Protocol I8H-MC-BDCY Version (c)

# A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared With Insulin Degludec in Participants With Type 1 Diabetes Treated With Multiple Daily Injection Therapy

NCT05463744

Approval Date: 12-Oct-2022

# Title Page



**Protocol Title:**

A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

**Protocol Number:** I8H-MC-BDCY

**Amendment Number:** c

**Compound:** LY3209590

**Brief Title:**

Efficacy and Safety of LY3209590 Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

**Study Phase:** Phase 3

**Acronym:** QWINT-5

**Sponsor Name:** Eli Lilly and Company

**Legal Registered Address:** Indianapolis, Indiana, USA 46285

**Regulatory Agency Identifier Number(s):**

IND: 129390

EudraCT: 2021-005892-38

**Approval Date:** Protocol Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

**Document ID:** VV-CLIN-074455

**Medical Monitor Name and Contact Information will be provided separately.**

# Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| *Amendment b* | *21-Jun-2022* |
| *Amendment a* | *10-May-2022* |
| *Original Protocol* | *08-Mar-2022* |

**Amendment [c]**

This amendment is considered to be nonsubstantial.

**Overall Rationale for the Amendment:**

The primary rationale for the current amendment is to add continuous glucose monitoring (CGM) download and review at Visits 20 and 22 in the Schedule of Activities.

These and other changes are detailed in the table below. Minor error correction and formatting changes are not reflected in the table.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3. Schedule of Activities | Added information for visit interval at the beginning of the section | For clarification |
| | An "X" has been added at Visits 20 and 22 for "Download and review CGM data in study vendor portal" | Added for study CGM download and review to be performed at all in-office visits |
| | Comment for Pharmacokinetic (PK) samples was revised to include the following,<br>"Visit 3: Collect sample at least 15 min after dosing. For participants randomized to degludec who are not dosed onsite during Visit 3, the sample may be collected at any time during Visit 3." | For clarification |
| 5.1. Inclusion Criteria | Inclusion Criterion #6 has been updated to clarify BMI must be ≤35.0 kg/$m^2$ at the time of screening | For clarification |
| 5.2. Exclusion Criteria | Exclusion Criterion #36 has been updated to clarify "study basal insulin" refers to LY3209590 or comparator | For clarification |
| 8.1.1.1. Self-Monitoring of Blood Glucose (SMBG) | Added "if the participants can safely do this" for participants advised to check SMBG readings for suspected hypoglycemia | For clarification |

| | | |
|---|---|---|
| 8.1.1.2. Continuous Glucose Monitoring (CGM) System | Added a note for participants to not manually calibrate the study CGM with fingerstick blood glucose readings | For clarification |

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# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:**

A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

**Brief Title:**

Efficacy and Safety of LY3209590 Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

**Regulatory Agency Identifier Number(s):**

IND: 129390

EudraCT: 2021-005892-38

**Rationale:**

This Phase 3 study will evaluate the efficacy and safety of once-weekly administration of LY3209590 on glycemic control compared with daily administration of insulin degludec in adult participants with type 1 diabetes (T1D) treated with multiple daily injection (MDI) therapy. This study will inform the clinical development of LY3209590.

**Objectives, Endpoints, and Estimands:**

| Objectives | Endpoints |
|---|---|
| Primary | |
| To demonstrate that LY3209590 is noninferior to insulin degludec for the treatment of T1D in adults | • Change in HbA1c from baseline to Week 26 |
| Key Secondary (multiplicity adjusted) | |
| To demonstrate superiority of LY3209590 to insulin degludec | • Change in HbA1c from baseline to Week 26<br>• Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive, measured by CGM 4 weeks prior to Week 26<br>• Event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 |

| | |
|---|---|
| | mmol/L] or severe) during treatment phase up to Week 52 |
| Other Secondary | |
| To investigate the effect of LY3209590 compared with insulin degludec in additional parameters of glycemic control | • Change in HbA1c from baseline to Week 52<br>• Change from baseline to Weeks 26 and 52 in fasting glucose as measured by SMBG<br>• Glucose variability, measured by CGM 4 weeks prior to Weeks 26 and 52<br>• Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive, measured by CGM 4 weeks prior to Week 52<br>• Insulin dose at Weeks 26 and 52<br>o basal<br>o bolus<br>o total, and<br>o basal/total insulin dose ratio. |
| To compare the safety of LY3209590 to insulin degludec | • Rate of composite of Level 2 and 3 hypoglycemia events during treatment period<br>• Body weight change from baseline to Weeks 26 and 52<br>• Time in hypoglycemia range with glucose <54 mg/dL (3.0 mmol/L), measured by CGM 4 weeks prior to Weeks 26 and 52<br>• Time in hyperglycemia range defined as glucose >180 mg/dL (10.0 mmol/L), measured by CGM 4 weeks prior to Weeks 26 and 52 |
| To compare treatment satisfaction and health-related quality of life between LY3209590 and degludec as assessed by patient-reported outcome questionnaires | • DTSQ change from baseline to Weeks 26 and 52<br>• Change in SF-36 v2 acute form domain scores from baseline to Weeks 26 and 52 |

Abbreviations: CGM = continuous glucose monitoring; DTSQ = Diabetes Treatment Satisfaction Questionnaire; HbA1c = hemoglobin A1c; PK/PD = pharmacokinetics/pharmacodynamics; SMBG = self-monitoring of blood glucose; SF-36 = Short Form-36 Version 2 Health Survey Acute Form; T1D = type 1 diabetes.

**Overall Design:**

This is a Phase 3, open-label, 2-arm, parallel-design, randomized control study to evaluate the efficacy and safety of once-weekly basal insulin LY3209590 compared to insulin degludec in adult participants with T1D who are treated with basal-bolus insulin MDI therapy.

**Brief Summary:**

The study consists of a 1-week screening period, a 2-week lead-in period, a 52-week treatment period, and a 5-week safety follow-up period.

All participants will use a study-provided, unblinded CGM system, glucometer, and e-diary to facilitate diabetes and hypoglycemia management and for data collection throughout the study.

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

**Study Population:**

In general, participants may take part in the study if they

- are 18 years of age or older
- have a diagnosis of T1D for at least 1 year
- have HbA1c value of 7.0% to 10.0%
- have received treatment with allowed basal-bolus insulin analog MDI therapy for at least 90 days prior to screening, and
- are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required.

In general, participants may not take part in the study if they

- have a diagnosis of Type 2 diabetes mellitus, latent autoimmune diabetes, or specific types of diabetes other than T1D
- are women who are pregnant, lactating, or breastfeeding, or
- have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.

**Number of Participants:**

Approximately 670 participants will be randomly assigned to LY3209590 and insulin degludec in a 1:1 ratio. With the assumption of 15% dropout at Week 26, approximately 284 and 284 participants will complete 26 weeks of treatment on LY3209590 and insulin degludec, respectively.

**Intervention Groups and Duration:**

Participants who meet entry criteria will be randomly assigned in a 1:1 ratio to LY3209590 or insulin degludec basal insulin treatment. LY3209590 will be administered once-weekly. Insulin degludec will be administered once-daily.

Participants will also be treated with insulin lispro as prandial insulin.

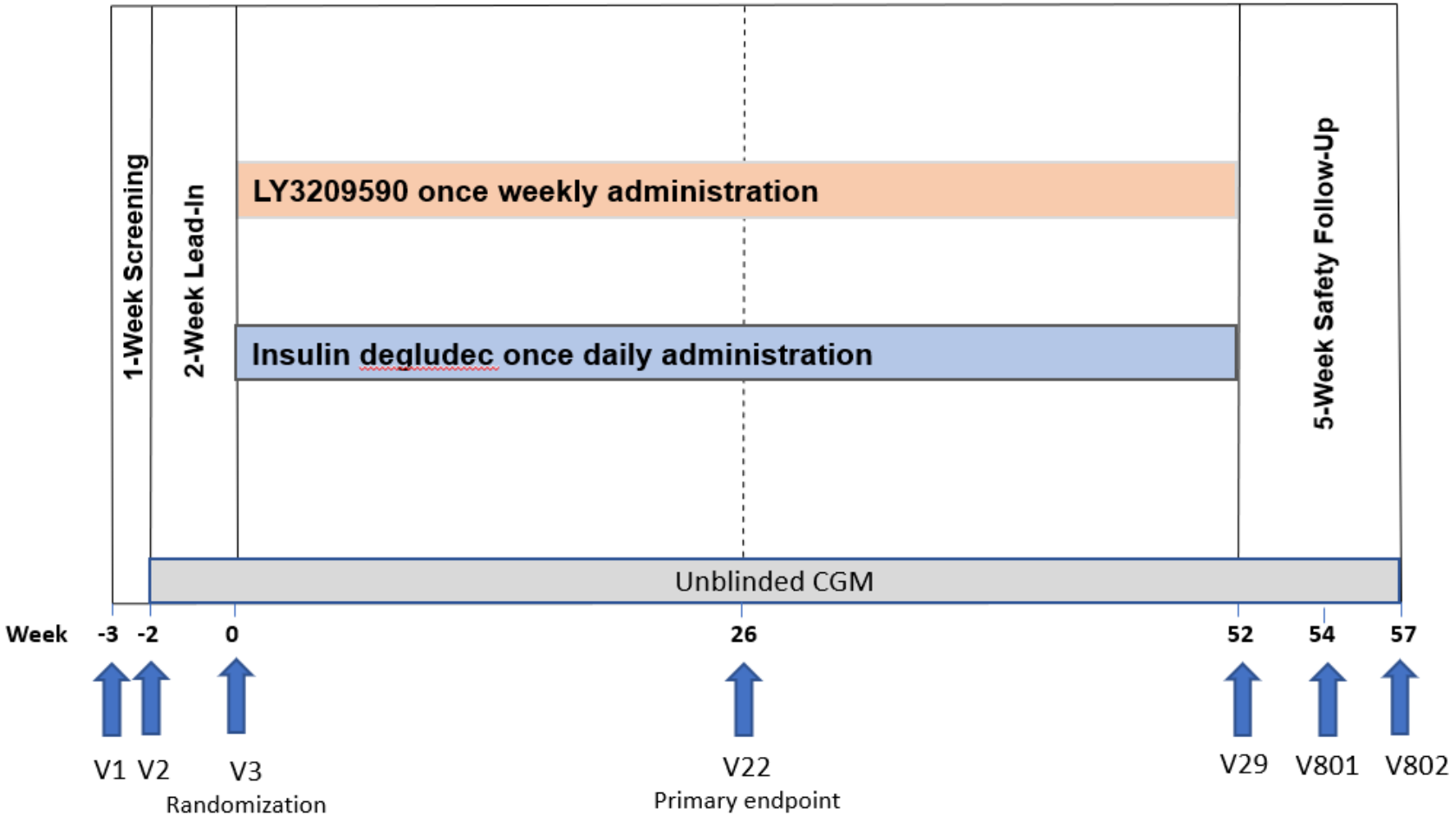
The study treatment period duration is 52 weeks.

**Ethical Considerations of Benefit/Risk:**

Considering the data that are available to date from previous clinical studies, and the measures taken to ensure the safety of the participants in this study, the potential risks related to LY3209590 are justified by the anticipated benefits a participant with T1D may experience in the study.

**Data Monitoring Committee: Yes**

## 1.2. Schema




Abbreviations: CGM = continuous glucose monitoring; V = visit.

## 1.3. Schedule of Activities (SoA)

Two tables describe the schedule of activities.

Table 1 (Section 1.3.1) describes procedures for Screening Visit 1, Lead-In Visit 2, and Treatment Visits 3 to 16.

Table 2 (Section 1.3.2) describes Treatment Visits 17-29, early discontinuation, unscheduled visits, and safety follow-up Visits 801 and 802.

**Telehealth visits**

Telehealth visits may be by telephone or other technology. Gray-shaded columns in the SoA represent telehealth visits.

**Unscheduled visits**

Unscheduled visits (UV) may occur as needed. The SoA reflects some of the procedures that may occur during these visits. Perform additional procedures per investigator discretion.

**Fasting visits**

Participants should not eat or drink anything but water for a minimum of 8 hours before a fasting visit.

If a participant attends these visits in a non-fasting state, the sample should be collected as non-fasting, and this will not be considered a protocol deviation.

**Visit interval**

The visit intervals, including the allowable visit window, should be scheduled relative to randomization Visit 3 (Week 0).

Visit 3 (Week 0) should occur 11-17 days after Visit 2.

### 1.3.1. Screening Visit 1, Lead-In Visit 2, and Treatment Visits 3-16

| **Study I8H-MC-BDCY Table 1** | **Screening and Lead-In** | | **Treatment** | | | | | | | | | | | | | | **Comments** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | |
| **Weeks from Randomization** | -3 | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | |
| **Visit Interval Tolerance (days)** | | ±3 | — | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | |
| **Visit Detail** | | | F | | | | F | | | | | | | | F | T | T = telehealth visit<br>F = fasting visit |
| Informed consent | X | | | | | | | | | | | | | | | | The ICF must be signed before any protocol-specific tests or procedures are performed. See Section 10.1.3 for additional details. |
| Inclusion and exclusion criteria, review and confirm | X | X | X | | | | | | | | | | | | | | Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention. |
| Demographics | X | | | | | | | | | | | | | | | | Includes ethnicity (where permissible), year of birth, sex, and race. |
| Preexisting conditions and medical history, including relevant surgical history | X | | | | | | | | | | | | | | | | Collect all ongoing conditions and relevant past surgical and medical history. |
| Prespecified medical history (indication and history of interest) | X | | | | | | | | | | | | | | | | |
| Prior treatments for indication | X | | | | | | | | | | | | | | | | |
| Substance use (recreational drugs, alcohol, caffeine, and tobacco use) | X | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

| **Study I8H-MC-BDCY Table 1** | **Screen-ing and Lead-In** | | **Treatment** | | | | | | | | | | | | | | **Comments** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | |
| **Weeks from Randomization** | -3 | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | |
| **Visit Interval Tolerance (days)** | | ±3 | — | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | |
| **Visit Detail** | | | F | | | | F | | | | | | | | F | T | T = telehealth visit<br>F = fasting visit |
| Adverse events (AEs) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | AEs are any events that occur after signing the informed consent. |
| Hypoglycemia events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Clinical assessment based on participant history, e-diary entries, and CGM data. |
| **Physical evaluation** | | | | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | | | Participant should remove shoes. |
| Weight | X | X | X | X | X | | X | | X | | X | | | | X | | |
| Vital signs | X | X | X | X | X | | X | | X | | X | | | | X | | Include blood pressure and pulse rate. Measure 3 times using the same arm, after participant has been sitting at least 5 min. The recordings should be taken at least 1 min apart. Vital signs should be taken before ECG tracing and collection of blood samples. Additional vital signs may be measured as necessary at investigator discretion. |
| Physical examination | X | | | | | | | | | | | | | | | | Additional physical examinations may be completed as necessary at investigator discretion. |

| Study I8H-MC-BDCY Table 1 | Screening and Lead-In | | Treatment | | | | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | |
| **Weeks from Randomization** | -3 | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | |
| **Visit Interval Tolerance (days)** | | ±3 | — | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | |
| **Visit Detail** | | | F | | | | F | | | | | | | | F | T | T = telehealth visit<br>F = fasting visit |
| 12-lead ECG (local) | X | | | | | | | | | | | | | | | | Collect prior to collection of blood samples. Participants should be supine for approximately 5 to 10 min before ECG collections and remain supine but awake during the ECG collection.<br>ECGs may be repeated at the investigator's discretion at any visit. |
| **Unblinded continuous glucose monitoring** | | | | | | | | | | | | | | | | | |
| Dispense CGM system | | X | | | | | | | | | | | | | | | Dispense CGM supplies as needed after Visit 2. |
| Download and review CGM data in study vendor portal | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Discuss CGM and hypoglycemia data | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| **Participant education** | | | | | | | | | | | | | | | | | |
| Diabetes counseling, training, and education | | X | X | | | | | | | | | | | | | | Includes glucose monitoring and hypoglycemia (see Sections 5.3, 8.1.1, and 8.3.6).<br>After Visit 3, conduct as needed. |
| e-diary, glucometer, and CGM training | | X | X | | | | | | | | | | | | | | After Visit 3, conduct as needed. |

| Study I8H-MC-BDCY Table 1 | Screen-ing and Lead-In | | Treatment | | | | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | |
| **Weeks from Randomization** | -3 | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | |
| **Visit Interval Tolerance (days)** | | ±3 | — | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | |
| **Visit Detail** | | | F | | | | F | | | | | | | | F | T | T = telehealth visit<br>F = fasting visit |
| **Electronic participant diary and glucometer** | | | | | | | | | | | | | | | | | |
| Dispense e-diary and glucometer | | X | | | | | | | | | | | | | | | Dispense glucometer supplies as needed after Visit 2. |
| Diary compliance check | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Review entries of BG, hypoglycemia events, and insulin dose. If participant is not compliant, study personnel will re-educate the participant on study requirements for continued study participation. See Sections 6.4 and 8.1.1 for additional details. |
| **Electronic patient-reported outcomes** | | | | | | | | | | | | | | | | | |
| Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs) | | | X | | | | | | | | | | | | | | |
| SF-36 v2 acute form | | | X | | | | | | | | | | | | | | |
| EQ-5D-5L | | | X | | | | | | | | | | | | | | |
| **Laboratory tests and sample collections** | | | | | | | | | | | | | | | | | |
| Hematology | X | | X | | | | | | | | | | | | X | | |
| Hemoglobin A1c (HbA1c) | X | | X | | X | | X | | | | | | | | X | | |

| Study I8H-MC-BDCY Table 1 | Screen-ing and Lead-In | | Treatment | | | | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | |
| **Weeks from Randomization** | -3 | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | |
| **Visit Interval Tolerance (days)** | | ±3 | — | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | |
| **Visit Detail** | | | F | | | | F | | | | | | | | F | T | T = telehealth visit<br>F = fasting visit |
| Clinical chemistry | X | | X | | | | | | | | | | | | X | | |
| Glucose | | | | | | | X | | | | | | | | | | |
| Lipid panel | | | X | | | | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | | | | | |
| Serum pregnancy | X | | X | | | | | | | | | | | | | | Collect for WOCBP only. |
| Urine pregnancy (local) | | | X | | | | | | | | | | | | | | The result must be available prior to first dose of intervention.<br>Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation. |
| Follicle-stimulating hormone (FSH) | X | | | | | | | | | | | | | | | | Perform as needed to confirm postmenopausal status. See Section 10.4. |
| C-Peptide | | | X | | | | | | | | | | | | | | |
| eGFR (CKD-EPI) | X | | X | | | | | | | | | | | | X | | |
| Urinary albumin/creatinine ratio (UACR) | X | | X | | | | | | | | | | | | X | | |

| Study I8H-MC-BDCY Table 1 | Screen-ing and Lead-In | | Treatment | | | | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | |
| **Weeks from Randomization** | -3 | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | |
| **Visit Interval Tolerance (days)** | | ±3 | — | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | |
| **Visit Detail** | | | F | | | | F | | | | | | | | F | T | T = telehealth visit<br>F = fasting visit |
| Pharmacokinetic (PK) samples | | | X | | X | | X | | | | | | | | X | | Visit 3: Collect sample at least 15 min after dosing. For participants randomized to degludec who are not dosed onsite during Visit 3, the sample may be collected at any time during Visit 3.<br>For all other visits, collect at any time during the visit (see Section 8.4). |
| Immunogenicity (ADA) samples | | | X | | X | | X | | | | | | | | X | | Visit 3: Collect samples before dosing.<br>If an immediate or nonimmediate systemic drug hypersensitivity reaction occurs, collect an additional unscheduled sample as detailed in Section 10.2.1. |
| **Stored samples** | | | | | | | | | | | | | | | | | |
| Exploratory biomarker samples | | | X | | | | | | | | | | | | | | Collect before dosing. |
| **Randomization and dosing** | | | | | | | | | | | | | | | | | |
| Process visit using IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Randomization using IWRS | | | X | | | | | | | | | | | | | | |
| Basal and prandial insulin dose assessment and documentation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | See Section 6.5. |

| Study I8H-MC-BDCY Table 1 | Screening and Lead-In | | Treatment | | | | | | | | | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | |
| **Weeks from Randomization** | -3 | -2 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 14 | |
| **Visit Interval Tolerance (days)** | | ±3 | — | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | |
| **Visit Detail** | | | F | | | | F | | | | | | | | F | T | T = telehealth visit<br>F = fasting visit |
| Dispense ancillary supplies as needed | | | X | | | | X | | | | X | | | | X | | |
| Dispense study intervention | | | X | | | | X | | | | X | | | | X | | |
| Training regarding study basal insulin. LY3209590 loading dose administered at site | | | X | | | | | | | | | | | | | | Visit 3: LY3209590 loading dose will be administered during the study visit. The loading dose may be administered by study personnel or by the participant under observation of study personnel. The LY3209590 loading dose and time is entered in the e-diary by the participant at the study visit. |
| Observe participant administer LY3209590 study intervention | | | | X | | | | | | | | | | | | | Visit 4: Weekly dose of LY3209590 will be administered by the participant during the study visit under observation of study personnel. The insulin dose amount and time is recorded for all LY3209590 doses. |
| Assess study intervention compliance | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Participant returns unused intervention | | | | | | | X | | | | X | | | | X | | |

Abbreviations: ADA = antidrug antibody; BG = blood glucose; CGM = continuous glucose monitoring; ECG = electrocardiogram; eGFR (CKD-EPI) = estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration); FSH = follicle-stimulating hormone; ICF = informed consent form;

IWRS = interactive web-response system; SF-36 v2 acute = Short Form-36 Version 2 Health Survey Acute Form; UACR = urinary albumin/creatinine ratio; WOCBP = women of childbearing potential.

### 1.3.2. Treatment Visits 17-29, Early Discontinuation, Unscheduled Visits, and Safety Follow-Up Visits 801 and 802

| **Study I8H-MC-BDCY Table 2** | **Treatment** | | | | | | | | | | | | | | | **Safety Follow-Up** | | **Comments** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ED** | **UV** | **801** | **802** | ED = early discontinuation<br>UV = unscheduled visit<br>801 and 802 = safety follow-up visits |
| **Weeks from Randomization** | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | — | — | 54 | 57 | |
| **Visit Interval Tolerance (days)** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | — | — | +7 | ±7 | |
| **Visit Detail** | | T | | | | F | | | F | | | | F | F | | | F | T = telehealth visit<br>F = fasting visit |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse events (AEs) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | AEs are any events that occur after signing the informed consent. |
| Hypoglycemia events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Clinical assessment based on participant history, e-diary entries, and CGM data. |
| **Physical evaluation** | | | | | | | | | | | | | | | | | | |
| Weight | X | | | X | | X | | | X | | | X | X | X | | | X | |
| Vital signs | X | | | X | | X | | | X | | | X | X | X | | | X | Include blood pressure and pulse rate. Measure 3 times using the same arm, after participant has been sitting at least 5 min. The recordings should be taken at least 1 min apart. Vital signs should be taken before ECG tracing and collection of blood samples. Additional vital signs may be measured as necessary at investigator discretion. |
| Physical examination | | | | | | X | | | | | | | X | X | | | X | Additional physical examinations may be completed as necessary at investigator discretion. |

| Study I8H-MC-BDCY Table 2 | Treatment | | | | | | | | | | | | | | | Safety Follow-Up | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ED** | **UV** | **801** | **802** | ED = early discontinuation<br>UV = unscheduled visit<br>801 and 802 = safety follow-up visits |
| **Weeks from Randomization** | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | — | — | 54 | 57 | |
| **Visit Interval Tolerance (days)** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | — | — | +7 | ±7 | |
| **Visit Detail** | | T | | | | F | | | F | | | | F | F | | | F | T = telehealth visit<br>F = fasting visit |
| 12-lead ECG (local) | | | | | | | | | | | | | X | X | | | | Collect prior to collection of blood samples. Participants should be supine for approximately 5 to 10 min before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit. |
| **Unblinded continuous glucose monitoring** | | | | | | | | | | | | | | | | | | |
| Dispense CGM supplies as needed | X | | X | X | X | X | X | X | X | X | X | X | X | | | X | | |
| Download and review CGM data in study vendor portal | X | | X | X | X | X | X | X | X | X | X | X | X | X | | X | X | |
| Discuss CGM and hypoglycemia data | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Return CGM receiver | | | | | | | | | | | | | | X | | | X | The CGM receiver must be returned at the last participant visit. |
| **Participant education** | | | | | | | | | | | | | | | | | | |
| Diabetes counseling, training, and education as needed after Visit 3 | | | | | | | | | | | | | | | | | | |

| Study I8H-MC-BDCY Table 2 | Treatment | | | | | | | | | | | | | | | Safety Follow-Up | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ED** | **UV** | **801** | **802** | ED = early discontinuation<br>UV = unscheduled visit<br>801 and 802 = safety follow-up visits |
| **Weeks from Randomization** | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | — | — | 54 | 57 | |
| **Visit Interval Tolerance (days)** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | — | — | +7 | ±7 | |
| **Visit Detail** | | T | | | | F | | | F | | | | F | F | | | F | T = telehealth visit<br>F = fasting visit |
| e-diary, glucometer, and CGM training as needed after Visit 3 | | | | | | | | | | | | | | | | | | |
| **Electronic participant diary and glucometer** | | | | | | | | | | | | | | | | | | |
| Dispense glucometer supplies as needed | X | | X | | X | | X | X | X | X | X | X | | | | | | |
| e-Diary compliance check | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Review entries of BG, hypoglycemia events, and insulin dose. If participant is not compliant, study personnel will re-educate the participant on study requirements for continued study participation. See Sections 6.4 and 8.1.1 for additional details. |
| e-diary return | | | | | | | | | | | | | | X | | | X | The e-diary must be returned at the last participant visit. |
| **Electronic patient-reported outcomes** | | | | | | | | | | | | | | | | | | |
| Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc) | | | | | | X | | | | | | | X | | | | | |
| SF-36 v2 acute form | | | | | | X | | | | | | | X | X | | | | |

| Study I8H-MC-BDCY Table 2 | Treatment | | | | | | | | | | | | | | | Safety Follow-Up | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ED** | **UV** | **801** | **802** | ED = early discontinuation<br>UV = unscheduled visit<br>801 and 802 = safety follow-up visits |
| **Weeks from Randomization** | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | — | — | 54 | 57 | |
| **Visit Interval Tolerance (days)** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | — | — | +7 | ±7 | |
| **Visit Detail** | | T | | | | F | | | F | | | | F | F | | | F | T = telehealth visit<br>F = fasting visit |
| Basal insulin experience: Likelihood of incorporating into routine | | | | | | X | | | | | | | X | X | | | | |
| Basal insulin experience: Preference | | | | | | X | | | | | | | X | X | | | | |
| EQ-5D-5L | | | | | | X | | | | | | | X | X | | | | |
| **Laboratory tests and sample collections** | | | | | | | | | | | | | | | | | | |
| Hematology | | | | | | X | | | | | | | X | X | | | X | |
| Hemoglobin A1c (HbA1c) | X | | | | | X | | | X | | | | X | X | | | X | |
| Clinical chemistry | | | | | | X | | | | | | | X | X | | | X | |
| Glucose | | | | | | | | | X | | | | | | | | | |
| Lipid panel | | | | | | X | | | | | | | X | X | | | X | |
| Urinalysis | | | | | | X | | | | | | | X | X | | | X | |
| Urine pregnancy (local) | | | | | | | | | | | | | | X | | | X | The result must be available prior to first dose of intervention.<br>Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation. |

| Study I8H-MC-BDCY Table 2 | Treatment | | | | | | | | | | | | | | | Safety Follow-Up | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ED** | **UV** | **801** | **802** | ED = early discontinuation<br>UV = unscheduled visit<br>801 and 802 = safety follow-up visits |
| **Weeks from Randomization** | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | — | — | 54 | 57 | |
| **Visit Interval Tolerance (days)** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | — | — | +7 | ±7 | |
| **Visit Detail** | | T | | | | F | | | F | | | | F | F | | | F | T = telehealth visit<br>F = fasting visit |
| C-Peptide | | | | | | X | | | | | | | X | X | | | | |
| eGFR (CKD-EPI) | | | | | | X | | | | | | | X | X | | | X | |
| Urinary albumin/creatinine ratio (UACR) | | | | | | X | | | | | | | X | X | | | X | |
| Pharmacokinetic (PK) samples | | | | | | X | | | | | | | X | X | | | X | Collect at any time during the visit. See Section 8.4. |
| Immunogenicity (ADA) samples | | | | | | X | | | | | | | X | X | | | X | If an immediate or nonimmediate systemic drug hypersensitivity reaction occurs, collect an additional unscheduled sample as detailed in Section 10.2.1 |
| **Stored samples** | | | | | | | | | | | | | | | | | | |
| Exploratory biomarker samples | | | | | | X | | | | | | | X | X | | | | |
| **Randomization and dosing** | | | | | | | | | | | | | | | | | | |
| Process visit using IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | | | X | X | |
| Basal and prandial insulin dose assessment and documentation | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | See Section 6.5. |

| Study I8H-MC-BDCY Table 2 | Treatment | | | | | | | | | | | | | | | Safety Follow-Up | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **ED** | **UV** | **801** | **802** | ED = early discontinuation<br>UV = unscheduled visit<br>801 and 802 = safety follow-up visits |
| **Weeks from Randomization** | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | — | — | 54 | 57 | |
| **Visit Interval Tolerance (days)** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | — | — | +7 | ±7 | |
| **Visit Detail** | | T | | | | F | | | F | | | | F | F | | | F | T = telehealth visit<br>F = fasting visit |
| Assessment for post study basal and prandial insulin treatment | | | | | | | | | | | | | X | X | | X | X | See Section 6.6.1. |
| Dispense ancillary supplies as needed | X | | X | | X | | X | X | X | X | X | X | | | | | | |
| Dispense study intervention | X | | X | | X | | X | X | X | X | X | X | | | | | | |
| Assess study intervention compliance | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Participant returns unused intervention and supplies | X | | X | | X | | X | X | X | X | X | X | X | X | | | | |

Abbreviations: ADA = antidrug antibody; BG = blood glucose; CGM = continuous glucose monitoring; eGFR (CKD-EPI) = estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration); ECG = electrocardiogram; IWRS = interactive web-response system; SF-36 v2 acute = Short Form-36 Version 2 Health Survey Acute Form; UACR = urinary albumin/creatinine ratio; WOCBP = women of childbearing potential.

# 2. Introduction

LY3209590 is a long-acting insulin receptor agonist in development for the once-weekly treatment of patients with T1D and T2D.

## 2.1. Study Rationale

This Phase 3 study will evaluate the efficacy and safety of once-weekly administration of LY3209590 on glycemic control compared with daily administration of insulin degludec in adult participants with T1D treated with MDI therapy. This study will inform the clinical development of LY3209590.

## 2.2. Background

**Current state of diabetes care**

There have been many advances in the treatment of T1D; however, reaching and maintaining glycemic goals while managing the risk of hypoglycemia remain challenging.

**Potential for improved treatment regimens**

Once-weekly basal insulins with a lower peak-to-trough profile during the week and a nearly flat insulin profile could reduce within-day glucose variability and result in more consistent and predictable glycemic control.

**LY3209590**

LY3209590 is a novel insulin receptor agonist that is in development as a once-weekly basal insulin for the treatment of patients with T1D and T2D. LY3209590 was designed as a divalent (dimer) insulin receptor agonist consisting of a single-chain insulin analog (comprised of an insulin B-chain analog, a short peptide linker, and an insulin A-chain analog) fused to a second peptide linker that is fused to an unmodified human IgG2 Fc domain.

A detailed description of the chemistry, pharmacology, non-clinical and clinical efficacy, and safety of LY3209590 is provided in the Investigator's Brochure.

***Summary of clinical results***

Phase 1 and Phase 2 studies have been completed to assess the PK/PD, safety, and efficacy of LY3209590. The results thus far support continued development of LY3209590 as a treatment for diabetes mellitus.

*Phase 1 study results*

LY3209590 pharmacokinetics show a low peak-to-trough ratio and extended mean half-life of 17 days that supports once-weekly dosing. Single-ascending doses of LY3209590 lowered fasting glucose in a dose- and concentration-dependent manner, with a prolonged time-action profile.

*Phase 2 study BDCM results comparing LY3209590 to insulin degludec in patients with T2D*

Study BDCM was a randomized, open-label, Phase 2 study to evaluate the safety and efficacy of LY3209590 in participants with T2D previously treated with basal insulin.

LY3209590 was noninferior to degludec for glycemic control as measured by change in HbA1c from baseline to Week 32 with significant improvement in HbA1c in all treatment groups with a lower risk of hypoglycemia with LY3209590.

The overall adverse event profile from Study BDCM showed no increased safety risk with LY3209590 compared with degludec treatment.

*Phase 2 study BDCP comparing LY3209590 to insulin degludec in patients with T1D*

Study BDCP was a randomized, open-label, Phase 2 study to evaluate the safety and efficacy of LY3209590 in patients with T1D treated with MDI therapy.

LY3209590 was noninferior to degludec as measured by change in HbA1c from baseline to Week 26, although participants treated with LY3209590 had higher fasting glucose at study endpoint. Over 26 weeks of study treatment, the rate of Level 2 hypoglycemia and nocturnal hypoglycemia as well as time below range from CGM were not significantly different between groups.

The overall adverse event profile from Study BDCP in patients with T1D showed no increased safety risk with LY3209590 compared with degludec treatment.

## 2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of LY3209590 may be found in the Investigator's Brochure, and that of insulin degludec may be found in the local product package insert.

### 2.3.1. Risk Assessment

**Potential risks for this study**

The potential risks associated with LY3209590 include

- hypoglycemia
- hyperglycemia
- hypersensitivity reaction
- injection site reactions, for example, injection site rash, erythema, pruritus, or lipohypertrophy
- immunogenicity, and
- cardiovascular risks.

It is expected that the known risks would be similar to other insulins.

Safety data available to date suggest that there is no increased risk to participants' safety with LY3209590 treatment compared to insulin degludec.

**Management of risks**

Sections 5.1, 5.2, 7, and 8.3 address known potential risks associated with LY3209590.

***Protocol risk management measures***

*Participant education for hypoglycemia*

After signing informed consent, all participants will be educated about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for hypoglycemia events. Hypoglycemia may be identified by spontaneous reporting of symptoms from participants, whether confirmed or unconfirmed by simultaneous glucose values, or by blood glucose samples collected between study visits.

*Monitoring of participant CGM and blood glucose levels*

All participants will use the study-provided, unblinded CGM system to facilitate diabetes and hypoglycemia management and for data collection throughout the study. A web interface will be available for site personnel to download and review CGM data.

Each participant will have a study-provided glucometer that will wirelessly transfer participant SMBG to their study-provided e-diary. Participants should check glucose values with the glucometer when hypoglycemia is experienced or suspected.

A web interface and reporting system will be available for use by study personnel to view participant e-diary entries, including SMBG, insulin doses, and hypoglycemia information throughout the study. Automated alerts will be transmitted to the investigator any time the participant reports a potential severe episode of hypoglycemia, defined as requiring assistance due to neurological impairment, in the e-diary.

*Dose modification*

The basal insulin dosing algorithm used in the study requires consideration and adjustment of insulin dosing by the investigator based on participant FBG, CGM data, and hypoglycemia events (see Section 6.5).

All participants will be treated with basal-bolus MDI therapy, which will be titrated to glycemic targets and as clinically indicated for hyperglycemia.

### 2.3.2. Benefit Assessment

Participants may benefit during the study by frequent engagement and support from health care providers for diabetes management and safety assessments with the potential to improve glycemic control.

### 2.3.3. Overall Benefit Risk Conclusion

Considering the clinical data to date and measures taken to minimize risk for the participants in this study, the potential risks identified in association with LY3209590 are justified by the anticipated benefits that may be afforded to participants with T1D.

# 3. Objectives, Endpoints, and Estimands

| Objectives | Endpoints |
|---|---|
| Primary | |
| To demonstrate that LY3209590 is noninferior to insulin degludec for the treatment of T1D in adults | • Change in HbA1c from baseline to Week 26 |
| Key Secondary (multiplicity adjusted) | |
| To demonstrate superiority of LY3209590 to insulin degludec | • Change in HbA1c from baseline to Week 26<br>• Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive, measured by CGM 4 weeks prior to Week 26<br>• Event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 52 |
| Other Secondary | |
| To investigate the effect of LY3209590 compared with insulin degludec in additional parameters of glycemic control | • Change in HbA1c from baseline to Week 52<br>• Change from baseline to Weeks 26 and 52 in fasting glucose as measured by SMBG<br>• Glucose variability, measured by CGM 4 weeks prior to Weeks 26 and 52<br>• Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive, measured by CGM 4 weeks prior to Week 52<br>• Insulin dose at Weeks 26 and 52<br>  o basal<br>  o bolus<br>  o total, and<br>  o basal/total insulin dose ratio |

| | |
|---|---|
| To compare the safety of LY3209590 to insulin degludec | • Rate of composite of Level 2 and 3 hypoglycemia events during treatment period<br>• Body weight change from baseline to Weeks 26 and 52<br>• Time in hypoglycemia range with glucose <54 mg/dL (3.0 mmol/L), measured by CGM 4 weeks prior to Weeks 26 and 52<br>• Time in hyperglycemia range defined as glucose >180 mg/dL (10.0 mmol/L), measured by CGM 4 weeks prior to Weeks 26 and 52 |
| To compare treatment satisfaction and health-related quality of life between LY3209590 and degludec as assessed by patient-reported outcome questionnaires | • DTSQ change from baseline to Weeks 26 and 52<br>• Change in SF-36 v2 acute form domain scores from baseline to Weeks 26 and 52 |
| Tertiary | |
| To investigate the effect of LY3209590 compared with insulin degludec on other measures of efficacy, safety, and patient-reported outcomes | Efficacy<br>• Percentage of participants achieving HbA1c < 7% at Weeks 26 and 52<br>• Percentage of participants achieving HbA1c ≤ 6.5% at Weeks 26 and 52<br>• Change from baseline to Weeks 26 and 52 in fasting serum glucose as measured by central laboratory |
| | Safety<br>• Rate and incidence of Level 2 hypoglycemia events during treatment period<br>• Rate and incidence of Level 3 hypoglycemia events during treatment period<br>• Incidence of positive treatment-emergent antibody of LY3209590 |

| | |
|---|---|
| | Patient-reported outcomes<br>• Frequency of responses to "Basal Insulin Experience: Likelihood of incorporating into routine" at Weeks 26 and 52<br>• Frequency of responses to "Basal Insulin Experience: Preference" at Weeks 26 and 52<br>• Change in EQ-5D-5L from baseline to Weeks 26 and 52 |
| To characterize the PK/PD of LY3209590 | • LY3209590 PK and concentration response relationships to key safety and efficacy measures. |

Abbreviations: CGM = continuous glucose monitoring; DTSQ = Diabetes Treatment Satisfaction Questionnaire; HbA1c = hemoglobin A1c; PK/PD = pharmacokinetics/pharmacodynamics; SF-36 = Short Form-36 Version 2 Health Survey Acute Form; SMBG = self-monitoring of blood glucose; T1D = Type 1 diabetes.

## Primary estimand

### *United States registration*

The primary clinical question of interest is

> What is the treatment difference between LY3209590 and insulin degludec in HbA1c change from baseline after 26 weeks of treatment, in study eligible participants with T1D treated with MDI therapy, regardless of treatment discontinuation for any reason and regardless of initiation of rescue medication?

*Treatment regimen estimand attributes*

This table describes the treatment regimen estimand attributes.

| **Treatment Regimen Estimand Attributes** | **Description** |
|---|---|
| Population | Targeted study population (see table in Section 9.2). |
| Endpoint | HbA1c change from baseline to Week 26. |
| Remaining intercurrent events | None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both addressed by the treatment condition of interest attribute. |
| Treatment condition | The randomized treatment regardless of treatment discontinuation and use of rescue medications. |

| | |
|---|---|
| Population-level summary | Difference in mean changes between treatment conditions. |

*Rationale for the treatment regimen estimand*

The treatment regimen estimand estimates how participants with T1D are treated in clinical practice and considers both efficacy and safety.

***Registration for countries outside the United States***

The primary clinical question of interest is

> What is the treatment difference between LY3209590 and insulin degludec in HbA1c change from baseline after 26 weeks of treatment, in study eligible participants with T1D treated with MDI therapy and adhere to the randomized treatment without an intercurrent event during the study treatment period?

*Efficacy estimand attributes*

This table describes the efficacy estimand attributes.

| **Efficacy Regimen Estimand Attribute** | **Description** |
|---|---|
| Population | Targeted study population. (see table in Section 9.2). |
| Endpoint | HbA1c change from baseline to Week 26. |
| Remaining intercurrent events | None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both addressed by the hypothetical strategy, for example, the potential outcome for those participants if the intercurrent events have not occurred will be estimated. |
| Treatment condition | The randomized treatment. |
| Population-level summary | Difference in mean changes between treatment conditions. |

*Rationale for the efficacy estimand*

The efficacy estimand supports the interpretation of the treatment effect as participants adhere to study treatment and free from the confounding effect of rescue medications.

**Secondary estimands for multiplicity-adjusted objectives**

The superiority test in change from baseline to Week 26 (Visit 22) in HbA1c will also be based on the primary estimand described above.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, measured by CGM in the 4 weeks prior to Visit 22 (Week 26) will use treatment regimen estimated for US registration and efficacy estimand for other countries.

The participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) is one of the safety measures for the study. The event rate will be based on all available data during the specific analysis period. Relative rate between randomized treatment groups will be used for treatment comparison.

# 4. Study Design

## 4.1. Overall Design

This is a Phase 3, open-label, 2-arm, parallel-design, randomized control study to investigate if LY3209590 is noninferior to insulin degludec in adult participants with T1D who are treated with basal-bolus insulin MDI therapy.

The study consists of a 1-week screening period, a 2-week lead-in period, a 52-week treatment period, and a 5-week safety follow-up period.

**Visit 1: Screening**

Interested participants will sign the appropriate informed consent document(s) prior to initiating any procedures.

The investigator will review medical history, symptoms, risk factors, and other inclusion and exclusion criteria prior to any diagnostic procedures. If the participant is eligible after this review, then the site will perform the diagnostic procedures to confirm eligibility.

**Visit 2: Lead-In**

Participants will receive their glucometer, electronic study diary, and unblinded CGM system.

Participants will receive training on

- diabetes self-monitoring and management
- unblinded CGM system
- glucometer and e-diary, and
- study requirements.

Starting with Visit 2, participants will use the study-supplied glucometer, e-diary, and unblinded CGM system for diabetes management and data collection throughout the study.

Participants will continue with their current basal-bolus insulin therapy until randomization.

**Treatment period**

***Visit 3 (Week 0): Randomization***

This is the general flow for Visit 3

- study personnel confirm enrollment criteria
- participants are randomly assigned to an intervention group (LY3209590 or insulin degludec)
- study personnel complete baseline procedures and sample collection
- study personnel will provide study insulin dosing training
    - For participants randomized to LY3209590, the first dose of LY3209590 will be administered at the site by study personnel or by the participant under observation of study personnel. Insulin dose information will be entered in the e-diary.
    - For participants randomized to insulin degludec, the first dose of degludec can be administered at the site or after the visit, depending upon the usual time of basal insulin dosing.

- study personnel complete all visit procedures.

Participants assigned to insulin degludec will be treated with daily dosing of degludec after Visit 3.

Participants will be treated with insulin lispro as prandial insulin throughout the treatment period as described in Section 6.5.3.

***Visit 4 (Week 1)***

Participants complete all visit procedures described in the SoA.

Study personnel will provide dosing training and observe participants administer their second dose of LY3209590.

***Visit 5 through Visit 29 (Week 2 through Week 52)***

Study personnel and participants complete all visit procedures described in the SoA.

The participant's BG and CGM data will be used to titrate basal and prandial insulin dosing as described in Section 6.5.

The investigator or study staff will review participant e-diary compliance for

- SMBG
- hypoglycemia events, including related signs and symptoms, and
- study intervention compliance, including insulin dose data.

***Last study treatment visit: either V29 (Week 52) or ED visit***

Participants complete all visit procedures described in the SoA.

Participants will return any unused study intervention to the investigative site.

The investigator will determine the participant's basal and prandial insulin treatment during the safety follow-up period as described in Section 6.6.1.

**Safety follow-up visits 801 and 802**

Study personnel and participants complete all visit procedures described in the SoA.

The investigator will follow up on the participant's transition to non-study basal and prandial insulin treatment.

Participants will return study devices at the final study visit.

## 4.2. Scientific Rationale for Study Design

**Primary endpoint**

The primary efficacy measurement is HbA1c, a widely used measure of glycemic control that reflects a cumulative history of glucose levels in the preceding 2 to 3 months.

**Overall design**

***Blinding***

This is an open-label study. Investigators, participants, and study-site personnel will be unblinded to the assigned treatment. To eliminate potential biases, designated members of the Lilly study team will remain blinded throughout the study (see Section 6.3). Only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

***Study duration***

The treatment duration is a reasonable timeframe to observe the effects of LY3209590 compared to insulin degludec.

The follow-up visits after the last dose is designed to capture any additional safety signals and to monitor the transition from study treatment to non-study insulins.

***Comparator***

Insulin degludec was chosen as the comparator because it is widely accepted as the best-in-class basal insulin. It has the longest half-life among other marketed basal insulins.

**Collection of race and ethnicity data**

In this study, collection of demographic information includes ethnicity (where permissible) and race. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

## 4.3. Justification for Dose

The dosing guidance for starting doses and dose titrations of LY3209590 and insulin degludec is derived from findings from Phase 2 studies and model-based simulations. These data informed the development of titration algorithms to safely and efficiently initiate and guide LY3209590 and insulin degludec dose adjustments to achieve the same glycemic goal of FBG between 80 and 120 mg/dL (4.4 and 6.6 mmol/L), while minimizing hypoglycemia risk.

See Section 6.5.2 for study basal insulin therapy details.

**LY3209590**

Following a once-weekly subcutaneous administration of LY3209590, the time to reach steady-state PK without a loading dose is estimated to be between 8 and 10 weeks, based on the long half-life of LY3209590. With a loading dose, the estimated time to reach steady state is estimated to be 2 to 3 weeks. For this reason, all participants randomly assigned to LY3209590 will receive a single loading dose of LY3209590 (see Section 6.5.2.1). This strategy was designed to minimize loss of glycemic control when transitioning from the shorter duration once-daily basal insulins to a weekly insulin. This approach is supported by findings in the Phase 2 Study BDCP and model-based simulations.

Directions for conversion of the prior daily basal insulin dose to the LY3209590 weekly dose and the titration algorithm are described in Section 6.5.2.1.

**Insulin degludec**

The starting dose for insulin degludec is based on the daily dose of basal insulin the participant was taking prior to Visit 3 (Week 0). The insulin degludec algorithm is based on well-established algorithms while balancing efficacy and hypoglycemia with the same FBG targets as LY3209590 (see Section 6.5.2.2).

## 4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

# 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:

**Age**

1. Are at least 18 years of age at screening, or older per local regulations.

**Type of participant and disease characteristics**

2. Have a clinical diagnosis of T1D for at least 1 year prior to screening.
3. Have HbA1c value of 7.0% to 10.0%, inclusive, as determined by the central laboratory at screening.
4. Have received treatment with basal-bolus insulin analog MDI therapy according to the local product label for at least 90 days prior to screening
    - Allowed basal insulin analogs (includes biosimilars)
        - insulin glargine U-100
        - insulin glargine U-300
        - insulin degludec U-100 or U-200, or
        - insulin detemir
    - Allowed bolus insulin analogs (includes biosimilars)
        - insulin lispro U-100 or U-200
        - insulin aspart
        - insulin glulisine
        - fast acting insulin aspart (Fiasp® [Novo Nordisk A/S., Bagsvaerd, Denmark]), or
        - insulin lispro-aabc U-100 or U-200 (Lyumjev™ [Eli Lilly and Co., Indianapolis, IN]).
5. Are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required, including
    - adhere to the study basal-bolus insulin MDI regimen and use of study insulins according to injection instructions and protocol
    - use the CGM system supplied for this study for glucose monitoring, diabetes management, and data collection per protocol
    - maintain an electronic study diary and use the glucometer supplied for use in the study as required for the protocol, and
    - must have a normal wake/sleep pattern, such that midnight to 0600 hours will reliably reflect a usual sleeping period.

**Weight**

6. have a body mass index $\leq 35.0$ kg/m$^2$ at the time of screening.

**Contraceptive/barrier requirements**

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7. **Female participants**: for the contraception requirements of this protocol, see Section 10.4.
   **Male participants**: no male contraception required except in compliance with specific local government requirements.

**Informed consent**

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

## 5.2. Exclusion Criteria

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

**Medical conditions**

***Diabetes related***

9. Have a diagnosis of T2D, latent autoimmune diabetes, or specific types of diabetes other than T1D, for example, monogenic diabetes, diseases of the exocrine pancreas, and drug-induced or chemical-induced diabetes.
10. Have a history of more than 1 episode of severe hypoglycemia, defined as requiring assistance due to neurologically disabling hypoglycemia, within the 6 months prior to screening.
11. Have hypoglycemia unawareness, in the opinion of the investigator.
12. Have a history of more than 1 episode of diabetic ketoacidosis or hyperosmolar state or coma requiring hospitalization within the 6 months prior to screening.
13. Have excessive insulin resistance, defined as having received a total daily dose of insulin >1.5 units/kg at the time of screening.

***Cardiovascular***

14. Have had New York Heart Association Class IV heart failure or any of the following cardiovascular conditions within 90 days prior to screening
    - acute myocardial infarction
    - cerebrovascular accident (stroke), or
    - coronary bypass surgery.

***Gastrointestinal***

15. Have undergone gastric bypass (bariatric) surgery, restrictive bariatric surgery, for example, Lap-Band© or sleeve gastrectomy within 1 year prior to screening.
16. Have presence of clinically significant gastroparesis, in the opinion of the investigator.

***Hepatic***

17. Have acute or chronic hepatitis, cirrhosis, or obvious clinical signs or symptoms of any other liver disease, except nonalcoholic fatty liver disease (that is, study participants with nonalcoholic fatty liver disease are eligible for participation), or have elevated liver enzyme measurements as determined by the central laboratory at screening:
    - total bilirubin >2x ULN except for participants with Gilbert's syndrome
    - ALT or serum glutamic pyruvic transaminase >3x ULN
    - AST or serum glutamic oxaloacetic transaminase >3x ULN, or
    - ALP >2.5x ULN.

***Renal***

18. Have a history of renal transplantation, are currently receiving renal dialysis, or have an estimated glomerular filtration rate <30 mL/min/1.73 $m^2$, calculated by the Chronic Kidney Disease-Epidemiology equation, as determined by the central laboratory at screening.

***Hematologic***

19. Have had a blood transfusion or severe blood loss within 90 days prior to screening.
20. Have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or any other hemoglobin abnormalities known to interfere with the measurement of HbA1c in the opinion of the investigator.

***Malignancy***

21. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy within 5 years prior to screening.
    **Exceptions:**
    - basal cell or squamous cell skin cancer.
22. Are at increased risk for developing cancer or a recurrence of cancer.

***General***

23. Have had a significant weight gain or loss in the past 3 months in the investigator's opinion, for example, ≥5%.
24. Have known hypersensitivity or allergy to any of the study medications or their excipients.
25. Have any other serious disease or condition that, in the opinion of the investigator, would pose a significant risk to the study participant or preclude the study participant from following and completing the protocol.
26. Are women who test positive for pregnancy or intend to become pregnant.
27. Are women who are lactating or breastfeeding.

**Prior or concomitant therapy**

28. Have been on an insulin treatment regimen, including NPH insulin, U-500 insulin, regular human insulin, or any premixed insulins within 90 days prior to screening.

29. Have used insulin human inhalation powder (Afrezza) within 90 days prior to screening.
30. Have used continuous subcutaneous insulin infusion therapy within 90 days prior to screening.
31. Are receiving any oral or injectable medication intended for the treatment of diabetes mellitus other than insulins as specified in Inclusion Criterion 4 in the 90 days prior to screening.
32. Are receiving chronic (>14 days) systemic glucocorticoid therapy or have received such therapy for >14 days within 30 days prior to screening.

    **Exceptions:**

    - replacement therapy for adrenal insufficiency, and
    - topical, intraocular, intranasal, or inhaled preparations or intra-articular injection
33. Have used any weight loss drugs within 90 days prior to screening.

    Examples:

    - glucagon-like peptide-1 (GLP-1) receptor agonists
    - lorcaserin
    - orlistat
    - phentermine
    - phentermine and topiramate combination
    - naltrexone and bupropion combination, or
    - over-the-counter weight loss medications.

**Prior or concurrent clinical study experience**

34. Are currently enrolled in any other clinical study involving an intervention 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 intervention. If the previous intervention 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 after having signed the informed consent form (ICF) or any other study investigating LY3209590 after receiving at least 1 dose of the study basal insulin (LY3209590 or comparator).

**Other exclusions**

37. Have evidence of any substance abuse disorder of any severity defined by the Diagnostic and Statistical Manual of Mental Disorders-5, within 6 months prior to screening.

    **Exceptions:** nicotine or caffeine.
38. 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.
39. Are Eli Lilly and Company employees or are employees of any third party involved in the study who require exclusion of their employees.

## 5.3. Lifestyle Considerations

**Diabetes management counseling**

Qualified study personnel will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and treatment of hypoglycemia. Diabetes self-management counseling may be reviewed throughout the study, as needed.

***Dietary and exercise considerations***

Study participants should generally follow a healthy meal plan and continue their usual exercise habits throughout the course of the study.

***Dietary and exercise restrictions***

Study participants should not initiate an intensive diet or exercise program with the intent of reducing body weight at any time during the study, other than the lifestyle and dietary measures for diabetes treatment.

**Blood donation**

Study participants should not donate blood or blood products during the study or for 4 weeks following their last study visit.

## 5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. 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).

Individuals who do not meet the criteria for participation in this study (screen failure) will not be rescreened.

## 5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable for this study. All entry criteria must be met within the specified intervals in the SoA.

# 6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

| **Intervention Name** | LY3209590 | Insulin Degludec | Insulin Lispro |
|---|---|---|---|
| **Dose Formulation** | Solution | Solution | Solution |
| **Unit Dose Strength(s)** | 500 units/mL | 100 units/mL | 100 units/mL |
| **Dosage Level(s)** | Individualized dosing (see Section 6.5.2.1) | Individualized dosing (see Section 6.5.2.2) | Individualized dosing (see Section 6.5.3) |
| **Frequency of Administration** | Once-weekly study basal insulin | Once-daily study basal insulin | Background prandial insulin therapy with meals and as needed |
| **Route of Administration** | Subcutaneous injection | Subcutaneous injection | Subcutaneous injection |
| **Authorized as defined by EU Clinical Trial Regulation** | No | Yes | Yes |

**LY3209590 frequency of administration and guidance for missed doses**

LY3209590 should be administered once weekly at approximately the same time and day each week.

If a dose is missed, it should be administered as soon as possible if at least 3 days (72 hours) remain until the next scheduled dose. If less than 3 days remain before the next scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, participants can then resume their regular once-weekly dosing schedule.

The day of weekly administration can be changed, if necessary, only if the last dose has been administered at least 3 days earlier.

**Insulin degludec frequency of administration**

Insulin degludec should be administered once daily at approximately the same time each day.

**Anatomical location of injections**

For both LY3209590 and insulin degludec, participants should rotate injection sites from one injection to the next, even when injecting within the same region. Injections may be administered in the abdomen, thigh, arm, or buttock. Refer to the Instructions for Use for complete instructions on dose administration.

**Packaging and labeling**

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

### 6.1.1. Medical Devices

LY3209590, insulin degludec, and insulin lispro will be provided as a solution in a prefilled pen injector for the administration of either LY3209590 or insulin degludec and insulin lispro.

Instructions for device use will be provided.

All Product Complaints, including malfunctions, use error, and inadequate labelling, shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.1) and appropriately managed by the sponsor.

### 6.1.2. Background Therapy

For patients with T1D, standard of care stipulates treatment with both basal and bolus insulin. In this study, participants will be treated with LY3209590 or insulin degludec as study basal insulin intervention and insulin lispro as prandial bolus background therapy.

Insulin lispro is being used to standardize the prandial insulin therapy.

### 6.1.3. Rescue Therapy for Management of Participants with Severe, Persistent Hyperglycemia during the Treatment Period

Participants in this clinical trial will be treated with basal insulin, that is LY3209590 or insulin degludec, in combination with prandial insulin lispro. Correction doses of insulin lispro can also be used.

If a participant develops severe, persistent hyperglycemia after randomization, based on meeting one of the criteria in this table, and in the absence of intercurrent cause of the hyperglycemia, rescue therapy with an additional therapeutic intervention should be considered.

| Average Fasting Glucose over 2-week Period | Timing of events |
|---|---|
| >270 mg/dL (15 mmol/L) | Weeks 12 to 16 (from Visit 15 until Visit 17) |
| >240 mg/dL (13 mmol/L) | Weeks 16 to 20 (after Visit 17 until Visit 19) |
| >200 mg/dL (11 mmol/L) | Weeks 20 to 52 (after Visit 19 until Visit 29) |

Investigators should first confirm that the participant is fully compliant with the assigned therapeutic regimen and that the participant does not have an acute condition causing severe hyperglycemia. If study basal and prandial insulin therapy is fully optimized, the investigator will decide, in consultation with the participant, on an appropriate intensification of insulin therapy after considering relevant clinical criteria. Participants who require a new non-study basal insulin intervention as rescue therapy for hyperglycemia management must discontinue study basal insulin therapy (LY3209590 or insulin degludec). The participant will remain in the study and follow procedures for the remaining study visits.

The investigator should ensure that the participant met the criteria for severe or persistent hyperglycemia before initiating rescue medicine and document this in the source files.

## 6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, 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 study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

**Participant responsibilities**

In-use storage conditions are expected to be followed according to the instructions for use provided by the sponsor. Study participants will be trained on the proper storage and handling of the study intervention.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

**Randomization and stratification**

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Participants will be randomly assigned in a 1:1 ratio to LY3209590:insulin degludec.

Participants will be stratified based on

- country
- HbA1c stratum (<8% and ≥8%) at screening Visit 1
- CGM use prior to study entry (yes/no), and
- carbohydrate counting for prandial insulin dosing (yes/no).

**Blinding**

This is an open-label study. Investigators and participants will be unblinded to the assigned treatment groups.

The Lilly study team members who are closely involved in data interpretation and analysis planning will remain blinded throughout the course of the study. Only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

The investigator should make every effort to preserve the blinding when contacting the Lilly study team members, including the Lilly clinical research physician or scientist.

**Unblinded reviews**

External committees reviewing unblinded data during the study are described in Section 10.1.5

## 6.4. Study Intervention Compliance

Study personnel will ensure participants enter in their e-diary

- the dose amount and date of their daily or weekly basal insulin dose, and
- prandial insulin dose.
    - Note: Record all prandial insulin doses injected each day with meals and additional doses if applicable.

The minimum required insulin dose e-diary entries differ by study period as described in the table below.

| During study period… | participants will record their dose for… | during… | at a minimum frequency of… |
|---|---|---|---|
| Lead in | prestudy basal insulin | Weeks -1 to 0<br>Visits 2 to 3 | 2 days per week |
| | prestudy prandial insulin | Weeks -1 to 0<br>Visits 2 to 3 | 2 days per week |
| Treatment | LY3209590 or insulin degludec | Weeks 0 to 52<br>Visits 3 to 29 | 1 day per week |
| | prandial insulin lispro | Weeks 0 to 12<br>Visits 3 to 15 | 2 days per week |
| | | the week prior to Weeks 16, 20, 24, 26, 28, 32, 36, 40, 44, 48, and 52<br>Visits 17, 19, 21, 22, 23, 24, 25, 26, 27, 28, and 29 | 2 days per week |
| Safety follow-up | basal insulin | Weeks 52 to 57<br>Visits 29 to 802 | 1 day per week |
| | prandial insulin | Weeks 52 to 57<br>Visits 29 to 802 | 1 day per week |

Additional recording of insulin dosing can be requested throughout the study as clinically indicated.

The investigator or trained designee will assess treatment compliance at each visit based on review of the participant's glycemic control, e-diary completion, and adherence to prescribed dose and study procedures.

If a participant is considered poorly compliant with their study procedures, for example, missed visits, specific diagnostic tests, or e-diary entries, they will be retrained as needed by designated study personnel.

## 6.5. Dose Modification

### 6.5.1. Glycemic Targets and Goals

The overall glycemic targets and goals for study participants during the study treatment period are similar to those recommended by the American Diabetes Association and the European Association for the Study of Diabetes (Holt et al. 2021). The glycemic targets and goals should be balanced with minimizing the risk of significant hypoglycemia.

| Glucose Timepoint | Glucose Target Range |
|---|---|
| Fasting or preprandial glucose | 80-120 mg/dL or 4.4-6.6 mmol/L |

| CGM Time in Ranges | Overall CGM Goals |
|---|---|
| Time in range (TIR) 70-180 mg/dL (3.9-10.0 mmol/L) | >70% |
| Time below range (TBR)<br>Readings and time < 54 mg/dL (3.0 mmol/L; Level 2 hypoglycemia) | <1% |
| Readings and time < 70 mg/dL (3.9 mmol/L; Level 1 and Level 2 hypoglycemia) | <4% |
| Time above range (TAR)<br>Readings and time >250 mg/dL (13.9 mmol/L) | <5% |
| Readings and time >180 mg/dL (10.0 mmol/L) | <25% |

### 6.5.2. Basal Insulin Therapy

During the lead-in period (Visits 2 to 3), participants will continue their prestudy basal and prandial insulin therapy.

At Visit 3, participants will be randomized to study basal insulin LY3209590 or degludec. Basal insulin is titrated based on the FBG target of 80 to 120 mg/dL (4.4 to 6.6 mmol/L) and hypoglycemia evaluation. CGM data including 24-hour glucose profiles and additional SMBG monitoring (if applicable) should also be considered.

Titration of the study basal insulin (LY3209590 or degludec) dose should be made at **weekly** intervals from **Weeks 0 to 12** (titration period, Visits 3 to 15), and then at a minimum of **every 4 weeks** from **Weeks 12 to 52** (Visits 16 to 29) or more often as clinically indicated.

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 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 is determined by, and the responsibility of, the investigator.

Participants will measure FBG using the e-diary-linked, study-provided glucometer as described in Section 8.1.1.1. The median FBG for basal insulin dose adjustment is obtained from the 3 most recent FBGs in the previous week. The median is the middle value when the 3 values are placed in ascending or descending order. For example, if a participant's FBGs for the past week measurements were 132, 140, and 128, the median is 132. Investigators should also consider CGM data for basal insulin dose titration.

Note: If the participant has only 2 FBG readings for the week, then the lesser of the readings should be used to determine the dose adjustments. If only 1 FBG measurement is available, determination if dose is changed using only a single FBG value is at the discretion of the investigator.

#### 6.5.2.1. LY3209590 Dose Initiation and Modification

This section outlines LY3209590

- loading dose (Week 0)
- starting weekly dose (Week 1)
- weekly dose (Weeks 2 to 52)
- dose modification guidance based on hypoglycemia, and
- dose modification guidance based on FBG.

**Visit 3 (Week 0 – Randomization) loading dose**

At Visit 3 (Week 0), participants randomized to LY3209590 will start study basal insulin therapy.

The LY3209590 **loading dose** is administered at the site and is based on the participant's prior daily basal insulin dose and median FBG from the week prior to randomization (Visit 3 [Week 0]).

> **Note**: If the participant's prestudy basal insulin is **glargine U-300**, the prior daily basal insulin dose should be **reduced by 20%** when determining usual daily basal insulin dose.

For participants with **median FBG ≤ 140 mg/dL (7.8 mmol/L),** follow instructions in this table to calculate the LY3209590 Loading Dose.

| LY3209590 Loading Dose – Participants with Median **FBG ≤ 140 mg/dL (7.8 mmol/L)** | | |
|---|---|---|
| **Step** | **Action** | **Example Participant A FBG ≤ 140 mg/dL (7.8 mmol/L)** |
| 1 | Determine usual daily basal insulin dose from the lead-in period | 24 units/day |
| 2 | Calculate **Starting Weekly Dose** (daily basal dose multiplied by 7 and round to nearest 10) | 170 units/week |
| 3 | Multiply Starting Weekly Dose by 3 to determine the **Loading Dose** | 510 units Loading Dose |

For participants with FBG > 140 mg/dL (7.8 mmol/L), an incremental addition to the prior daily basal insulin dose was instituted to reduce transient hyperglycemia while LY3209590 achieves steady state.

For participants with **median FBG 141 to 160 mg/dL (>7.8 to 8.9 mmol/L),** the prior daily basal insulin dose should be increased by **10 to 20%.** Follow instructions in this table to calculate the LY3209590 Loading Dose.

| LY3209590 Loading Dose – Participants with Median **FBG 141 to 160 mg/dL (7.8 to 8.9 mmol/L)** | | |
|---|---|---|
| **Step** | **Action** | **Example Participant B FBG 141 to 160 mg/dL (>7.8 to 8.9 mmol/L)** |
| 1 | Determine usual daily basal insulin dose from the lead-in period | 24 units/day |
| 2 | Increase the usual daily basal insulin dose by **10 to 20%** to determine the adjusted daily basal dose | 26 units/day |
| 3 | Calculate **Starting Weekly Dose** (adjusted daily basal dose multiplied by 7 and round to nearest 10) | 180 units/week |
| 4 | Multiply Starting Weekly Dose by 3 to determine the **Loading Dose** | 540 units Loading Dose |

For participants with **median FBG >160 mg/dL (8.9 mmol/L),** the prior daily basal insulin dose should be increased by **20 to 30%.** Follow instructions in this table to calculate the LY3209590 Loading Dose.

| LY3209590 Loading Dose – Participants with Median **FBG >160 mg/dL (8.9 mmol/L)** | | |
|---|---|---|
| **Step** | **Action** | **Example Participant C FBG >160 mg/dL (>8.9 mmol/L)** |
| 1 | Determine usual daily basal insulin dose from the lead-in period | 24 units/day |
| 2 | Increase the usual daily basal insulin dose by **20 to 30%** to calculate the adjusted daily basal dose | 30 units/day |
| 3 | Calculate **Starting Weekly Dose** (adjusted daily basal dose multiplied by 7 and round to nearest 10) | 210 units/week |
| 4 | Multiply Starting Weekly Dose by 3 to determine the **Loading Dose** | 630 units Loading Dose |

**Visit 4 (Week 1) starting weekly dose**

The **Starting Weekly Dose** (Week 1) is administered at the site at Visit 4

If the participant experienced hypoglycemia in the previous week and met any of the criteria for a dose reduction as listed in the hypoglycemia dose reduction for LY3209590 table below, the Visit 4 starting weekly dose may be reduced by 10% or as clinically indicated.

CAUTION: Do NOT repeat administration of the loading dose.

**Visits 5 to 29 (Weeks 2 to 52) weekly dosing**

Titration of the study basal insulin LY3209590 dose should be made at weekly intervals from Weeks 0 to 12 (titration period, Visits 3 to 15), and then at a minimum of every 4 weeks from Weeks 12 to 52 (Visits 16 to 29) or more often as clinically indicated.

Assess hypoglycemia events over the previous week.

Reduce the LY3209590 dose if the participant meets criterion for hypoglycemia dose reduction according to this table.

| Hypoglycemia Dose Reduction Criteria | Decrease the LY3209590 Dose |
|---|---|
| 2 nocturnal hypoglycemia events ≤70 mg/dL[a] (3.9 mmol/L) | to previous lower dose[b] |
| 2 fasting hypoglycemia events ≤70 mg/dL[a] (3.9 mmol/L) | |
| 1 nocturnal and 1 fasting hypoglycemia event ≤70 mg/dL[a] (3.9 mmol/L) | |
| Any confirmed severe hypoglycemia | by 20 to 40 units or as clinically indicated |

[a] Investigator should use discretion to adjust for daytime hypoglycemia that is not attributed to prandial insulin.

[b] If there is no previous lower dose, then decrease basal insulin dose by 10% or as clinically indicated.

If the participant does not meet criteria for hypoglycemia dose reduction, determine the median fasting glucose and adjust the LY3209590 dose according to this table.

| LY3209590 Dose Adjustment | | | |
|---|---|---|---|
| **Median FBG (mg/dL)** | **Median FBG (mmol/L)** | **LY3209590 Dose <100 Units per Week** | **LY3209590 Dose ≥100 Units per Week** |
| <80 | <4.4 | Decrease to previous lower dose[a] | Decrease to previous lower dose[a] |
| 80-120 | 4.4-6.6 | No change | No change |
| 121-150 | 6.7-8.3 | Increase by 5 units | Increase by 10 units |
| 151-180 | 8.4-10.0 | Increase by 10 units | Increase by 20 units |
| >180 | >10.0 | Increase by 20 units | Increase by 30 units |

[a] If there is no previous lower dose, then decrease basal insulin dose by 10% or as clinically indicated.

### 6.5.2.2. Insulin Degludec Dose Initiation and Modification

This section outlines insulin degludec

- dose initiation at Visit 3 (Week 0)
- dose modification guidance based on hypoglycemia, and
- dose modification guidance based on FBG.

**Visit 3 (Week 0 – Randomization)**

At Visit 3 (Week 0), participants randomized to insulin degludec will start study basal insulin therapy.

The initial degludec dose may be unit-for-unit of the prior basal insulin regimen.

> **Note**: If the participant's prestudy basal insulin is **glargine U-300**, **reduce** the prior basal insulin dose by **20%**.

**Visits 4 to 29 (Weeks 1 to 52)**

Titration of the study basal insulin degludec dose should be made at weekly intervals from Weeks 0 to 12 (titration period, Visits 3 to 15), and then at a minimum of every 4 weeks from Weeks 12 to 52 (Visits 16 to 29) or more often as clinically indicated.

Assess hypoglycemia events over the previous week.

Reduce the insulin degludec dose if the participant meets criterion for hypoglycemia dose reduction according to this table.

| **Hypoglycemia Dose Reduction Criteria** | **Decrease the Insulin Degludec Dose** |
|---|---|
| 2 nocturnal hypoglycemia events ≤70 mg/dL[a] (3.9 mmol/L) | to previous lower dose[b] |
| 2 fasting hypoglycemia events ≤70 mg/dL[a] (3.9 mmol/L) | |
| 1 nocturnal and 1 fasting hypoglycemia event ≤70 mg/dL[a] (3.9 mmol/L) | |
| Any confirmed severe hypoglycemia | by 2 to 6 units or as clinically indicated |

[a] Investigator should use discretion to adjust for daytime hypoglycemia that is not attributed to prandial insulin.

[b] If there is no previous lower dose, then decrease basal insulin dose by 10% or as clinically indicated.

If the participant does not meet criteria for hypoglycemia dose reduction, determine the median fasting glucose and adjust the insulin degludec dose according to this table.

| **Insulin Degludec Dose Adjustment** | | | |
|---|---|---|---|
| **Median FBG (mg/dL)** | **Median FBG (mmol/L)** | **Degludec Dose <15 Units per Day** | **Degludec Dose ≥15 Units per Day** |
| <80 | <4.4 | Decrease to previous lower dose[a] | Decrease to previous lower dose[a] |
| 80-120 | 4.4-6.6 | No change | No change |
| 121-150 | 6.7-8.3 | Increase by 1 unit | Increase by 2 units |
| 151-180 | 8.4-10.0 | Increase by 2 units | Increase by 3 units |
| >180 | >10.0 | Increase by 3 units | Increase by 4 units |

[a] If there is no previous lower dose, then decrease basal insulin dose by 10% or as clinically indicated.

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

### 6.5.3. Prandial Insulin Therapy

During the lead-in period (Visits 2 to 3), participants will continue their prestudy basal and prandial insulin therapy.

During the treatment period (Visits 3 to 29), all participants will be treated with insulin lispro. The initial insulin lispro doses may be unit-for-unit of the prestudy prandial insulin regimen.

Prandial insulin is titrated based on glucose and hypoglycemia data from CGM and SMBG. Decreases to the prandial insulin dose may be made at any time during the study based upon the judgment of the investigator, for example, in response to hypoglycemia. The prandial insulin dose may be influenced by other clinical circumstances and safety considerations known to the investigator; thus, the prescribed prandial insulin dose during the study is determined by, and the responsibility of, the investigator.

The investigator, in consultation with the participant, will determine the prandial dosing plan to use during the study. The following prandial dosing plans may be considered:

- 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.

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, SMBG, and hypoglycemia data at clinic and telephone visits and as clinically indicated. Twenty-four-hour glucose profiles, including premeal glucose and postprandial glucose levels, from CGM can be evaluated.

For participants who are using the **fixed-dose plan**: the prandial insulin dose, and correction factor if applicable, should be reviewed and adjusted by the investigator, in discussion with the patient, based on CGM, SMBG, and hypoglycemia data at clinic and telephone visits and as clinically indicated. Twenty-four-hour glucose profiles, including premeal glucose and postprandial glucose levels, from CGM can be evaluated.

In the fixed-dose plan, assessment of the prandial insulin dose may include review of the pattern of CGM glucose levels from the previous week or as clinically indicated 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 values from the previous week pre-mid-day meal.*

| **Prandial Insulin Dose Assessed** | **Corresponding CGM Glucose for Review** |
|---|---|
| Fasting or morning premeal | Pre-midday meal glucose values |
| Midday premeal | Pre-evening meal glucose values |
| Evening premeal | Bedtime glucose values |

Abbreviation: CGM = continuous glucose monitoring.

The pattern of CGM glucose values from the premeal or bedtime is used as the "adjustment value" and the change in dose, either increase or decrease, is based upon this value as described in the table below.

| **If Meal Time Dose of Insulin Lispro is** | **Pattern of CGM Glucose Below Target Range** | **Pattern of CGM Glucose at Target Range** | **Pattern of CGM Glucose Above Target Range** |
|---|---|---|---|
| ≤10 units | Decrease by 1 unit | No change | Increase by 1 unit |
| 11-19 units | Decrease by 1-2 units | No change | Increase by 1-2 units |
| ≥20 units | Decrease by 2-3 units | No change | Increase by 2-3 units |

Source: Adapted from Bergenstal et al. 2008.

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, 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. Continued Access to Study Intervention after the End of the Study

The sponsor will not provide participants with ongoing supplies of study intervention after they have completed the study treatment period or permanently discontinued the study intervention.

### 6.6.1. Transitioning off of Study Basal Insulin

At the last treatment visit (Visit 29 [Week 52] or ET visit), the investigator will prescribe a non-study basal insulin for use during the safety follow-up period.

The investigator, in consultation with the participant, will decide on prandial insulin therapy for use during the safety follow-up period.

**Study participants treated with LY3209590**

Participants will administer their last dose of LY3209590 at Week 51 of the study and can begin the transition to the non-study insulins after Visit 29 (Week 52). At Visit 29 (Week 52), the investigator will review instructions for transitioning to the non-study insulins with the participant. The non-study daily basal insulin treatment should be started slowly and under regular review of glucose profiles after discontinuation of LY3209590.

Since LY3209590 has a half-life of approximately 17 days, a slow up-titration of the non-study daily basal insulin is necessary to prevent hypoglycemia due to overlapping insulin action. Non-study basal insulin would not be required until the study participant's fasting glucose is above 100 mg/dL (5.5 mmol/L), and then daily basal insulin would be initiated and adjusted based on fasting glucose, CGM profile, and hypoglycemia evaluation. The investigator should consider titration of the non-study basal insulin to reach 50% of the required daily basal insulin dose at approximately 2 weeks and 80% of the required daily basal insulin dose at approximately 4 weeks. An unscheduled visit in addition to Visit 801 may occur during this time to facilitate the transition to non-study daily basal insulin.

**Study participants treated with insulin degludec**

Participants assigned to the insulin degludec treatment arm will transition to their non-study basal insulin after Visit 29 (Week 52) with dose adjustment per investigator discretion based on fasting glucose, CGM profile, and hypoglycemia evaluation and in accordance with the local product label for the basal insulin.

## 6.7. Treatment of Overdose

Study intervention overdose, dangerously large amount of insulin compared to the protocol-prescribed dose, will be reported as per Section 10.3.1. In the event of an overdose, refer to the IB for LY3209590 or product label for insulin degludec depending on the participant treatment assignment.

In the event of an overdose, the investigator/treating physician should

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect
- Obtain a plasma sample for PK analysis if the participant is assigned to LY3209590.

## 6.8. Concomitant Therapy

**Concomitant therapy regimens**

All participants should maintain their usual medication regimens for concomitant conditions or diseases throughout the study, unless those medications are specifically excluded in the protocol (Section 5.2).

**Changing concomitant therapy**

Participants should consult with authorized study personnel before taking any new medications during the study, except when initiated for treatment of medical emergencies. Authorized study personnel should consult the sponsor's medical monitor if there are any questions about concomitant therapies during the study.

**Concomitant therapy data collection**

For therapy that the participant is receiving at the time of enrollment or receives during the study, including over-the-counter medications, authorized study personnel should collect

- the name of medication, vaccine, or therapy
- the reason for use, and
- dates of administration, including start and end dates.

Non-study medications taken by study participants who have signed informed consent, but are not randomized to study insulin, will not be reported unless an SAE or AE occurs that the investigator believes may have been caused by a study procedure.

**Excluded concomitant medications**

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

  **Exception:** Short-term use of non-study insulins is permissible as outlined in Section 7.1.3.

  Note: Participants who require treatment with non-study basal insulins as rescue therapy for management of severe or persistent hyperglycemia as outlined in Section 6.1.3., must discontinue study basal insulin therapy (LY3209590 or insulin degludec). The participant will remain in the study and follow procedures for the remaining study visits.

- chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy excluding topical, intraocular, intranasal, inhaled, or intraarticular preparations, and
- weight loss drugs, for example, prescription drugs: glucagon-like peptide-1 (GLP-1) receptor agonists, lorcaserin, orlistat, phentermine, phentermine and topiramate combination, naltrexone and bupropion combination, or over-the-counter weight loss medications.

# 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

## 7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from LY3209590 or insulin degludec. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA.

Participants who stop LY3209590 or insulin degludec permanently will receive another non-study basal insulin (see Section 6.6.1). The new insulin will be recorded on the CRF.

A participant should be permanently discontinued from LY3209590 or insulin degludec if

- the participant becomes pregnant during the study
- the participant requests to discontinue intervention
- the participant is diagnosed with an active or untreated malignancy, except for successfully treated basal or squamous cell skin carcinoma
- the participant has not taken insulin degludec for more than 21 consecutive days or missed more than 3 consecutive doses of LY3209590, or
- in the opinion of the investigator, the participant should permanently discontinue LY3209590 or insulin degludec for safety reasons.

### 7.1.1. Liver Chemistry Stopping Criteria

The study intervention should be interrupted or discontinued if 1 or more of these conditions occur.

| Elevation | Exception |
|---|---|
| ALT or AST >8x ULN | |
| ALT or AST >5x ULN for more than 2 weeks | |
| ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5 | In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for intervention interruption or discontinuation decisions rather than TBL >2x ULN. |
| ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) | |
| ALP >3x ULN, when the source of increased ALP is the liver | |
| ALP >2.5x ULN and TBL > 2x ULN | In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for intervention interruption or discontinuation decisions rather than TBL >2x ULN. |

| | |
|---|---|
| ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) | |

Resumption of the study intervention can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited, non-intervention etiology is identified.

### 7.1.2. Hypersensitivity Reactions

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be **permanently discontinued** from the study intervention, and the sponsor's designated medical monitor should be notified.

If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

### 7.1.3. Temporary Discontinuation of LY3209590 or Insulin Degludec

**Criteria for temporary discontinuation of LY3209590 or insulin degludec**

The investigator may temporarily interrupt study treatment, due to an AE, clinically significant laboratory value, hospital visits, travel, or shortage of study treatment supply.

This will be allowed for up to 3 consecutive weeks for degludec or 3 consecutive doses for LY3209590. During this time, non-study insulins may have been used. This information should be documented by the investigator.

**Guidance when temporary discontinuation of LY3209590 or insulin degludec occurs**

Every effort should be made by the investigator to maintain participants in the study and to restart LY3209590 or insulin degludec promptly, as soon as it is safe to do so.

Participants will continue their study visits and follow up according to the SoA.

Participants should resume the dose prescribed before the temporary dosing interruption at the discretion of the investigator.

**Recording temporary discontinuation of LY3209590 or insulin degludec**

The dates of LY3209590 or insulin degludec interruption and restart must be documented in source documents and entered on the CRF.

Participant noncompliance should not be recorded as interruption of LY3209590 or insulin degludec on the CRF.

## 7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent, and
- if a study participant is diagnosed with any type of diabetes mellitus other than T1D.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA.

If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

## 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 or designee 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.

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

Efficacy will be measured by

- HbA1c
- time in range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, and
- patient-reported outcomes questionnaires
    - Diabetes Treatment Satisfaction Questionnaire - Status
    - Diabetes Treatment Satisfaction Questionnaire - Change
    - SF-36v2 acute form
    - EQ-5D-5L
    - Basal Insulin Experience: Preference, and
    - Basal Insulin Experience: Likelihood of incorporating into routine.

See Section 3 for specific efficacy endpoints.

This section will outline glucose monitoring and patient-reported outcome measures.

### 8.1.1. Glucose Monitoring

Participants **must** use only the study-provided glucose monitors during the study.

#### 8.1.1.1. Self-Monitoring of Blood Glucose (SMBG)

**Glucometer for participant use during the study**

Participants will receive a study-approved glucometer and related testing supplies for use during the study.

Site personnel will train the participant on correct use of the glucometer for self-monitoring blood glucose and reporting of hypoglycemia data in the e-diary.

***Fasting blood glucose (FBG) measurement***

The FBG should be measured upon waking in the morning, prior to food or caloric beverage intake.

This table describes when participants will measure their FBG using the study-provided glucometer.

| **The participant must measure their FBG during…** | **At a frequency of…** |
|---|---|
| Weeks -1 to 0<br>Visits 2 to 3 | 3 days per week |
| Weeks 0 to 12<br>Visits 3 to 15 | |
| the week prior to<br>Weeks 16, 20, 24, 26, 28, 32, 36, 40, 44, 48, and 52<br>Visits 17, 19, 21, 22, 23, 24, 25, 26, 27, 28, and 29 | |

Additional FBG and SMBG measurements can be obtained as clinically indicated.

**SMBG for suspected hypoglycemia**

Participants will be advised to check SMBG readings when they experience signs and symptoms of hypoglycemia and for CGM glucose < 70 mg/dL (3.9 mmol/L) prior to treatment with carbohydrates (if the participants can safely do this).

The participant's SMBG readings and hypoglycemia events in conjunction with CGM data will be used to determine insulin dosing during the study (Section 6.5).

**Glucometer data transfer**

The study-provided glucometer will wirelessly transmit blood glucose measurements to the participant's e-diary. Site personnel will be able to view SMBG data that have been transmitted to the e-diary through a web-based portal as well as any reported events of hypoglycemia.

#### 8.1.1.2. Continuous Glucose Monitoring (CGM) System

The unblinded Dexcom G6® CGM system will be used continuously throughout the stud y to facilitate diabetes management and for data collection. The Dexcom G6 CGM system includes the sensor, transmitter, and receiver.

**Training and initiation**

At Visit 2, participants will receive the study supplied CGM system and training on its use and study requirements. The sensor can be worn for up to 10 days. Participants will be instructed to change the sensor and transmitter before they expire according to the product label information and to keep the transmitter within 20 feet (6 meters) of the receiver during use. Study participants will use the receiver to review CGM data during the study. A CGM participant user

guide that provides an overview of device components and study-specific instructions will be available for at-home use.

Site personnel will download the CGM data from the receiver to a vendor online portal where data can be reviewed as per the SoA and as clinically indicated.

**Notes:**

- Participants are not allowed to connect the transmitter of the study supplied Dexcom G6 system to a personal smartphone, smartphone application, or other system.
- The sensor code must be entered into the CGM receiver. Participants are not allowed to manually calibrate the study CGM with fingerstick blood glucose readings.
- Participants may not use their own personal CGM device.

In the CGM receiver, a hypoglycemia alert at 70 mg/dL (3.9 mmol/L) will be required. Participants will be advised to check SMBG readings when they experience signs and symptoms of hypoglycemia and for CGM glucose <70 mg/dL (3.9 mmol/L) prior to treatment with carbohydrates (if the participant can safely do this).

**CGM data compliance**

Sites will be required to review data capture compliance following CGM data downloads using the available vendor portal reports and visualization tools. A compliance threshold of 80% will be used to assess minimum CGM data capture requirements are met and is defined as the percentage of actual data versus expected data collected in between data downloads. Site personnel will re-educate participants on CGM requirements when download compliance is <80%.

To minimize data loss, the CGM service vendor will review site downloads and notify site users when sessions do not meet the compliance threshold. CGM compliance reports will also be provided to the sponsor and site monitors during the study for review and to determine if further mitigation is necessary.

### 8.1.2. Patient-Reported Outcomes

The self-administered questionnaires will be translated into the native language of the region and administered at the site during the designated visits in the SoA (Section 1.3).

**Order of administering the questionnaires during the visit**

The questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator or study personnel, if the participant is not adversely affected by their fasting condition.

The order of administration of these questionnaires, where applicable, is

- Diabetes Treatment Satisfaction Questionnaire - Status
- Diabetes Treatment Satisfaction Questionnaire - Change
- SF-36v2 acute form
- EQ-5D-5L
- Basal Insulin Experience: Preference, and
- Basal Insulin Experience: Likelihood of incorporating into routine.

#### 8.1.2.1. Diabetes Treatment Satisfaction Questionnaire – Status

The Diabetes Treatment Satisfaction Questionnaire-Status Version (Bradley and Lewis 1990; Bradley 1994) is a diabetes-specific patient-reported outcome instrument that assesses the overall treatment satisfaction and perceived frequency of hyperglycemia and hypoglycemia. It is appropriate for use in both T1D and T2D.

The Diabetes Treatment Satisfaction Questionnaire-Status Version consists of 8 items that assess treatment satisfaction as well as concerns about hyperglycemia and hypoglycemia over the past few weeks, prior to the visit.

Each item is rated on a 7-point Likert scale. Items 1, 4, 5 to 7, and 8 are rated from 0 (very dissatisfied) to 6 (very satisfied) and can be summed up to produce a treatment satisfaction score. Items 2 and 3 evaluate the perceived frequency of hyperglycemia and hypoglycemia and are rated from 0 (none of the time) to 6 (most of the time).

#### 8.1.2.2. Diabetes Treatment Satisfaction Questionnaire – Change

The Diabetes Treatment Satisfaction Questionnaire-Change Version (Bradley 1999) was designed to overcome potential ceiling effects in the status version. The Diabetes Treatment Satisfaction Questionnaire-Change Version has the same 8 items as the status version but is reworded slightly to measure the change in treatment satisfaction rather than absolute treatment satisfaction.

Each item is scored on a scale of -3 to +3. For all items except Item 2 (perceived frequency of hyperglycemia) and Item 3 (perceived frequency of hypoglycemia):

- the higher the score, the greater the improvement in treatment satisfaction
- the lower the score, the greater the deterioration in treatment satisfaction, and
- a score of 0 represents no change.

For Items 2 and 3: the lower the score, the better the perception.

#### 8.1.2.3. Short Form-36 Version 2 Health Survey Acute Form

**Description of SF-36v2**

The SF-36 v2 Health Survey Acute form is a participant self-administered measure designed to assess these 8 domains

- Physical Functioning
- Role Physical
- Bodily Pain
- General Health
- Vitality
- Social Functioning
- Role Emotional, and
- Mental Health.

The Physical Functioning domain assesses limitations due to health "now" while the remaining domains assess functioning "in the past week." Participants answer each item using Likert 3-point, 5-point, or 6-point scales for the responses.

**Scoring**

Each domain is scored individually and information from these 8 domains is further aggregated into 2 health component summary scores, the Physical Component Summary and Mental Component Summary.

Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10.

Higher scores indicate better levels of function and/or better health (Maruish 2011).

#### 8.1.2.4. EQ-5D-5L

**Description of EQ-5D-5L**

The EQ-5D-5L (EuroQol Research Foundation 2019) is a standardized, 5-item, self-administered instrument for use as a measure of health outcome. It provides a simple, descriptive health profile and a single health state index value that can be used in the clinical and economic evaluation of health care as well as population health surveys.

The EQ-5D-5L assesses 5 dimensions of health

- mobility
- self-care
- usual activities
- pain/discomfort, and
- anxiety/depression.

The 5L version scores each dimension at 5 levels

- no problems
- slight problems
- moderate problems
- severe problems, and
- unable to perform/extreme problems.

A total of 3125 health states is possible.

**Scoring**

The scores on the 5 dimensions can be presented as a health profile or converted to a single health state index value.

The single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 to 1, where negative values are valued as worse than dead, 0 is a health state equivalent to death, and 1 represents perfect health.

***EQ Visual Analog Scale***

The EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated visual analog scale from 0 to 100, where 0 represents the worst imaginable health and 100 represents the best imaginable health.

In conjunction with the health state data, this provides a composite picture of the respondent's health status.

#### 8.1.2.5. Basal Insulin Experience: Preference

The Basal Insulin Experience: preference is a self-report scale consisting of a single question to understand the participant's preference for their pre-study or current study treatment.

The question is rated on a 5-point scale with responses ranging from "strongly prefer the study insulin" to "strongly prefer my previous insulin." The question also includes a "not applicable" option for participants that stayed on the same insulin in the treatment phase.

#### 8.1.2.6. Basal Insulin Experience: Likelihood of Incorporating into Routine

**Description of questionnaire**

The Basal Insulin Experience: Likelihood of incorporating into routine is a self-reported scale consisting of a single question to understand the participant's likelihood of incorporating their study insulin into their diabetes management routine.

**Scoring**

The question is rated on a 5-point scale with responses ranging from "very unlikely" to "very likely."

## 8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1. Physical Examinations

**Physical examination at screening**

The complete physical examination will include, at a minimum, assessments of these systems

- cardiovascular
- respiratory
- gastrointestinal, and
- neurologic.

Height and weight will be measured and recorded.

Additional assessments include clinical signs and symptoms related to T1D, T1D-related illnesses, and injection site reactions.

### 8.2.2. Vital Signs

Blood pressure and pulse rate will be measured when specified in the SoA and as clinically indicated. Additional vital signs may be measured during study visits if warranted, as determined by the investigator.

### 8.2.3. Electrocardiograms

Local and single 12-lead ECG will be obtained as outlined in the SoA.

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

The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document their review of the ECG printed at the time of evaluation.

### 8.2.4. Clinical Safety Laboratory Tests

See 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 results, document this review, and report any clinically relevant changes occurring during the study as an AE.

The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

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 or within 5 weeks after the last dose of intervention 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 Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated 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 report the information as an AE.

### 8.2.5. Hepatic Monitoring

**Close hepatic monitoring**

***Initiating laboratory and clinical monitoring for abnormal liver laboratory test results***

Laboratory tests, including ALT, AST, ALP, TBL, direct bilirubin, GGT, 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. This table shows when to repeat laboratory tests.

| 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 ≥1.5x baseline (except for participants with Gilbert's syndrome) |

***What to do if the abnormal condition persists or worsens***

If the abnormal liver test result persists or worsens, 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

1. symptoms
2. recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
3. recent travel
4. history of concomitant medications, including over-the-counter, herbal and dietary supplements, and
5. history of alcohol drinking and other substance abuse.

***Frequency of monitoring***

Initially, monitoring of symptoms and liver tests should be done 1 to 3 times weekly, based on the participant's clinical condition and liver test results.

Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize.

Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

**Comprehensive hepatic evaluation**

***When to perform a comprehensive evaluation***

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in this table 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 or symptoms[a], or<br>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 or symptoms[a], or<br>ALT or AST ≥3x baseline |
| ALP ≥1.5x ULN | ALP ≥2x baseline |
| TBL ≥1.5x ULN | TBL ≥2x baseline (except for participants with Gilbert's syndrome) |

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

***What a comprehensive evaluation should include***

At a minimum, this evaluation should include

- physical examination and a thorough medical history, as outlined above
- tests for
    - PT-INR
    - viral hepatitis A, B, C, or E, and
    - autoimmune hepatitis, and
- an abdominal imaging study, for example, ultrasound or computed tomography scan.

Based on the patient'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
- blood 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 (hepatic safety CRF) in study participants who have abnormal liver tests during the study**

Collect additional hepatic safety data collection in the hepatic safety CRFs if a participant

- develops a hepatic event considered to be an SAE, or
- discontinues study intervention due to a hepatic event, or
- has changes in laboratory results described in this table.

| If a participant with baseline results of... | develops the following elevations… | Then… |
|---|---|---|
| **Elevated serum ALT** | | Collect additional hepatic safety data in the hepatic safety CRF. |
| ALT <1.5x ULN | ALT to ≥5x ULN on 2 or more consecutive blood tests | |
| ALT ≥1.5x ULN | ALT ≥3x baseline on 2 or more consecutive blood tests | |
| **Elevated TBL** | | |
| TBL <1.5x ULN | TBL ≥2x ULN (except for participants with Gilbert's syndrome) | |
| TBL ≥1.5x ULN | TBL ≥2x baseline | |
| **Elevated ALP** | | |
| ALP <1.5x ULN | ALP ≥2x ULN on 2 or more consecutive blood tests | |
| ALP ≥1.5x ULN | ALP to ≥2x baseline on 2 or more consecutive blood tests | |

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

See Section 10.5 for hepatic laboratory tests.

### 8.2.6. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected as outlined in Sections 8.3.1 and 8.3.2.

## 8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

These 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 these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial 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).

For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3.

### 8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-Up Method of Reporting |
|---|---|---|---|---|---|
| **Adverse Event** | | | | | |
| AE | Signing of the informed consent form (ICF) | The last safety follow-up visit | As soon as possible upon site awareness | AE CRF | N/A |
| **Serious Adverse Event** | | | | | |
| SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures | Signing of the ICF | Start of intervention | Within 24 hours of awareness | SAE CRF | SAE paper form |
| SAE and SAE updates – after start of study intervention | Start of intervention | The last safety follow-up visit | Within 24 hours of awareness | SAE CRF | SAE paper form |

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-Up Method of Reporting |
|---|---|---|---|---|---|
| SAE[a] – after participant's study participation has ended **and** the investigator becomes aware | After participant's study participation has ended | N/A | Promptly | SAE paper form | N/A |
| **Pregnancy** | | | | | |
| Pregnancy in female participants and female partners of male participants | After the start of study intervention | 90 days after the last dose | Within 24 hours (see Section 8.3.2) | Pregnancy paper form | Pregnancy paper form |
| **Product Complaints** | | | | | |
| PC associated with an SAE or might have led to an SAE | Start of study intervention | End of study intervention | Within 24 hours of awareness | Product Complaint form | N/A |
| PC not associated with an SAE | Start of study intervention | End of study intervention | Within 1 business day of awareness | Product Complaint form | N/A |
| Updated PC information | — | — | As soon as possible upon site awareness | Originally completed Product Complaint form with all changes signed and dated by the investigator | N/A |
| PC (if investigator becomes aware) | Participation in study has ended | N/A | Promptly | Product Complaint form | |

[a] Serious adverse events should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

### 8.3.2. Pregnancy

**Collection of pregnancy information**

***Male participants with partners who become pregnant***

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

After learning of a pregnancy in the female partner of a study participant, the investigator will obtain a consent to release information from the pregnant female partner directly, and within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

***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 post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. 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 discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

### 8.3.3. Cardiovascular Events

A blinded external Clinical Event Committee will adjudicate potential cerebrocardiovascular events in a consistent and unbiased manner.

Events include

- death
- myocardial infarction
- coronary revascularization procedure
- hospitalization for unstable angina
- hospitalization for heart failure, and
- stroke or transient ischemic attack.

### 8.3.4. Systemic Hypersensitivity Reactions

Many drugs, including biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

### 8.3.5. Injection Site Reactions

Symptoms and signs of a local injection site reaction may include erythema, induration, pain, pruritus, and edema.

If an injection site reaction is reported by a participant or study personnel, additional information about this reaction will be collected in the CRF.

### 8.3.6. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia. Hypoglycemia events entered into the participant e-diary will be available for review through a web-based portal that can be accessed by designated investigative site personnel at any time. CGM data will be available for site personnel to download and review through a web-based portal.

**Hypoglycemia classification and definitions**

***Level 1***

Glucose <70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L)

Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

***Level 2***

Glucose <54 mg/dL (3.0 mmol/L)

Level 2 hypoglycemia is also referred to as documented or blood glucose-confirmed hypoglycemia. The glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

***Level 3 Severe***

A severe hypoglycemic event is characterized by altered mental or physical status requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions for the treatment of hypoglycemia.

The determination of an episode of severe hypoglycemia 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.

Examples of severe hypoglycemia in adults are

- altered mental status and the inability to assist in their own care
- semiconscious or unconscious, or
- coma with or without seizures.

Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

***Nocturnal hypoglycemia***

Nocturnal hypoglycemia is a hypoglycemia event, including severe hypoglycemia, that occurs at night and presumably during sleep between midnight and 0600 (6:00 am).

**Reporting of severe hypoglycemic events**

If a hypoglycemic event meets the criteria of severe, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

The investigator should also determine if repeated or prolonged episodes of hypoglycemia occurred prior to the severe event.

## 8.4. Pharmacokinetics

At the visits and times specified in the SOA, blood samples will be collected for all participants. Only samples from participants assigned to treatment with LY3209590 will be analyzed for drug concentration.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

The actual date and time (24-hour clock time) of each sampling will be recorded.

**Bioanalytical**

Samples will be analyzed at a laboratory designated by the sponsor and stored at a facility designated by the sponsor. Concentrations of LY3209590 will be assayed using a validated bioanalytical method.

Sample retention is described in Section 10.1.12.

## 8.5. Pharmacodynamics

Pharmacodynamic parameters are described in Section 8.1.

## 8.6. Genetics

Genetics are not evaluated in this study.

## 8.7. Biomarkers

Serum and plasma samples will be used for exploratory biomarker research, where local regulations allow. See Clinical Laboratory Tests, and the SoA for sample collection information.

Samples will be used for research on the drug target, disease process, variable response to LY3209590 pathways associated with T1D, mechanisms of action of LY3209590 or research methods, or in validating diagnostic tools or assay(s) related to T1D.

Samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to the intervention target, disease state, pathways associated with disease, and/or the mechanism of action of the study intervention.

Sample retention is described in Section 10.1.12.

## 8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples from all study participants will be collected for analysis to determine antibody production against LY3209590. Antibodies may be further characterized for cross-reactive binding to endogenous insulin.

To interpret the results of immunogenicity, a corresponding venous blood sample will be collected at the same visits to determine the concentrations of LY3209590 (PK sample). At Visit 3, the sample for immunogenicity should be taken before dosing and the PK sample for LY3209590 after dosing.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

Treatment-emergent ADAs are defined in Section 9.3.6.2.

Immunogenicity will be assessed by a validated assay designed to detect and characterize ADA in the presence of LY3209590 at a laboratory approved by the sponsor.

Sample retention is described in Section 10.1.12.

## 8.9. Health Economics

Health economics parameters are not evaluated in this study.

# 9. Statistical Considerations

The first version of the SAP will be finalized prior to first participant 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.

## 9.1. Statistical Hypotheses

**Primary hypothesis**

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control as measured by change in HbA1c from baseline to Week 26 (Visit 22) in adults with T1D currently on basal-bolus insulin.

The null hypothesis ($H_0$) is the difference between LY3209590 and insulin degludec in the change in HbA1c from baseline to Week 26 (Visit 22) is greater than the NIM.

The NIMs of 0.4% and 0.3% will both be tested to meet different regulatory requirements. The 2-sided 95% CI will be used for testing the noninferiority.

**Secondary hypotheses**

The key secondary (multiplicity adjusted) objectives are to test the hypotheses that LY3209590 is superior to insulin degludec with respect to

- change in HbA1c from baseline to Week 26 (Visit 22)

  $H_0$: the difference (LY3209590 – insulin degludec) ≥ 0.0

- time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM 4 weeks prior to Week 26 (Visit 22)

  $H_0$: the difference (LY3209590 – insulin degludec) ≤ 0.0

- the event rate of nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment period up to Week 52 (Visit 29)

  $H_0$: the relative event rate (LY3209590 vs. insulin degludec) ≥ 1

These hypotheses and the primary hypothesis will be tested using a strategy to control the overall Type I error (see Section 9.1.1).

### 9.1.1. Multiplicity Adjustment

A graphical approach (Bretz et al. 2009, 2011) for multiple comparisons will be used to ensure the strong control of overall Type I error rate for testing the primary and key secondary (multiplicity adjusted) objectives.

The overall significance level (α) will be set to 0.05. The total α will be used for the primary objective first, then the α will be allocated and transitioned to key secondary objectives once the primary objective is met. The testing procedure and α allocation will be established according to the clinical importance and statistical power of the endpoints in this study population.

The details of graphical testing scheme will be described in the SAP.

## 9.2. Analyses Sets

For the purposes of analysis, this table defines the analysis sets for this study.

| Analysis Populations/Sets | Description |
|---|---|
| Entered population | All participants who sign the informed consent form. |
| Randomized population | All randomized participants. Participants will be analyzed according to the treatment they were assigned. |
| Modified Intent-to-Treat (mITT) Population | All randomized participants who took at least 1 dose of LY3209590 or insulin degludec. Participants will be analyzed according to the treatment they were assigned. |
| Efficacy Analysis Set 1 (EAS1) for treatment regimen estimand | The data will include<br>• mITT Population excluding participants discontinuing the study treatment due to inadvertent enrollment<br>• all measurements regardless of the use of study treatment or rescue medications |
| Efficacy Analysis Set 2 (EAS2) for efficacy estimand | The data will include<br>• mITT Population excluding participants discontinuing the study treatment due to inadvertent enrollment<br>• measurement up to discontinuation of study treatment or the initiation of rescue medication |
| Safety Analysis Set (SS) | The data will include<br>• mITT Population<br>• all measurements regardless of the use of study treatment or rescue medications |

## 9.3. Statistical Analyses

### 9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designees.

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 changes to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the clinical study report. Additional exploratory analyses of data will be conducted as deemed appropriate.

Unless otherwise stated, the efficacy analyses will be conducted on either EAS1 or EAS2, and the safety analysis will be conducted on the SS. All tests of treatment effects using statistical models will be conducted at a 2-sided alpha level of 0.05 and 2-sided 95% CI will be provided.

Unless otherwise stated, the other secondary and tertiary efficacy measures will be analyzed on EAS2 using the data up to the discontinuation of LY3209590 or insulin degludec, defined by the date of last study dose +10 days or the initiation of rescue medication whichever is earlier.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

### 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

The primary objective is to compare the HbA1c change from baseline to Week 26 (Visit 22) between LY3209590 and insulin degludec and will be based on either of the 2 estimands

***treatment regimen estimand*** for the US FDA submission, and

***efficacy estimand*** for registrations in other countries as defined in Section 3 of this protocol.

**Treatment regimen estimand**

The treatment regimen estimand will be estimated using the HbA1c data at baseline and Week 26 (Visit 22) from the EAS1 regardless of the use of LY3209590 or insulin degludec or rescue medication.

***Missing measures***

The missing measures at the primary endpoint will be imputed using multiple imputation by the retrieved dropout approach. The retrieved dropout participants are those who discontinue LY3209590 or insulin degludec prior to Week 26 (Visit 22) but have non-missing measures at Week 26 (Visit 22).

If there are only a limited number of retrieved participants that leads to a failure in performing the multiple imputation analysis, such as the model cannot converge, or the number of retrieved dropout participants is small, the missing HbA1c at Week 26 (Visit 22) will be imputed by return-to-baseline multiple imputations.

*Analysis model*

After the imputation, the observed and imputed data will be analyzed by the ANCOVA.

The model will include treatment, strata (country, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), and baseline value of the dependent variable (HbA1c). The statistical inference will be based on the multiple imputation framework by Rubin (1987).

**Efficacy estimand**

The efficacy estimand is the treatment differences in the change in HbA1c from baseline to Week 26 (Visit 22) if all participants would adhere to the treatment without intercurrent events.

The HbA1c collected at all planned postbaseline visits from the EAS2 will be used in the analysis.

***Missing measures***

There may be missing values due to the early discontinuation of LY3209590 or insulin degludec or use of rescue medication. The MMRM model will be used, and the missing values will be handled implicitly in the MMRM analysis under the assumption of missing at random.

*Analysis model*

The MMRM model will include treatment, strata (country, CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), visit and treatment-by-visit interaction as fixed effects, and baseline of the dependent variable (HbA1c) as a covariate.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for the MMRM models. An unstructured covariance structure will be used to model the within-participant errors. If this structure fails to converge, the following covariance structures will be used in order until one converges:

1. Toeplitz with heterogeneity
2. autoregressive with heterogeneity
3. compound symmetry with heterogeneous variances
4. Toeplitz
5. autoregressive, and
6. compound symmetry without heterogeneous variances.

The 2-sided 95% CI of the LS mean for individual treatment groups and treatment LS mean difference for the HbA1c change from baseline to Week 26 (Visit 22) will be estimated. For both estimands, LY3209590 will be declared noninferior to insulin degludec if the upper limit of the 2-sided 95% CI for the LS mean difference in the HbA1c change from baseline is below NIM (+0.4% or +0.3% for different regulatory requirements).

The HbA1c is reported in % units and will be converted to mmol/mol using this formula.

> HbA1c in mmol/mol = 10.93 × HbA1c in % - 23.5 (NGSP IFCC Standardization of HbA1c page [www.ngsp.org/ifccngsp.asp]).

### 9.3.3. Secondary Endpoints Analysis

#### 9.3.3.1. Multiplicity Adjusted Endpoints

A graphical approach will be used to control the overall Type I error for the primary objective and testing the superiority of LY3209590 compared with insulin degludec for

- change in HbA1c from baseline to Week 26 (Visit 22)
- time in normal glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive, measured by CGM 4 weeks prior to Week 26 (Visit 22), and
- event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 52 (Visit 29).

The superiority test in change from baseline to Week 26 (Visit 22) in HbA1c will be based on the same primary endpoint analysis methods as described above.

The rate of nocturnal hypoglycemia will be analyzed by a negative binomial regression with treatment, baseline HbA1c, baseline incidence of nocturnal hypoglycemia, and carbohydrate counting for prandial insulin dosing (yes/no) as independent variables, and log (exposure in year) as the offset.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM will be analyzed using an ANCOVA model for treatment regimen estimand (using data from EAS1) and an MMRM model for efficacy estimand (using data from EAS2).

In the ANCOVA model, treatment, strata (country, baseline HbA1c stratum [<8.0%, ≥8.0%], CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), and baseline of the dependent variable will be used.

The MMRM model will include treatment, strata (country, baseline HbA1c stratum [<8.0%, ≥8.0%], CGM use prior to study entry [yes/no], and carbohydrate counting for prandial insulin dosing [yes/no]), visit and treatment-by-visit interaction as fixed effects, and baseline of the dependent variable as a covariate.

For treatment regimen estimand, the missing data will be imputed by multiple imputation with the approach similar to the imputation used for the primary endpoint.

#### 9.3.3.2. Other Secondary Endpoints

Other secondary endpoints include various measures for efficacy, safety, and patient-reported outcome questionnaires.

Efficacy measures and patient-reported questionnaires will be analyzed using the EAS2 unless otherwise noted.

Safety measures will be analyzed using the SS regardless of LY3209590 or insulin degludec discontinuation and use of rescue medications.

Analysis details will be provided in the SAP.

### 9.3.4. Tertiary Endpoints Analysis

Refer to the SAP for analyses related to tertiary endpoints.

### 9.3.5. Safety Analyses

Safety measures include

- treatment exposure
- AE
- vital signs
- weight
- hypoglycemia
- laboratory measures and
- immunogenicity.

All safety analyses will be based on the SS.

Events that are newly reported after the first dose of LY3209590 or insulin degludec or reported to worsen in severity from baseline will be considered TEAEs. The Medical Dictionary for Regulatory Activities lowest level term will be used in the treatment-emergent assessment. The maximum severity for each lowest level term during the baseline period will be used as baseline severity.

Summary statistics will be provided for incidence of

- TEAEs
- SAEs

- study discontinuation due to AEs
- intervention discontinuation due to AEs, and
- deaths.

For continuous safety variables, such as laboratory measures, vital signs, and weight, the MMRM or ANCOVA models will be used.

For categorical safety variables, such as AEs, incidence of hypoglycemia, treatment-emergent abnormal laboratory measurements, either the Fisher's exact test or logistic regression will be used for treatment comparison.

**Hypoglycemia analysis**

The participant-reported hypoglycemia will be analyzed using data from the e-diary by

- Level 1 (defined by glucose value ≥ 54 to < 70 mg/dL [3.0 to 3.9 mmol/L])
- Level 2 (defined by glucose < 54 mg/dL [3.0 mmol/L])
- Level 3 (severe hypoglycemia), and
- the composite of Levels 2 and 3.

The analysis periods of 0 to 6, 0 to 12, 0 to 26, 0 to 52, 12 to 26, and 26 to 52 weeks of treatment will be considered. Documented hypoglycemia will be defined as

- All documented hypoglycemia - episodes for the 24-hour period
- Non-nocturnal hypoglycemia - episodes during 6 AM to midnight, and
- Nocturnal hypoglycemia - episodes during midnight to 6 AM.

The incidence and rate of hypoglycemia will be summarized by treatment and analysis period for different types of hypoglycemia.

Further details for assessing all safety measures will be described in the SAP.

### 9.3.6. Other Analyses

#### 9.3.6.1. Pharmacokinetic and Pharmacodynamic Analyses

LY3209590 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software.

The relationships between LY3209590 dose and/or concentration and efficacy, and safety as well as biomarker endpoints may be characterized.

In addition, if population PK and PK/PD models can be established, the impact of additional participant factors, such as age, weight, sex, and renal function on PK and/or PD parameters, may be examined.

Should antidrug antibody be detected from immunogenicity testing, its impact on LY3209590 PK or any relevant PD parameters will also be examined.

#### 9.3.6.2. Evaluation of Immunogenicity

The baseline anti-LY3209590-antibody (ADA) status (detected or not detected) will be summarized by treatment for the participants evaluable for TEADA defined as participants with non-missing baseline and at least 1 non-missing postbaseline measurement.

The number and percentage of participants who are TEADA+ will be summarized by treatment group.

The frequency of cross-reactive binding to endogenous insulins may also be summarized for the participants with TEADA+.

The relationship between the presence of TEADA and the safety and efficacy measures may be assessed.

**Definition of TEADA+**

A participant is considered TEADA+ if either treatment-induced ADA or treatment-boosted ADA occur.

*Treatment-induced ADA* is defined as the participant has baseline status of ADA Not Present and at least 1 postbaseline status of ADA Present with titer ≥ 2-fold (1 dilution) of the minimum required dilution (1:20).

*Treatment-boosted ADA* is defined as the participant has baseline status of ADA Present and at least 1 postbaseline status of ADA Present with the titer being ≥ 2 dilutions (4-fold) of the baseline titer. That is, the participant has baseline status of ADA Present, with titer 1:B, and at least 1 postbaseline status of ADA Present, with titer 1:P and P/B≥4.

## 9.4. Interim Analysis

A program-level safety review using selected efficacy and safety data will be conducted on a periodic basis across all ongoing Phase 3 clinical trials evaluating LY3209590. The analysis will be performed using the unblinded data and be reviewed by the DMC consisting of experienced members external to Lilly (Section 10.1.5).

Study team personnel will remain blinded. Detailed information for the data review and the unblinding are specified in the DMC Charter or a separate unblinding plan document.

## 9.5. Sample Size Determination

Approximately 670 participants will be randomized to LY3209590 and insulin degludec in a 1:1 ratio. With the assumption of 15% dropout at Week 26, approximately 284 and 284 participants will complete 26 weeks of treatment on LY3209590 and insulin degludec, respectively.

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control as measured by change from baseline to Visit 22 (Week 26) in HbA1c in participants with T1D currently basal-bolus insulin.

Assuming an NIM of 0.4%, no true difference between treatment groups, and an SD of 1.1%, 568 completers (284 on LY3209590 and 284 on insulin degludec) will provide at least 99% statistical power to show noninferiority between LY3209590 and insulin degludec using the upper limit of a 2-sided 95% CI (LY3209590 – insulin degludec). This sample size also has at least 90% statistical power to show noninferiority between LY3209590 and insulin degludec using a 0.3% NIM at Week 26.

The 568 completers will provide 90% statistical power to demonstrate the superiority (LY3209590 vs. insulin degludec) of change in HbA1c from baseline to 26 weeks (assuming an SD of 1.1% and true mean difference is -0.3%) using the alpha of 0.05.

The 568 completers will provide at least 99% statistical power to show the superiority of the percentage of time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM 4 weeks prior to Week 26 between LY3209590 and insulin degludec (assuming an SD of 10% and true mean difference is 5%) at alpha = 0.05.

The 568 completers will provide 80% statistical power to show the superiority of the event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 52 (assuming event rate of 3.37 [SD = 7.13] and 4.87 [SD = 7.13] events per participant per year for LY3209590 and insulin degludec, respectively) using a negative binomial distribution at alpha = 0.05.

# 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 (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- International Organization for Standardization (ISO) 14155
- 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 study conduct for participants under their responsibility 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, and
- Reporting significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection 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 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 the participant's 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 their 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. Committees Structure

#### 10.1.5.1. Internal Safety Review Team

Participant safety will be continuously monitored by the sponsor's internal safety review team, which includes safety signal detection at any time during the study.

All safety data collected will be summarized and reviewed by the sponsor's internal safety review team for agreement of next steps.

#### 10.1.5.2. Clinical Event Committee for Adjudication of Events

A blinded Clinical Event Committee, external to Lilly, will adjudicate cerebrocardiovascular events. The committee will include physicians external to Lilly with cardiology expertise.

#### 10.1.5.3. Data Monitoring Committee

An independent, external DMC will be responsible for reviewing unblinded data during the study.

The committee will include, at a minimum, a medical physician with appropriate expertise and a statistician.

Access to the unblinded data will be limited to the DMC and the external Statistical Analysis Center statisticians who are providing the analysis of the data. These statisticians will be independent from the study team. The study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded interim analysis.

Details about the membership, purpose, responsibilities, and operation will be included in the DMC charter.

### 10.1.6. 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.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

**Data**

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic 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, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

### 10.1.7. Data Quality Assurance

**Investigator responsibilities**

All participant data relating to the study will be recorded on printed or electronic CRFs 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.

**Data monitoring and management**

Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.

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 transcribed 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 retention and audits**

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 (CTA) 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, 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 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.

**Electronic data capture system**

An electronic data capture 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 electronic data capture 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.

Additionally, electronic Clinical Outcome Assessment data (participant-focused outcome instrument) will be directly recorded by the participant, into an instrument, for example, hand held smart phone or tablet. The electronic Clinical Outcome Assessment data will serve as the source documentation, and the investigator does not maintain a separate written or electronic record of these data.

**Data storage and access**

Data collected via the sponsor-provided data capture systems will be stored at third parties.

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 or access 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.

### 10.1.8. 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 or entered in the CRF and 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 10.1.7.

### 10.1.9. Study and Site Start and Closure

**First Act of Recruitment**

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

**Study or Site Termination**

The sponsor or sponsor's 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

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.

### 10.1.10. 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.

### 10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

### 10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3209590 or after LY3209590 become(s) commercially available.

| Sample Type | Custodian | Maximum Retention Period after Last Patient Visit[a] |
|---|---|---|
| Exploratory biomarkers | Sponsor or designee | 15 years |
| Pharmacokinetic | Sponsor or designee | 1 year |
| Immunogenicity | Sponsor or designee | 15 years |

[a] Sample retention periods may differ dependent upon local regulations.

## 10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or the local laboratory as specified in the table below.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

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 the laboratory safety results.

| Clinical Laboratory Tests | Comments |
|---|---|
| **Hematology** | Assayed by a Lilly-designated laboratory |
| Hemoglobin | |
| Hematocrit | |
| Erythrocyte count (RBCs - red blood cells) | |
| Mean cell volume | |
| Mean cell hemoglobin | |
| Mean cell hemoglobin concentration | |
| Leukocytes (WBCs - white blood cells) | |
| Differential | |
| Percent and absolute count of: | |
| Neutrophils, segmented | |
| Lymphocytes | |
| Monocytes | |
| Eosinophils | |
| Basophils | |
| Platelets | |
| **Clinical Chemistry** | Assayed by Lilly-designated laboratory |
| Sodium | |
| Potassium | |
| Chloride | |
| Bicarbonate | |
| Total bilirubin | |
| Direct bilirubin | |
| Alkaline phosphatase (ALP) | |
| Alanine aminotransferase (ALT) | |
| Aspartate aminotransferase (AST) | |
| Gamma-glutamyl transferase (GGT) | |
| Blood urea nitrogen (BUN) | |
| Creatinine | |
| Uric acid | |
| Total protein | |
| Albumin | |
| Calcium | |
| Phosphorus | |
| Glucose | Fasting or random (refer to SOA) |
| Cholesterol | |
| Triglycerides | |
| **Lipid Panel** | Assayed by Lilly-designated laboratory |
| High-density lipoprotein (HDL) | |
| Low-density lipoprotein (LDL-C) | This value will be calculated. If triglycerides >400 mg/dL, the direct LDL will be assayed |
| Very low-density lipoprotein (VLDL-C) | |
| **Urinalysis** | Assayed by Lilly-designated laboratory |
| Specific gravity | |
| pH | |
| Protein | |
| Glucose | |

| | |
|---|---|
| Ketones | |
| Bilirubin | |
| Urobilinogen | |
| Blood | |
| Nitrite | |
| Urine leukocyte esterase | |
| Microscopic examination of sediment | |
| **Hormones (Female)** | |
| Serum pregnancy | Assayed by Lilly-designated laboratory |
| Urine pregnancy | Evaluated locally |
| Follicle stimulating hormone (FSH) | Assayed by Lilly-designated laboratory. Performed as needed to confirm participant's postmenopausal status |
| **Urine Chemistry** | Assayed by Lilly-designated laboratory |
| Albumin | |
| Creatinine | |
| **Calculations** | Generated by Lilly-designated laboratory |
| eGFR (CKD-EPI) | |
| Urinary albumin/creatinine ratio (UACR) | |
| **Pharmacokinetic Samples**<br>LY3209590 concentration | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites |
| **Additional Testing** | Assayed by Lilly-designated laboratory |
| C-Peptide | |
| Glucose | Fasting per SOA |
| HbA1c | |
| **Exploratory Biomarker Storage Samples** | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites |
| Serum | |
| Plasma (EDTA) | |
| **Immunogenicity Samples** | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites |
| Anti-LY3209590 antibodies | |

### 10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

**Purpose of collecting samples after a systemic hypersensitivity event**

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

**When to collect samples after a systemic hypersensitivity event occurs**

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

| Timing | Sample Type | Laboratory Test[a] |
|---|---|---|
| Collect from 30 min to 4 hr after the start of the event.<br>Note: The optimal collection time is from 1 to 2 hours after the start of event. | Serum | Total tryptase |
| | Serum/Plasma | Complements (C3, C3a, and C5a) |
| | Serum | Cytokine panel (IL-6, IL-1β, IL-10, or any cytokine panel that includes these 3 cytokines) |
| Collect samples on the same day as the event.<br>If samples were already collected per the SoA on the same day as the event, then duplicate samples are not collected.<br>Note: The optimal collection time is up to 12 hours after the start of the event. | Serum | LY3209590 anti-drug antibodies (ADA) |
| | Plasma | LY3209590 concentration |

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

Abbreviations: ADA = anti-drug antibodies; IL = interleukin.

### Information to record

Record the date and time when the samples are collected.

### Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

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

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

### 10.3.1. Definition of AE

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. 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 a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.<br>• An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. |

| **Events Meeting 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).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. See definitions in Section 10.8.<br>• 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 AE or SAE if they fulfill the definition of an AE or SAE.

**Events NOT Meeting the AE Definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

**An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:**

**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 or emergency ward (usually involving at least an overnight stay) 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 pre-existing 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**

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

**f. Other situations:**

- Medical or scientific judgment should be exercised by the investigator 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 one 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.

**g.** Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

### 10.3.3. Definition of Product Complaints

**Product Complaint**

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

### 10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

**AE, SAE, and Product Complaint Recording**

- When an AE/SAE/product complaint 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/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by 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 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 one of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. 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 one 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. The investigator will use clinical judgment to determine the relationship.
- 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.
- 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 for LY3209590 and the Product Information for degludec in their 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 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 Sponsor or designee.
- The investigator may change their 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 one 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 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 Sponsor or designee with a copy of any post-mortem findings including histopathology.

### 10.3.5. 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 SAE paper 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 SAE paper form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found in site training documents.

**SAE Reporting via Paper Form**

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor.
- 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 in site training documents.

### 10.3.6. Regulatory Reporting Requirements

**SAE Regulatory Reporting**

- 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 (IRB)/Independent Ethics Committees (IEC), 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.

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Definitions

**Women of childbearing potential**

Females are considered a woman of childbearing potential if

- they have had at least 1 cycle of menses, or
- they have Tanner 4 breast development.

Any amount of spotting should be considered menarche.

**Women not of childbearing potential**

Females are considered women not of childbearing potential if

- they have a congenital anomaly such as Mullerian agenesis
- they are infertile due to surgical sterilization, or
- they are postmenopausal.

Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.

**Postmenopausal**

The postmenopausal state should be defined as

- A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note
  OR
- A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL
  OR
- A woman 55 years of age or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea
  OR
- A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[a] Women should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

### 10.4.2. Contraception Guidance

**Guidance for women of childbearing potential**

**WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:**

| Must… | Must not… |
|---|---|
| agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males | • use periodic abstinence methods<br>  ○ calendar<br>  ○ ovulation<br>  ○ symptothermal, or<br>  ○ post-ovulation<br>• declare abstinence just for the duration of a trial, or<br>• use the withdrawal method |

**WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:**

| Topic | Condition |
|---|---|
| Pregnancy testing | Have a negative serum test result at screening followed by a negative urine and serum result at randomization. See the protocol Schedule of Activities for subsequent pregnancy testing requirements. |
| Contraception | Agree to use 1 highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception.<br><br>These forms of contraception must be used for the duration of the study. |

**Guidance for all men**

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

**Methods of contraception for women of childbearing potential**

| Methods | Examples |
|---|---|
| Highly effective contraception (less than 1% failure rate) | • combination oral contraceptive pill<br>• progestin-only contraceptive pill (mini-pill)<br>• implanted contraceptives<br>• injectable contraceptives<br>• contraceptive patch (only women <198 pounds or 90 kg)<br>• total abstinence<br>• vasectomy (if only sexual partner)<br>• fallopian tube implants (if confirmed by hysterosalpingogram)<br>• combined contraceptive vaginal ring, or<br>• intrauterine devices |
| Effective contraception | • male or female condoms with spermicide<br>• diaphragms with spermicide or cervical sponges<br>• barrier method with use of a spermicide<br>  o condom with spermicide<br>  o diaphragm with spermicide, or<br>  o female condom with spermicide<br><br>Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide) to be considered effective. |
| Ineffective forms of contraception | • spermicide alone<br>• periodic abstinence<br>• fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)<br>• withdrawal<br>• post coital douche, or<br>• lactational amenorrhea |

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

**Hepatic Evaluation Testing**

See Section 8.2.5 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed *in addition to central testing* when necessary 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 |
| | Copper |
| **Coagulation** | 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 | Anti-nuclear antibody (ANA) |

| | |
|---|---|
| Hepatitis B core IgG antibody | Anti-smooth muscle antibody (ASMA)[a] |
| HBV DNA[b] | Anti-actin 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 | |

[a] Not required if anti-actin antibody is tested.

[b] Reflex or confirmation dependent on regulatory requirements, testing availability, or both.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

## 10.6. Appendix 6: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

## 10.7. Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances

**Implementation of this appendix**

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

**Exceptional circumstances**

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

**Implementing changes under exceptional circumstances**

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, for example, upon implementation and suspension of changes. All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

**Considerations for making a change**

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

**Informed consent**

Additional consent from the participant will be obtained, if required, for

- participation in remote visits, as defined in Section "Remote Visits"
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

**Changes in study conduct during exceptional circumstances**

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

***Remote visits***

*Types of remote visits*

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments according to the SoA, if written approval is provided by the sponsor.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor.

Other alternative locations: Laboratory draws may be done at an alternate location in exceptional circumstances, if written approval is provided by the sponsor.

*Data capture*

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

*Safety reporting*

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

*Return to on-site visits*

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

***Local laboratory testing option***

Local laboratory testing may be conducted in lieu of central laboratory testing, except for HbA1c and serum glucose testing. Lilly-designated laboratory testing must be retained for HbA1c and serum glucose.

The local laboratory must be qualified in accordance with applicable local regulations.

Obtain local labs for safety hematology, chemistry, hormone panel, and urinalysis, when applicable, per the SoA. Safety labs should be obtained as specified in the SoA.

All labs will be reviewed by the investigators. Sign and date review of local labs per normal process and follow up with the participant as needed. Results will not be recorded in the eCRF.

Lilly Medical should be informed of any labs that meet criteria for temporary or permanent study intervention discontinuation.

***Study intervention and ancillary supplies (including participant diaries)***

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site, for example, participant's home, the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality, that is, storage conditions maintained and intact packaging upon receipt.
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

***Screening period guidance***

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening or the lead-in visits are valid for a maximum of 24 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 24 days from the signing of the ICF to the randomization visit, the participant will proceed to the next study visit per the usual SoA, provided that the randomization visit is conducted within 30 days from first screening.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 24 days from signing of the ICF to the randomization visit, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by the randomization visit.

***Adjustments to visit windows***

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

The primary endpoint visit, Visit 22 Week 26, should be completed per original schedule whenever possible and safe to do so. However, the visit windows should be within ±7 days relative to the target visit date.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

**Documentation**

*Changes to study conduct will be documented*

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing or shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

*Source documents at alternate locations*

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

## 10.8. Appendix 8: Abbreviations and Definitions

| Term | Definition |
|---|---|
| **abuse** | Use of a study intervention for recreational purposes or to maintain an addiction or dependence |
| **ADA** | antidrug antibody |
| **AE** | adverse event |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **ANCOVA** | analysis of covariance |
| **AST** | aspartate aminotransferase |
| **authorized IMP** | *Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product |
| **authorized AxMP** | *Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product |
| **AxMP** | Auxiliary medicinal product. See also NIMP.<br>A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial |
| **BG** | blood glucose |
| **CGM** | continuous glucose monitoring<br>CGM-derived variables may include time in range, time below range, time above range, daily average glucose, glucose management indicator, between- and within-day glucose variability, low blood glucose index, high blood glucose index, blood glucose risk indicator, ambulatory glucose profiles |
| **CI** | confidence interval |
| **Companion diagnostic** | An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product |
| **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** | case report form: a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant |
| **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. |
| **DMC** | data monitoring committee: a data monitoring committee or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study |
| **Device deficiencies** | equivalent to product complaint |
| **EAS1** | Efficacy Analysis Set 1 |
| **EAS2** | Efficacy Analysis Set 2 |
| **ECG** | electrocardiogram |
| **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 |
| **eGFR (CKD-EPI)** | estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration) |
| **FBG** | fasting blood glucose |
| **GCP** | good clinical practice |
| **GGT** | gamma-glutamyl transferase |
| **HbA1c** | hemoglobin A1c |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IMP** | Investigational Medicinal Product (see also "investigational product")<br>A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial |

| | |
|---|---|
| **informed consent** | A process by which a participant voluntarily confirms their 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 |
| **interim analysis** | An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created or locked |
| **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. See also "IMP." |
| **IRB/IEC** | Institutional Review Board/Independent Ethics Committee |
| **ITT** | intention to treat: the principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment |
| **IWRS** | interactive web-response system |
| **LS** | least-squares |
| **MDI** | multiple daily injection |
| **medication error** | Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold one or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time.<br>In addition to the core 5 rights, the following may also represent medication errors:<br>• dose omission associated with an AE or a product complaint<br>• dispensing or use of expired medication<br>• use of medication past the recommended in-use date<br>• dispensing or use of an improperly stored medication<br>• use of an adulterated dosage form or administration technique inconsistent with the medication's labeling, for example, Summary of Product Characteristics, IB, local label, and protocol, or<br>• shared use of cartridges, prefilled pens, or both |
| **misuse** | Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription |
| **MMRM** | mixed-model repeated measures |
| **NIM** | noninferiority margin |

| | |
|---|---|
| **NIMP** | Non-investigational Medicinal Product. See AxMP.<br>A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment |
| **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 |
| **PC** | product complaint |
| **PK/PD** | pharmacokinetics/pharmacodynamics |
| **PPS** | per-protocol set: the set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model |
| **PRO/ePRO** | patient-reported outcomes/electronic patient-reported outcomes |
| **QTc** | corrected QT interval |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study |
| **SERM** | selective estrogen receptor modulator |
| **SMBG** | self-monitoring of blood glucose |
| **T1D** | Type 1 diabetes |
| **T2D** | Type 2 diabetes |
| **TBL** | total bilirubin level |
| **TEADA** | treatment-emergent antidrug antibody |
| **TEAE** | Treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment |
| **ULN** | upper limit of normal |

## 10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

**Amendment (b): 21-June-2022**

**Overall Rationale for the Amendment:**

The primary rationale for the current amendment is to address the change in the study continuous glucose monitoring (CGM) system. The unblinded CGM receiver will be used. These and other changes are detailed in the table below. Minor error correction and formatting changes are not reflected in the table.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3 Schedule of Activities (SoA) | Thirteen telehealth visits have been changed to in-office visits and Visit Interval Tolerance (days) have been changed from ±7 to ±3 in Table 1.3.2. | To accommodate CGM data downloads |
| | Added new activity row to SoA stating to "Download and review CGM data in study vendor portal" | Added to prompt sites to capture CGM data |
| | Deleted word "review" from the activity "Review and discuss CGM and hypoglycemia data" | For clarity |
| | Updated "Dispense of CGM supplies" schedule to include each in-office visit and Visit 801 | To align with the revised in-office visit schedule |
| | Deleted "mobile device" from activity "Return CGM mobile device" and added the term "receiver" | The term "mobile device" is no longer appropriate |
| | Updated "Dispense glucometer supplies as needed" | To align with "dispense study intervention" activity schedule |
| | Updated "Dispense ancillary supplies as needed" | To align with "dispense study intervention" activity schedule |
| | Updated schedules in activities "Dispense study intervention and in Participant returns unused intervention and supplies | To reduce the longer visit intervals to 4 weeks for study intervention dispensing |

| | | |
|---|---|---|
| Section 2.3.1 Risk Assessment | Added text “to download and” | For clarification |
| | Deleted text “at any time throughout the study” | Text is no longer applicable |
| Section 3 Objectives, Endpoints, and Estimands | Deleted text “Potential intrinsic and extrinsic factors” from tertiary endpoints for PK/PD of LY3209590 | Error correction |
| Section 8.1.1.2 Continuous glucose monitoring (CGM) system | Edited text to describe use of the unblinded CGM receiver | To address change in CGM strategy to use unblinded CGM receivers |
| Section 8.3.6 Hypoglycemia | Deleted text “at any time” | No longer applicable |
| Section 10.2.1 Laboratory Samples to be Obtained at the Time of Systemic Hypersensitivity Event | Changed complements sample type to “Serum/Plasma” | Correction-serum and plasma are used in this series of tests |

**Amendment a: (10-May-2022)**

**Overall Rationale for the Amendment**

The primary rationale for the current amendment is to address regulatory feedback regarding exclusionary ALT and AST thresholds, rescue medication, and stratification factors. These and other changes are detailed in the table below. Minor error correction and formatting changes are not reflected in the table.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1. Synopsis | In Other Secondary endpoints for first objective, deleted Week 26. | Redundant; Week 26 is already an endpoint of Key Secondary. |
| 3. Objectives, Endpoints, and Estimands | In Other Secondary endpoints for first objective, deleted Week 26. | Redundant; Week 26 is already an endpoint of Key Secondary. |

| | | |
|---|---|---|
| 3. Objectives, Endpoints, and Estimands | In Primary estimand subsection, United States registration, added text in primary clinical question to clarify "study eligible" participants, use of MDI, and potential rescue therapy. | For clarity. |
| 3. Objectives, Endpoints, and Estimands | Edited Treatment regimen estimand attributes table<br>- Population: added cross reference to Section 9.2, and removed other cross references<br>- Remaining intercurrent events: inserted text for initiation of rescue medication<br>- Treatment condition: inserted text for use of rescue medications | For clarity and to address regulator feedback. |
| 3. Objectives, Endpoints, and Estimands | In Primary estimand section, Registration for countries outside the United States, added text in primary clinical question of interest to clarify "study eligible" participants and use of MDI therapy. | For clarity. |
| 3. Objectives, Endpoints, and Estimands | Edited Efficacy estimand attributes table<br>- Population: added cross reference to Section 9.2, and removed other cross references<br>- Remaining intercurrent events: inserted text for initiation of rescue medication | For clarity and to address regulator feedback. |
| 3. Objectives, Endpoints, and Estimands | In Rationale for the efficacy estimand subsection, added text addressing confounding effect of rescue medications. | For clarity and to address regulator feedback. |
| 5.1. Inclusion Criteria | In inclusion criterion 3, added "as determined by the central laboratory". | For clarity. |
| 5.1. Inclusion Criteria | In inclusion criterion 4, added trademark information. | For clarity. |
| 5.2. Exclusion Criteria | In exclusion criterion 17, corrected "of" to "or" in "obvious clinical signs or symptoms of any other liver disease" | Error correction. |
| 5.2. Exclusion Criteria | In exclusion criterion 17, ALT and AST thresholds were increased from 2.5x ULN to 3x ULN. | Addressing regulator feedback. |
| 5.2. Exclusion Criteria | In exclusion criterion 36, added wording "after having signed the informed consent form | For clarity. |

| | | |
|---|---|---|
| | (ICF)" and "after receiving at least 1 dose of the study basal insulin". | |
| 6.1.3. Rescue Therapy for Management of Participants with Severe, Persistent Hyperglycemia during the Treatment Period | Added new subsection and content for management of severe, persistent hyperglycemia. | Addressing regulator feedback. |
| 6.3. Measures to Minimize Bias: Randomization and Blinding | In the Randomization and stratification subsection, replaced the stratification factor "prestudy basal insulin treatment with insulin glargine U-300 or other basal insulin" with a new stratification factor "CGM use prior to study entry (yes/no)". | Addressing regulator feedback. |
| 6.5.2.1. LY3209590 Dose Initiation and Modification | Corrected "30" to "29" in subheading for "Visits 5 to 29 (Weeks 2 to 52) weekly dosing". | Error correction. |
| 6.5.2.2. Insulin Degludec Dose Initiation and Modification | Corrected "30" to "29" in subheading for "Visits 4 to 29 (Weeks 1 to 52)". | Error correction. |
| 6.8. Concomitant Therapy | In Excluded concomitant medications, Exceptions, added "Note: Participants who require treatment with non-study basal insulins as rescue therapy for management of severe or persistent hyperglycemia as outlined in Section 6.1.3., must discontinue study basal insulin therapy (LY3209590 or insulin degludec). The participant will remain in the study and follow procedures for the remaining study visits". | For clarity. |
| 9. Statistical Considerations | Made updates to endpoint word order throughout section and subsections. | For clarity. |
| 9.2. Analyses Sets | Updated the analysis populations/sets. | To meet the anticipated requirement for excluding inadvertently enrolled participants in some countries. |

| | | |
|---|---|---|
| 9.3. Statistical Analyses | Made updates throughout section and subsections according to changes in analysis sets table. | As in Section 9.2, and for clarity. |
| 9.3.1. General Considerations | In the fourth paragraph, inserted text regarding the initiation of rescue medication. | Addressing regulator feedback. |
| 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis | In Treatment regimen estimand subsection, added text “or rescue medication”. | For clarity. |
| 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis | Replaced the stratification factor “prestudy basal insulin glargine U-300 or other basal insulin” with a new stratification factor “CGM use prior to study entry [yes/no]” in ANCOVA and MMRM models. | Related to change in stratification factor in Section 6.3 to address regulator feedback. |
| 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis | In the Efficacy estimand, Missing measures subsection, replaced “imputed” with “handled”. | For clarity. |
| 9.3.2. Primary Endpoint(s)/Estimand(s) Analysis | In the Treatment regimen Estimand subsection, and in the Efficacy estimand Missing measures subsection, added text regarding rescue medication. | Addressing regulator feedback. |
| 9.3.3.1. Multiplicity Adjusted Endpoints | Replaced the stratification factor “prestudy basal insulin glargine U-300 or other basal insulin” with a new stratification factor “CGM use prior to study entry [yes/no]” use in ANCOVA and MMRM models. | Related to change in stratification factor in Section 6.3 to address regulator feedback. |
| 9.3.3.2. Other Secondary Endpoints | Added text regarding rescue medication. | Addressing regulator feedback. |
| 9.3.5. Safety Analyses | Removed inadvertently hidden text format applied to hypoglycemia time period definitions. | Error correction. |
| 10.8. Appendix 8: Abbreviations and Definitions | Under CGM term, added a list of possible CGM-derived variables. | Addressing regulator feedback. |
| Throughout protocol | Following glucose values in units of mg/dL, added corresponding values in mmol/L. | For clarity. |

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| Approval | PPD<br>Statistician<br>12-Oct-2022 15:33:11 GMT+0000 |

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