treatment with LY900014 and will administer their first study prandial insulin dose with the next meal following Visit 4. The total daily bolus insulin dose of LY900014 may be initiated unit-for-unit.

Study prandial insulin will be administered 0 to 2 minutes prior to the start of each meal (premorning meal, premidday meal, and preevening meal). Participants should follow a general daily pattern of administering prandial insulin doses with 3 main meals per day (morning, midday, and evening). Participants may have additional bolus insulin doses, such as with a snack, if clinically indicated.

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

- Carbohydrate-counting plan: If the participant performed flexible 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 on the participant's estimated carbohydrate content of the meal (such as unit insulin per grams carbohydrate).
- Fixed-dose plan: The participant 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.

The participant 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.

Prandial insulin should be titrated to reach the protocol target glucose values during the treatment period. Decreases to the prandial insulin dose may be made at any time during the study based on the judgment of the investigator (for example, in response to hypoglycemia).

For participants who are using the carbohydrate-counting plan: the insulin to carbohydrate ratio (and correction factor if applicable) should be reviewed and adjusted by the investigator, in discussion with the patient, based on CGM and hypoglycemia data at all clinic and telephone visits during the 12-week treatment period. Twenty-four-hour glucose profiles, including premeal glucose and PPG levels, from CGM should be evaluated for optimization of prandial insulin dosing. Additional discussion between visits may be required to enable the participant to reach the glucose targets. The insulin to carbohydrate ratio may be adjusted every 3 days, or more often when appropriate, based on the participant's glycemic needs and glucose levels. Investigators may use discretion and provide direction for participants to adjust prandial insulin dosing. The participant should contact the site with any questions or concerns regarding insulin dosing.

For participants who are using the fixed-dose plan: A participant self-titration prandial insulin algorithm will be utilized as described below. At all clinic and telephone visits during the 12-week treatment period, prandial insulin dose (and correction factor if applicable) should be reviewed by the investigator in discussion with the participant based on CGM and hypoglycemia data. Twenty-four-hour glucose profiles, including premeal glucose and PPG levels, from CGM should be evaluated for optimization of prandial insulin dosing. Additional discussion between visits may be required to enable the participant to reach the glucose targets. The participant should contact the site with any questions or concerns regarding insulin dosing.

In the fixed-dose participant self-titration plan, assessment of the prandial insulin dose includes review of the previous day of CGM glucose values for the corresponding meal or bedtime as described in the table below. *For example, if assessing the need to adjust the morning meal prandial insulin dose, review the CGM glucose value from the previous day premidday meal.*

Prandial Insulin Dose Assessed	**Corresponding CGM Glucose Value for Review**
Fasting or morning premeal	previous day premidday meal glucose value
Midday premeal	previous day preevening meal glucose value
Evening premeal	previous day bedtime glucose value

Abbreviation: CGM = continuous glucose monitoring.

The CGM glucose value from the premeal or bedtime from the previous day is used by the participant as the "adjustment value" and the change in dose (either increase or decrease) is based upon this value as described in the table below.

CGM Glucose <80 mg/dL (<4.4 mmol/L)	CGM Glucose 80-109 mg/dL (4.4-6.1 mmol/L)	CGM Glucose >109 mg/dL (>6.1 mmol/L)
Decrease by 1 unit	No change	Increase by 1 unit

Abbreviations: CGM = continuous glucose monitoring.

Source: Adapted from Bergenstal et al. 2008 and Edelman et al. 2014.

For either prandial insulin dosing plan, the investigator may determine the appropriate correction factor for the participant to administer when premeal glucose levels are above target based on clinical judgment, taking into account the participant'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 glucose (mg/dL) level per unit of prandial insulin administered, or

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

6.6.4. Transitioning off Study Prandial Insulin Therapy

Participants will take their last doses of study prandial insulin (LY900014) and study-provided basal insulin glargine prior to Visit 12 or at early discontinuation.

No special instructions for transition to nonstudy prandial insulin are necessary. The investigator, in consultation with the participant, will decide on the new prandial and basal insulin regimen, or other diabetes therapy, to be initiated.

6.7. Intervention after the End of the Study

LY900014 and basal insulin glargine will not be provided to participants after completion of the study treatment period. Prandial and basal insulins, as well as other diabetes therapies, are available for the treatment of T2D.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants who need to discontinue from study treatment will also be discontinued from the study. Please refer to Section 7.2.

7.1.1. Temporary Discontinuation

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

The participant has not taken IP for 14 consecutive days or less:

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

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be withdrawn from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if participant has not taken IP for more than 14 consecutive days (see Section 7.1.1)
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- use of prohibited concomitant medication (see Section 6.5)

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued unless there are extenuating circumstances that make it medically necessary for the participant to continue in the study.

If the investigator and the sponsor clinical research physician (CRP) agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study. Safety follow-up is as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

A participant 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 participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Primary Efficacy Assessments

The percentage and duration of time with sensor glucose values between 70 and 180 mg/dL (3.9-10.0 mmol/L) during the daytime hours.

Secondary Efficacy Assessments

The secondary efficacy measures in this study collected with CGM are

- change in HbA1c
- percentage and duration of time with sensor glucose values between 70 and 180 mg/dL (3.9-10.0 mmol/L) over 24 hours
- percentage and duration of time with sensor glucose values <54 mg/dL (<3.0 mmol/L) during daytime and 24-hour periods
- percentage and duration of time with sensor glucose values >180 mg/dL (>10.0 mmol/L) and >250 mg/dL (>13.9 mmol/L), during daytime and 24-hour periods
- incremental area under the glucose concentration-time curve from 0 to 1 hour, 0 to 2 hours after a meal

Other secondary efficacy measures in this collected in this study are

- proportion of participants with HbA1c ≤6.5% and <7.0%
- bolus, basal and total insulin dose (units and units/kg) and bolus/total insulin ratio
- change in Insulin Treatment Satisfaction Questionnaire (ITSQ) glycemic control domain score

8.1.1. Continuous Glucose Monitoring

The unblinded FreeStyle Libre 14-day CGM system will be used by all study participants from Visit 2 to Visit 12. This is an FDA-approved CGM system indicated for replacing blood glucose testing and detecting trends and tracking patterns aiding in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments in persons (age 18 and older) with diabetes.

Participants will use the:

- FreeStyle Libre sensor
    - The sensor can be worn for up to 14 days. Participants will be instructed to change the sensor according to the product information.
- FreeStyle Libre reader:
    - for participants to scan the sensor and for sites to upload CGM data to the CGM vendor
    - The reader also has a built-in blood glucose meter.
- LibreLink application (app) on a study-provided mobile device
    - for participants to scan the sensor and for sites to have remote access to CGM data for telephone visits and as clinically indicated
- Participants will be able to review CGM data for daily diabetes management with the reader and/or app.

Participants will receive training on the use of the system according to product information, and will be expected to complete the following study requirements:

- **Start** each **new sensor** session with the **reader first** and then with the LibreLink **app**.
- Change the sensor every 14 days or earlier if needed.
- Scan with the reader and app at least 4 times throughout the day (morning upon waking, prior to meals, bedtime) and as needed. After the start of a new sensor session, the sensor can be scanned with the reader and app in any order.
    - Make every effort to scan with the **reader and app** at least every 8 hours to avoid gaps in glucose data.
    - More frequent scanning is encouraged.
    - Participants should not ignore symptoms that may be due to hypoglycemia or hyperglycemia. Note that the FreeStyle Libre does not have alarms unless if the sensor is scanned.
- Participants should check sensor glucose readings with a blood glucose meter as instructed according to product information when the “Check Blood Glucose” symbol appears, when symptoms do not match sensor readings, or when readings are suspected to be inaccurate.

- The sensor must be removed before magnetic resonance imaging (MRI), computed tomography (CT) scan, X-ray, or diathermy treatment.
- Note and avoid substances that may interfere with sensor glucose readings including:
    - higher dose ascorbic acid (vitamin C) >1000 mg, which may raise sensor readings, and/or
    - salicylic acid (contained in some pain relievers such as aspirin) >650 mg, which may slightly lower sensor readings

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination with measurement and record of height and weight.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).

8.2.3. Electrocardiograms

- Single 12-lead electrocardiograms (ECGs) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures pulse rate, QRS, QT, and corrected QT intervals.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2) and Appendix 5 (Section 10.5), must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Hypoglycemia

Participants will use unblinded CGM for diabetes management. Participants should check sensor glucose readings with a blood glucose meter as instructed (also refer to Section 8.1.1). Participants will be instructed to treat glucose <70 mg/dL (<3.9 mmol/L) as hypoglycemia. The participant should contact the site as necessary.

Hypoglycemia will be described using the following definitions :

- **Level 1** hypoglycemia: glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L) as assessed by CGM
- **Level 2** hypoglycemia: glucose <54 mg/dL (<3.0 mmol/L) as assessed by CGM
- **Level 3: Severe Hypoglycemia**: A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Participants have altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and require assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.
  - The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
  - All episodes of severe hypoglycemia must be reported as serious on the AE eCRF page and on the SAE eCRF page. Episodes of hypoglycemia not meeting the criteria for severe hypoglycemia should not be reported as an AE.

8.2.6. Safety Monitoring

8.2.6.1. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Appendix 2 (Section 10.2). Laboratory results are provided to the sponsor via the central laboratory.

8.2.6.2. Hepatic Monitoring

If a participant develops symptoms that warrant liver function assessment, liver function tests as detailed in Appendix 5 (Section 10.5) should be performed. If these tests are abnormal, clinical and laboratory monitoring should be initiated by the investigator.

Laboratory tests including ALT, AST, alkaline phosphatase (ALP), TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention, study device, or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs occurring after signing the ICF are recorded in the AE eCRF and assessed for serious criteria.

The SAE reporting to sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving LY900014, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Pregnancy (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.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. When the ability to use the product safely is impacted, the following are also product complaints:

a. deficiencies in labeling information, and
b. use errors for device or combination products due to ergonomic design elements of the product

The sponsor collects product complaints on IPs, medical devices, 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. Complaints are also collected on comparators and other clinical trial material supplied, as required.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP or device, so that the situation can be assessed.

Product complaints will be reported by the investigator to the sponsor per instructions provided on the study specific Product Complaint Form.

As required by local regulations, and per instructions on the product complaint form, the investigator will report to the sponsor and to their IRB/IEC any unanticipated adverse device effect or unanticipated problem that resulted in an SAE (UADE), or any device-related product complaint that could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

Excess insulin administration may result in hypoglycemia (Section 8.2.5).

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity will not be assessed in this study.

8.10. Health Economics

8.10.1. Insulin Treatment Satisfaction Questionnaire

The 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)

- Hypoglycemic Control (5 items)
- Glycemic Control (3 items)
- Delivery System (6 items)

8.10.2. Study Mealtime Insulin Experience Question

Study participants will be asked to complete a single Study Mealtime Insulin Experience question specifically developed for this study. This is a participant-rated assessment of their likelihood of incorporating the mealtime insulin used in this study (that is, LY900014) in their diabetes management routine. The question is rated on a 5-point scale ranging from "1- Very unlikely" to "5- Very likely."

8.10.3. Diabetes-Specific Attitudes about Technology Use (DSAT)

The Diabetes-Specific Attitudes about Technology Use scale (DSAT) is a 5-item scale that was originally developed to assess T1D patients' attitudes towards diabetes-specific technology (Tanenbaum et al. 2017). Each item is rated on a 5-point Likert scale to indicate agreement with the statement, with higher scores indicating more positive attitudes about devices and technology. Individual ratings are summed to obtain a total score.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective of this study is to evaluate the change of time glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period from baseline to endpoint at Week 12 with LY900014 treatment.

9.2. Sample Size Determination

Approximately 167 participants will be assigned to treatment with LY900014 such that 150 participants complete the study through the primary endpoint at Week 12. This sample size has approximately 80% power to detect an increase of 4.5% time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period from baseline, assuming no true difference in time in target range between baseline and endpoint, and a standard deviation (SD) of 19.5%. Assuming a 10% dropout rate for 12 weeks, approximately 167 participants will need to be assigned.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who give informed consent
Enrolled	All participants who continue the study after Visit 2.
Treated	All enrolled participants who receive at least 1 dose of the assigned IP after Visit 4

Abbreviations: IP = investigational product.

9.4. Statistical Analyses

9.4.1. General 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 SAP will be finalized prior to the first patient first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. The primary analysis is for the treatment period through Week 12.

To ensure that the CGM outcome variables are only calculated from CGM session days with

sufficient data within the 24-hour and daytime periods, the following criterion will be used to determine a valid CGM session day to be counted into the calculation for a visit:

> minimum number of measures per day – at least 70% of the total measures that are supposed to be obtained for the 24-hour period

Efficacy analyses will be conducted on the treated population, including data collected prior to permanent discontinuation of IP. When change from baseline is included as a *response variable of analysis models*, the participant will be included in the analysis only if a baseline and a postbaseline measurement are available.

Safety analyses will be conducted on the treated population. Analyses of AEs and severe hypoglycemia will include data collected during the treatment period (Visit 4-12). AEs during the follow-up period will be listed. Analyses of AEs for the baseline period may be conducted as needed.

Unless otherwise noted, all tests will be conducted at a 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. A gatekeeper method (Westfall and Krishen 2001) will be used to control the overall type 1 error for the primary and gated secondary objectives.

Baseline is defined as the last nonmissing measurement at or before Visit 4 unless otherwise specified. Daytime is defined as 0600 hours to midnight (06:00-23:59 on the 24-hour clock) and nighttime is defined as midnight to 0600 hours (00:00-05:59 on the 24-hour clock).

A restricted-maximum-likelihood-based, mixed 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 time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during daytime period will include the fixed class effect of visit, the covariate of baseline, and the random effect of participant. An unstructured covariance structure will be used to model the within-participant errors. Significance tests will be based on least-squares 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 collected only at baseline and endpoint. The model will include 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 continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-square means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements.

For categorical measures, summary statistics will include sample size, frequency, and percentages.

9.4.2. Primary Endpoint

The primary efficacy comparison will be based on the MMRM analysis of change from baseline in time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during daytime period including data collected prior to permanent discontinuation of IP. The analysis model and selection of covariance structure is described in Section 9.4.1.

9.4.3. Gated/Other Secondary Endpoints

The analysis of the secondary gated objectives will be conducted if the time in target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the daytime period at study endpoint versus baseline is found statistically significant for the primary efficacy analysis at a 2-sided 0.05 significance level (Westfall and Krishen 2001). If this contrast is significant, the secondary objectives were tested in sequence until the first null hypothesis in the sequence failed to be rejected at a 2-sided 0.05 significance level. The sequential testing for gated secondary objectives is conducted in the following order to assess whether value at study endpoint is superior to baseline:

1. To evaluate HbA1c
2. To evaluate time glucose values from CGM are within target range (70-180 mg/dL [3.9-10.0 mmol/L]) during the 24-hour period.

For continuous longitudinal secondary endpoints, the MMRM model similar to that for the primary analysis will be used. Duration and percent time in range, time in hypoglycemia, and time in hyperglycemia derived from CGM data will also be analyzed using an MMRM model. Continuous nonlongitudinal secondary endpoints will be analyzed using the ANCOVA. Postprandial incremental area under the curve $(AUC)_{0\text{-}1\ hour}$ and incremental $AUC_{0\text{-}2\ hour}$ will be analyzed by ANCOVA. Analysis details will be documented in the SAP. Proportion of participants 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 with the fixed class effect of visit, the covariate of baseline HbA1c, and the random effect of participant. Actual and change from baseline in basal, bolus, and total dose, as well as the bolus/total insulin dose ratio will be analyzed by the MMRM models described in Section 9.4.1.

9.4.4. Tertiary/Exploratory Endpoints

Continuous variables and the change from baseline for these variables will be analyzed by either MMRM or ANCOVA described in Section 9.4.1. Analysis details for the tertiary endpoints will be described in the SAP.

9.4.5. Other Safety Analyses

Safety measures will include AEs, severe hypoglycemia, vital signs and weight, and treatment exposure.

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

Serious adverse events, AEs reported as reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the MedDRA preferred term (PT), sorted by decreasing frequency. TEAEs will also be summarized by PT sorted by decreasing frequency within system organ class for all TEAEs and by maximum severity. For events that are specific to only 1 sex, the denominator and computation of the percentage will include only participants from the given sex. The number and proportion of participants with at least 1 event for each type of event will be summarized.

Severe hypoglycemia rates and incidence during the treatment period (Visits 4-12) will be summarized.

9.4.6. Other Analyses

9.4.6.1. Health Economics Analyses

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

For the DSAT, the change from baseline to LOCF endpoint, while on treatment, in each item will be analyzed using ANCOVA.

Summary statistics, including number of participants and proportion of a categorical outcome (5 levels) for the study mealtime insulin experience question will be provided.

9.4.6.2. Subgroup Analyses

The following subgroups will be analyzed using data collected prior to permanent discontinuation of IP to evaluate consistency of results on the primary efficacy measure if there are sufficient numbers of participants by subgroup (for example, 10%):

- age (<65 years, ≥65 years)
- baseline HbA1c (≤8%, >8%)
- participant's prior personal CGM use (yes/no)
- participant's SGLT2 use (yes/no)
- participant's injectable GLP-1 use (yes/no)
- prandial dosing plan (carbohydrate counting, fixed dose)

- sex (male or female)
- BMI (<35, ≥35 kg/m^2)
- duration of diabetes (using the median as the cutoff)
- race
- ethnicity

Analyses for primary efficacy measure will be performed using an MMRM model that includes the same fixed effect and covariate given for the primary analysis model plus factors of subgroup and 2-way interaction of subgroup and visit. The effect of subgroup at the primary endpoint (Week 12) will be evaluated to assess subgroup effect.

Additional subgroup analyses may also be performed.

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

9.6. Data Monitoring Committee (DMC)

No DMC is planned for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

No financial disclosure information will be collected.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, except for PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, SAP, CSR, blank or annotated CRFs, will be provided in a secure data sharing environment for up to 2 years per proposal.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system will be stored at a third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Trial and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.10. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the central laboratory except where indicated.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

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)	Chloride
Neutrophils, segmented	Blood urea nitrogen (BUN)
Lymphocytes	Creatinine
Monocytes	Glucose
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Aspartate aminotransferase (AST)
Platelets	Magnesium
	Uric acid
Pregnancy Test (females only)[b]	Total protein
	Albumin
Follicle-stimulating hormone[c]	
	Calcium
	Creatine kinase (CK)
	HbA1c

Abbreviations: HbA1c = hemoglobin A1c; IP = investigational product; 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 at randomization and at other times at the investigator's discretion.

c Follicle-stimulating hormone test must be performed at Visit 1 for women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had cessation of menses for at least 1 year without an alternative medical cause.

Hypersensitivity Clinical Laboratory Tests

Lab testing should be performed at the time of a systemic hypersensitivity event related to study drug administration. Important information about why, when, and what to test for are provided below. The management of the AE may warrant lab testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a systemic hypersensitivity event is not performed for diagnostic purposes. Its intent is several fold:

- to help characterize and classify systemic hypersensitivity reactions
- to meet regulatory expectations
- to improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis

When should labs be obtained?

- In the presence of generalized urticaria or if anaphylaxis is suspected
- After the subject has been stabilized, obtain a sample within 1-2 hours of the event, however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

What labs* should be obtained?

- Tryptase**
- Antidrug antibody and LY900014 concentration (PK)
  - Antidrug antibody testing should include drug-specific immunoglobulin E (IgE) or the basophil activation test (BAT).# These tests are not routinely available and need to be developed for individual molecules based on their evolving safety profile. Samples are collected, and testing is conducted once the assay is available, as appropriate. Please consult an immunologist within Global Patient Safety (GPS) for further guidance.
- Complement
  - C3, C3a, and C5a
- Cytokines
  - Interleukin (IL)-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

* These labs are bundled in the Clinical Laboratory Operations Hypersensitivity Lab Testing Kit.

** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2-12 hours) or is not obtained because more than 12 hours have lapsed since the event, obtain urine for *N*-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2-12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

The BAT is an *in vitro* cell-based assay that only requires a serum sample. It is a surrogate assay for drug-specific IgE but is not specific for IgE.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is

appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE form (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes

available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found on the paper SAE form.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper Form is the preferred method to transmit this information to Lilly (GPS).
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found on the SAE paper form.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women <u>not</u> of Childbearing Potential

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, Mullerian agenesis, androgen insensitivity) investigator discretion should be applied to determining study entry.
   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as women with:
   - 12 months of amenorrhea for women >55, with no need for follicle-stimulating hormone (FSH)
   - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy that induced amenorrhea)

Contraception Guidance:

Male Participants

No male contraception required

Female Participants

A female participant is eligible to participate if she is not pregnant, intending to become pregnant, or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential

OR

- Is a WOBCP with the following study requirements:
    - A WOCBP must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy text within 24 hours prior to exposure to investigational product (IP) at Visit 4.
    - WOCBP who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
    - WOCBP (who are not abstinent or in a same-sex relationship) must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of two effective methods of contraception for the entirety of the study.

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods of contraception
• 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 pounds or 90Kg
• Total Abstinence
• Vasectomy
• Fallopian tube implants (Essure) [if confirmed by hysterosalpingogram]
Effective methods of contraception (must use two forms combined)[a]
• Male condom with spermicide[b]
• Female condom with spermicide[b]
• Diaphragm with spermicide
• Cervical sponge
• Cervical cap with spermicide

a participants may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide.

b Male and female condoms should not be used in combination as a double barrier method due to the high failure rate when these methods are combined.

Collection of Pregnancy Information

Female Participants who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy, pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

If a participant with baseline results of ...	Develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

Clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests, should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive Hepatic Evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline results of...	Develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms,[a] or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms,[a] or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper-quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time, international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional Hepatic Data Collection

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    a. In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests

2. Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    a. In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    a. In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the 2 consecutive blood tests should be at least 2 days.

Hepatic Monitoring Laboratory Tests

If the investigator has confirmed liver test abnormality, he or she should select the appropriate tests. For the selected testing, analysis is required to be completed by the Lilly-designated central laboratory, except for microbiology.

Local testing may be performed in addition to central testing when required for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (Quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin IgG (Quantitative)
HAV Total Antibody	Immunoglobulin IgM (Quantitative)
HAV IgM Antibody	Phosphatidylethanol (PEth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Antinuclear antibody (ANA)
Hepatitis B core IgG antibody	Antismooth muscle antibody (ASMA)[a]
HBV DNA[b]	Antiactin antibody[c]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA[b]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

Abbreviations: INR = international normalized ratio.

[a] This is not required if Anti-Actin Antibody is tested.

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

[c] This is not required if Anti-smooth muscle antibody (ASMA) is tested.

[d] Assayed by Investigator-designated local laboratory ONLY; no Central Testing available.

10.6. Appendix 6: Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BAT	basophil activation test
BMI	body mass index
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CI	confidence interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF/eCRF	case report form/electronic case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSR	clinical study report
CT	computed tomography
Device deficiencies	Equivalent to product complaint
DPP-4	dipeptidyl peptidase-4
DSAT	Diabetes-Specific Attitudes about Technology Use
ECG	electrocardiogram
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.

enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
gestational age	The estimated age of the fetus calculated from the first day of the last menstrual period to the delivery of the fetus. It is expressed in the number of completed weeks. This is based on 40 weeks or 10 months.
GLP-1	glucagon-like peptide 1
GPS	Global Patient Safety
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IL	interleukin
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
IRB	Institutional Review Board
ITSQ	Insulin Treatment Satisfaction Questionnaire
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.
Lilly	Eli Lilly and Company
LLT	lowest-level term
LOCF	last-observation-carried-forward
MDI	multiple daily injection
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
NMH	*N*-methylhistamine
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)
PPG	postprandial glucose
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SGLT2	sodium glucose cotransporter 2
SoA	Schedule of Activities
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
T1D	Type 1 diabetes
T2D	Type 2 diabetes
ULN	upper limit of normal
WOCBP	woman of childbearing potential

11. References

Anderson RT, Skovlund SE, Marrero D, et al. Development and validation of the insulin treatment satisfaction questionnaire. *Clin Ther*. 2004;26(4):565-578. https://doi.org/10.1016/s0149-2918(04)90059-8

Bailey TS, Grunberger G, Bode BW, et al; American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE). American Association of Clinical Endocrinologists and American College of Endocrinology 2016 outpatient glucose monitoring consensus statement [published correction appears in *Endocr Pract*. 2016;22(4);516. https://doi.org/10.4158/1934-2403-22.4.516]. *Endocr Pract*. 2016;22(2):231-261. https://doi.org/10.4158/EP151124.CS

Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal-bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. *Diabet Med*. 2008;25(4):442-449. https://doi.org/10.1111/j.1464-5491.2007.02407.x

Bergenstal RM, Johnson M, Powers MA, et al. Adjust to target in type 2 diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. *Diabetes Care*. 2008;31(7):1305-1310. https://doi.org/10.2337/dc07-2137

Bolli GB, Kerr D, Thomas R, et al. Comparison of a multiple daily insulin injection regime (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study [published correction appears in *Diabetes Care*. 2009;32(10):1944. https://doi.org/ 10.2337/dc09-er10]. *Diabetes Care.* 2009;32(7):1170-1176. https://doi.org/10.2337/dc08-1874

Edelman SV, Liu R, Johnson J, Glass LC. AUTONOMY: the first randomized trial comparing two patient-driven approaches to initiate and titrate prandial insulin lispro in type 2 diabetes. *Diabetes Care*. 2014;37(8):2132-2140. https://doi.org/10.2337/dc13-2664

Runge AS, Kennedy L, Brown AS, et al. Does time-in-range matter? Perspectives from people with diabetes on the success of current therapies and the drivers of improved outcomes. *Clin Diabetes*. 2018;36(2):112-119. https://doi.org/10.2337/cd17-0094

Tanenbaum ML, Hanes SJ, Miller KM, et al. Diabetes device use in adults with Type 1 diabetes: barriers to uptake and potential intervention targets. *Diabetes Care*. 2017;40(2):181-187. https://doi.org/10.2337/dc16-1536

Westfall PH and Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Stat Plan Inference*. 2001;99(1):25-40. https://doi.org/10.1016/S0378-3758(01)00077-5

Leo Document ID = 3705d4cb-e98e-4654-b936-57b20fe946ca

Approver: PPD

Approval Date & Time: 12-Jul-2020 14:33:46 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 13-Jul-2020 15:43:53 GMT

Signature meaning: Approved