Protocol I8H-MC-BDCV (b)

A Phase 3, Parallel-Design, Open-Label, Randomized Controlled Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Glargine in Adults With Type 2 Diabetes on Multiple Daily Injections

NCT05462756

Approval Date: 17-OCT-2022

Title Page

Protocol Title:

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Protocol Number: I8H-MC-BDCV

Amendment Number: b

Compound: LY3209590

Brief Title:
Efficacy and Safety of LY3209590 Compared with Daily Insulin Glargine in Adults with Type 2 Diabetes on Multiple Daily Injections

Study Phase: 3

Acronym: QWINT-4

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

IND: 129390

EudraCT: 2021-005878-25

Document ID: VV-CLIN-074596

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

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	*10-May-2022*
Original Protocol	*05-Apr-2022*

Amendment [b]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The overall rationale for the current amendment is to add the Diabetes Injection Device Experience Questionnaire (DID-EQ) scale. Additional minor clarifying changes and corrections have also been made. Individual changes are described in this table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added DID EQ to Other Secondary objectives.	To meet regulatory requirement
1.3. Schedule of Activities (SoA)	Added bullet above the SoA to describe Visit Interval.	For clarity
1.3. Schedule of Activities (SoA)	Patient-Reported Outcomes line item: Removed "(Electronic)" from line title and added "Collected using electronic device (eCOA)" in comment column for the existing sub rows under Patient-Reported Outcomes.	For clarity
1.3. Schedule of Activities (SoA)	Added entry for DID-EQ.	To meet regulatory requirement
1.3. Schedule of Activities (SoA)	The comment column of the Pharmacokinetic (PK) samples line item was edited to add "For participants randomly assigned to glargine who are not dosed onsite during Visit 3, the sample may be collected anytime during Visit 3."	For clarity
3. Objectives, Endpoints, and Estimands	Added DID EQ to Other Secondary objectives.	To meet regulatory requirement
3. Objectives, Endpoints, and Estimands	Secondary estimands (for multiplicity-adjusted objectives) sub section: Analysis details removed from protocol and described in the SAP.	To address regulatory feedback

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Edited inclusion criterion 7, changing the final part of the 2nd sentence, replacing “prior to” with “at”; it now reads “at the evening meal.”	For clarity
6.5.2.2. Insulin Glargine Dose Adjustment	In the first sentence, “Visit 5” was changed to “Visit 4”.	Error correction
8.1. Efficacy Assessments	Added the DID-EQ in the list of questionnaires and reordered the list.	To meet regulatory requirement
8.1.2. Patient-reported Outcomes	Added the DID-EQ in the list of questionnaires.	To meet regulatory requirement
8.1.2.2. Diabetes Injection Device Experience Questionnaire	Added DID-EQ description.	To meet regulatory requirement
9.1 Statistical Hypotheses	Added “Each NIM will have its own familywise error rate” for NIM 0.4% and 0.3%.	For clarity
9.3.3.2. Other Secondary Endpoints	Added “patient-reported outcome measures” and “and patient-reported outcome" in first and second sentences, respectively.	To meet regulatory requirement
10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event	In row 1 of table, added “Plasma” in the sub row associated with laboratory tests for complements C3, C3a, and C5a.	Error correction
10.7.1.2. Changes Related to “Legally Authorized Representative,” “Legal Guardian,” “Parents”	Deleted “10.1.3 Informed Consent Process” from table.	Error correction
10.10. Appendix 10: Protocol Amendment History	In 2nd entry for Section 5.1 Inclusion Criteria, inserted “added”; now it reads “In inclusion criterion 7, removed “stable regimen” and added “any”.	Error correction
11. References	Added reference for Matza et al. 2018 to support addition of the DID-EQ.	To meet regulatory requirement

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 3, Parallel-Design, Open-Label, Randomized Controlled Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Glargine in Adults with Type 2 Diabetes on Multiple Daily Injections

Brief Title:

Efficacy and Safety of LY3209590 Compared with Daily Insulin Glargine in Adults with Type 2 Diabetes on Multiple Daily Injections

Regulatory Agency Identifier Numbers:

IND: 129390

EudraCT: 2021-005878-25

Rationale:

This Phase 3 study will evaluate the efficacy and safety of once-weekly administration of LY3209590 compared to daily administration of insulin glargine in participants with type-2 diabetes (T2D) who are on once- or twice-daily basal insulin and at least 2 injections per day of prandial insulin prior to entering the study. Participants will continue prior stable therapy with 0 to 3 allowed noninsulin diabetes medications during the study.

This study will inform the clinical development of LY3209590.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
Demonstrate noninferiority of LY3209590 compared to insulin glargine on glycemic control.	Change in HbA1c from baseline at Week 26
Key Secondary (Multiplicity Adjusted)	
Demonstrate LY3209590 is superior to insulin glargine in the selected parameters of glycemic control.	• Change in HbA1c from baseline at Week 26 • The percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 26 • The event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0

	mmol/L] or severe) during treatment phase up to Week 26
Other Secondary	
To investigate the effect of LY3209590 compared with insulin glargine in additional parameters of diabetes management.	• Change in fasting glucose measured by SMBG from baseline to Week 26 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive measured during the CGM session that occurs between Week 22 and Week 26 • Time in hypoglycemia range with glucose <54 mg/dL (3.0 mmol/L), measured by CGM that occurs between Week 22 and Week 26 • Time in hyperglycemia range with glucose >180 mg/dL (10.0 mmol/L), measured by CGM that occurs between Week 22 and Week 26 • Glucose variability measured during the CGM session that occurs between Week 22 and Week 26 • Insulin dose at Week 26 o basal o bolus o total, and o basal/total insulin dose ratio.
To investigate the safety of LY3209590 compared with insulin glargine.	• Incidence and rate of composite of Level 2 and 3 hypoglycemia events during treatment period • Body weight change from baseline to Week 26
To investigate the treatment impact of LY3209590 compared with insulin glargine on patient-reported outcome measures.	• Treatment experience at Week 26 for DID-EQ

Abbreviations: CGM = continuous glucose monitoring; HbA1c = hemoglobin A1c; SMBG = self-monitoring of blood glucose.

Overall Design:

Study I8H-MC-BDCV is a Phase 3, parallel-design, open-label, randomized control trial that will evaluate the efficacy and safety of LY3209590 compared to insulin glargine in participants with T2D who are on once- or twice-daily basal insulin and at least 2 injections per day of prandial insulin prior to entering the study. Participants will continue prior stable therapy with 0 to 3 allowed noninsulin diabetes medications during the study.

Brief Summary:

The study consists of a 1-week screening period, a 2-week lead-in period, a 26-week treatment period, and a 5-week safety follow-up period.

All participants will use a study-provided, blinded continuous-glucose monitoring (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 hemoglobin A1c (HbA1c) from baseline at Week 26.

Study Population:

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

- are at least 18 years of age or older
- have a diagnosis of T2D currently treated with basal insulin and at least 2 injections of prandial insulin per day
- are receiving at least 10 units of total basal insulin per day
- are receiving less than or equal to 2 units/kg/day of total daily insulin at screening, and
- have an HbA1c value of 7.0% to 10%, inclusive, at screening.

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

- have a diagnosis of type 1 diabetes mellitus or latent autoimmune diabetes, or specific type of diabetes other than T2D
- are persons of childbearing potential who are pregnant, lactating, or breastfeeding
- 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, or
- 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.

Number of Participants:

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

Intervention Groups and Duration:

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

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

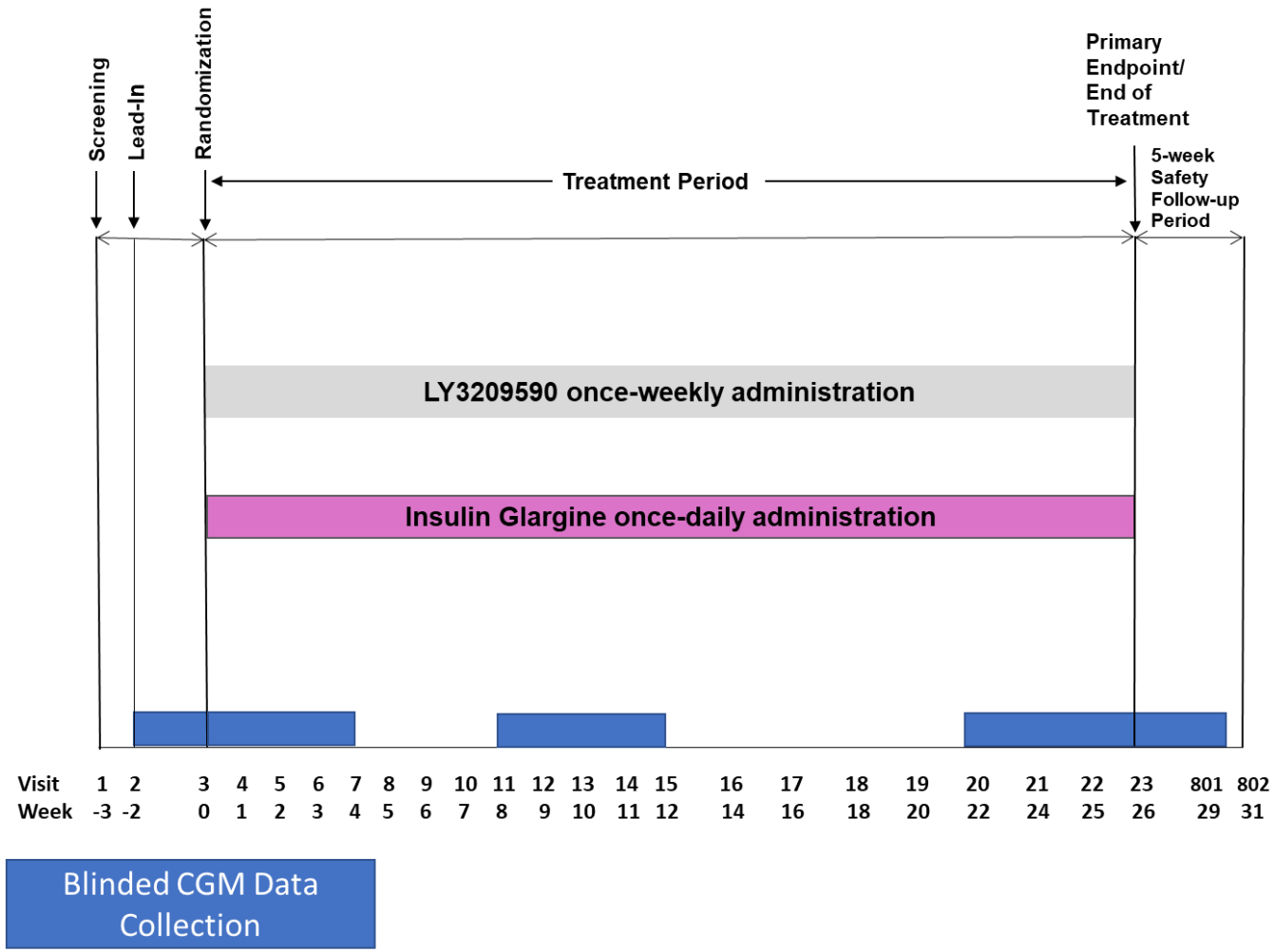
The study treatment period duration is 26 weeks.

Ethical Considerations of Benefit/Risk:

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 persons with T2D.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviation: CGM = continuous glucose monitoring.

1.3. Schedule of Activities (SoA)

Screening

Screening procedures may be conducted over 1 to 3 days.

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 to 17 days after Visit 2.

	Screen-ing and Lead-In		Treatment																							Safety Follow-up		
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ED	UV	V801	V802	V1 = Screening V2 = Lead-In ED: Early Discontinuation UV: Unscheduled Visit V801, V802: Safety Follow-up
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24	25	26	—		29	31	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	—		+7	±7	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
Informed consent	X																											The ICF must be signed before any protocol-specific tests/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																											

	Screen-ing and Lead-In		Treatment																							Safety Follow-up		
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Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
Substance use (alcohol, caffeine, recreational drugs, and tobacco use)	X																											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	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	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	X	X	X	X	X	X	X	X	X	X	Clinical assessment based on participant history and e-diary entries.
Physical Evaluation																												
Height	X																											Participant should remove shoes.
Weight	X	X	X	X	X		X		X		X				X		X			X			X	X			X	
Vital signs	X	X	X	X	X		X		X		X				X		X			X			X	X			X	Includes blood pressure and pulse rate. Measure 3 times, using the same arm, after participant has been sitting at least 5 minutes and before ECG tracing and collection of blood samples for laboratory testing. Additional vital signs may be measured as necessary at investigator discretion.

	Screen-ing and Lead-In		Treatment																						Safety Follow-up		
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Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
Physical examination	X																						X	X			X	Additional physical examinations may be completed as necessary at investigator discretion.
12-lead ECG (local)	X																						X	X				Collect prior to collection of blood samples for laboratory testing. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit.
Blinded Continuous Glucose Monitoring																												
Dispense CGM system		X									X									X								Dispense supplies as needed.
CGM sensor insertion		X	X								X									X			X					At Visits 3 and 23, sites may continue with the current sensor rather than removing and inserting a new sensor before the end of the 10-day wear period.
CGM system return							X								X									X			X	ED Visit: if the ED visit occurs during a CGM session, the device must be returned.

	Screen-ing and Lead-In		Treatment																							Safety Follow-up		
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Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
CGM data download			X				X								X								X	X			X	ED Visit: if the ED visit occurs during a CGM session, the data must be downloaded.
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). After Visit 3, conduct as needed.
e-diary, glucometer, CGM training		X	X																									After Visit 3, conduct as needed.
Participant Diary (Electronic) and Glucometer and Related Supplies																												
Dispense e-diary and glucometer		X																										Dispense supplies as needed.
e-diary compliance check			X	X	X	X	X	X	X	X	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.
e-diary return																								X			X	The e-diary must be returned on the last participant visit.

	Screen-ing and Lead-In		Treatment																							Safety Follow-up		
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Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
Patient-Reported Outcomes																												
EQ-5D-5L			X																				X	X				Collected using electronic device (eCOA).
Basal Insulin Experience: Preference																							X	X				Collected using electronic device (eCOA).
Basal Insulin Experience: Likelihood of Incorporating into Routine																							X	X				Collected using electronic device (eCOA).
Diabetes Injection Device Experience Questionnaire (DID-EQ)																							X	X				Collected on paper form.
Laboratory Tests and Sample Collections																												
Hematology	X		X												X								X	X			X	
Hemoglobin A1c (HbA1c)	X		X		X		X								X		X						X	X			X	
Clinical chemistry	X		X												X								X	X			X	
Glucose							X																					
Lipid panel			X																				X	X			X	

	Screen-ing and Lead-In		Treatment																						Safety Follow-up		
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Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
Urinalysis	X																						X	X			X	
Serum pregnancy	X		X																									Collect for WOCBP only.
Urine pregnancy (local)			X																					X			X	The result must be available prior to first dose of intervention. 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. Definition in Section 10.4.
C-peptide			X																				X	X				
eGFR (CKD-EPI)	X		X												X								X	X			X	
Urinary albumin/creatinine ratio (UACR)	X		X												X								X	X			X	
Pharmacokinetic (PK) samples			X		X		X								X								X	X			X	Visit 3: collect sample at least 15 minutes after dosing. For participants randomly assigned to glargine who are not dosed onsite during Visit 3, the sample may be collected anytime during Visit 3.

	Screen-ing and Lead-In		Treatment																						Safety Follow-up		
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ED	UV	V801	V802	V1 = Screening V2 = Lead-In ED: Early Discontinuation UV: Unscheduled Visit V801, V802: Safety Follow-up
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Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
																												For all other visits, collect at any time during the visit.
Immunogenicity (ADA) samples			X		X		X								X								X	X			X	Visit 3: Collect sample before dosing. If an immediate or nonimmediate systemic drug hypersensitivity reaction occurs, collect additional unscheduled samples as detailed in Section 10.2.1.
Stored Samples																												
Exploratory biomarker samples			X														X						X	X				Visit 3: 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	X	X	X	X	X	X	X	X		X	X	ED: Register the participant's discontinuation at next numbered visit.
Randomization using IWRS			X																									
Insulin dose assessment/adjustment/ documentation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						See Section 6.5. Visits 3-15, 17, 19, and 21 are routine basal insulin titration visits but doses should be assessed and titrated at any time, if clinically indicated.

	Screen-ing and Lead-In		Treatment																							Safety Follow-up		
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	ED	UV	V801	V802	V1 = Screening V2 = Lead-In ED: Early Discontinuation UV: Unscheduled Visit V801, V802: Safety Follow-up
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Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T		T	T	F	F		T	F	T = telehealth visit; F = fasting visit
Dispense LY3209590 or insulin glargine			X				X				X				X		X			X								
Provide prandial insulin			X				X				X				X		X			X								
Dispense ancillary supplies			X				X				X				X		X			X								Dispense ancillary supplies at other visits as needed.
Administer study intervention at study site			X	X																								• Visits 3 and 4: (Weeks 0 and 1) - LY3209590 will be administered during the study visit. • Visit 3: Insulin glargine may be administered by participants during study visit if usual basal dosing time overlaps with visit.
Study intervention training			X																									After Visit 3, review as needed.
Assess study intervention compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Participant returns unused study intervention							X				X				X		X			X			X	X				
Assess post-study basal and bolus insulin																							X	X		X	X	

Abbreviations: ADA = anti-drug antibody BG = blood glucose; CGM = continuous-glucose monitoring; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ED = early discontinuation; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; ICF = informed consent form; IWRS = interactive web-response system; SMBG = self-monitoring of blood glucose; WOCBP = women of childbearing potential.

2. Introduction

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

2.1. Study Rationale

This Phase 3 study will evaluate the efficacy and safety of once-weekly administration of LY3209590 compared to daily administration of insulin glargine in participants with T2D who are on once- or twice-daily basal insulin and at least 2 injections per day of prandial insulin prior to entering the study. Participants will continue prior stable therapy with 0 to 3 allowed noninsulin diabetes medications during the study.

This study will inform the clinical development of LY3209590.

2.2. Background

Current state of diabetes care

Most people with diabetes are not achieving glycemic targets. Treatment complexity, fear of hypoglycemia, delays in insulin initiation and intensification, and suboptimal dosing may pose challenges to diabetes care. There is a need for a basal insulin experience that incorporates simple dosing algorithms, rapid achievement of glycemic targets, and a predictable PK/PD profile with low likelihood of contributing to hypoglycemia.

Potential for improved treatment regimens and compliance

For people already using basal insulin to manage diabetes, availability of basal insulin administered weekly may improve treatment compliance and lead to better real-world patient outcomes. A weekly insulin with a lower peak-to-trough profile across a week and a nearly flat within-day insulin profile could also 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 hyperglycemia in patients with T2D and T1D. LY3209590 has the potential to decrease patient burden, overcome barriers to initiation of insulin therapy, and may improve glycemic control and quality of life for these patients.

A detailed description of the chemistry, pharmacology, non-clinical and clinical efficacy, and safety of LY3209590 is provided in the IB.

Summary of clinical results

Phase 1 and Phase 2 studies, including healthy participants and participants with T1D or T2D, 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 results

LY3209590 pharmacokinetics show a low peak-to-trough ratio and extended half-life 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.

Overall, LY3209590 was well tolerated in healthy participants and participants with T2D.

Phase 2 Study BDCM results

Phase 2 Study BDCM evaluated the effects of LY3209590 on glycemic control using 2 different dosing algorithms compared with insulin degludec in study participants with T2D previously treated with basal insulin. The two LY3209590 dosing algorithms and the degludec dosing algorithm each had a different FBG target.

Safety data indicate that there was no increased risk with LY3209590 treatment compared to insulin degludec.

LY3209590, when administered according to either dosing algorithm, was noninferior to insulin degludec for glycemic control as measured by change in HbA1c after 32 weeks of treatment.

Treatment differences in FBG were consistent with the preset FBG targets of the dosing algorithms used.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3209590 may be found in the IB.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of insulin glargine 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 suggests that there is no increased risk to participants' safety with LY3209590 treatment compared to degludec, a best-in-class basal insulin.

Management of risks

Sections 5.1, 5.2, 6.8.1, 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 each episode of hypoglycemia. 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 blood glucose levels

Each participant will have a study-provided glucometer that will wirelessly transfer participant SMBG to their study-provided e-diary. Participants should use the glucometer to check glucose values whenever 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 visit schedule allows for close clinical oversight and dose modification.

The dosing algorithm used in the study requires consideration and adjustment of insulin dosing by the investigator based on participant FBG 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 by receiving personal health information, routine safety assessments, and frequent engagement with health care providers during the study which provide opportunities for coaching and support.

The weekly administration of LY3209590 along with prandial insulin has the potential to offer more consistent 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 T2D.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
Demonstrate noninferiority of LY3209590 compared to insulin glargine on glycemic control.	Change in HbA1c from baseline at Week 26
Key Secondary (Multiplicity Adjusted)	
Demonstrate LY3209590 is superior to insulin glargine in the selected parameters of glycemic control.	• Change in HbA1c from baseline at Week 26 • The percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 26 • The event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 26
Other Secondary	
To investigate the effect of LY3209590 compared with insulin glargine in additional parameters of diabetes management.	• Change in fasting glucose measured by SMBG from baseline to Week 26 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive measured during the CGM session that occurs between Week 22 and Week 26 • Time in hypoglycemia range with glucose <54 mg/dL (3.0 mmol/L), measured by CGM that occurs between Week 22 and Week 26 • Time in hyperglycemia range with glucose >180 mg/dL (10.0 mmol/L), measured by CGM that occurs between Week 22 and Week 26 • Glucose variability measured during the CGM session that occurs between Week 22 and Week 26 • Insulin dose at Week 26 o basal o bolus o total, and o basal/total insulin dose ratio.

To investigate the safety of LY3209590 compared with insulin glargine.	• Incidence and rate of composite of Level 2 and 3 hypoglycemia events during treatment period • Body weight change from baseline to Week 26
To investigate the treatment impact of LY3209590 compared with insulin glargine on patient-reported outcome measures.	• Treatment experience at Week 26 for DID-EQ
Tertiary	
• Investigate the treatment impact of LY3209590 compared with insulin glargine on other measures of efficacy, safety, and patient-reported outcomes.	Efficacy • Percentage of participants achieving HbA1c <7% at Week 26 • Percentage of participants achieving HbA1c ≤6.5% at Week 26 • Change from baseline to Week 26 in fasting serum glucose as measured by central laboratory
	Safety • Rate and incidence of Level 2 hypoglycemia events during treatment period • Rate and incidence of Level 3 hypoglycemia events during treatment period • Incidence of positive treatment-emergent antibody of LY3209590
	Patient-reported outcomes • Frequency of responses to "Basal Insulin Experience: Likelihood of incorporating into routine" at Week 26 • Frequency of responses to "Basal Insulin Experience: Preference" at Week 26 • Change in EQ-5D-5L from baseline at Week 26
• To characterize the PK/PD of LY3209590.	• LY3209590 PK and concentration response relationships to key safety and efficacy measures.

Abbreviations: CGM = continuous glucose monitoring; DID-EQ = Diabetes Injection Device Experience Questionnaire; EQ-5D-5L = EuroQol 5 dimensions 5 levels; HbA1c = hemoglobin A1c; SMBG = self-monitoring of blood glucose.

Primary estimand (for primary objective)

United States registration

The *primary* clinical question of interest is:

> What is the treatment difference between LY3209590 and insulin glargine in change from baseline at Week 26 in HbA1c in study eligible participants regardless of treatment discontinuation for any reason or initiation of rescue therapy?

The ***treatment regimen estimand*** will be used for the primary objective and is described by the attributes in this table.

Treatment Regimen Estimand Attribute	Description
Treatment condition	randomized treatment regardless of treatment discontinuation or initiation of rescue therapy.
Population	targeted study population. See Section 9.2 for details.
Endpoint	change from baseline to Week 26 in HbA1c.
Remaining intercurrent events	none. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue therapy, are addressed by the treatment condition of interest attribute.
Population-level summary	difference in mean changes between treatment conditions.

Rationale for treatment regimen estimand:
The treatment regimen estimand estimates how participants with T2D are treated in clinical practice and takes into account 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 glargine in change from baseline at Week 26 in HbA1c in study eligible participants who adhere to the randomized treatment without an intercurrent event during the study treatment period?

The ***efficacy estimand*** will be used for the primary objective and is described by the attributes in this table.

Efficacy Regimen Estimand Attribute	Description
Treatment condition	randomized treatment
Population	targeted study population. See Section 9.2 for details.
Endpoint	change from baseline to Week 26 in HbA1c.

Remaining intercurrent events	none. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue therapy, are handled by the hypothetical strategy, for example, the potential outcome for those participants if the intercurrent events have not occurred will be estimated.
Population-level summary	difference in mean changes between treatment conditions.

Rationale for efficacy estimand: The treatment efficacy estimand supports the interpretation of the treatment effect as participants adhere to study treatment.

Secondary estimands (for multiplicity-adjusted objectives)

The superiority test in change from baseline to Week 26 in HbA1c will also be based on the primary estimands described above.

The percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L], or severe) during treatment phase up to Week 26 will be based on a composite estimand. The details will be described in the SAP.

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, parallel-design, open-label, randomized controlled trial that will evaluate the efficacy and safety of LY3209590 compared to insulin glargine in participants with T2D who are on once- or twice-daily basal insulin and at least 2 injections per day of prandial insulin prior to entering the study. Participants will continue prior stable therapy with 0 to 3 allowed noninsulin diabetes medications during the study.

The study consists of a 1-week screening period, a 2-week lead-in period, a 26-week treatment period, and a 5-week safety follow-up period.

Screening and Lead-In

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 e-diary, glucometer, and the CGM system.

Participants will receive training on

- diabetes self-monitoring and management
- study glucometer
- CGM
- electronic study diaries, and
- study requirements.

The CGM sensor will be inserted at Visit 2, and participants will be required to wear the sensor when indicated per the SoA.

Starting with Visit 2, participants must measure their FBG levels each day when possible or at a minimum 3 times per week. Starting with Visit 2, participants are strongly encouraged to measure 4-point SMBG profiles at least 3 times per week. Participants will use the study supplied glucometer and e-diary for data collection throughout the study.

Participants will continue their current insulin therapy until randomization. On the day of Visit 3, participants who typically take a morning dose of basal insulin should omit their morning dose of basal insulin as they will receive basal insulin at Visit 3.

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
- Study personnel complete baseline procedures and sample collection
- Study personnel will provide dosing training
- Study personnel or the participant will administer the first study dose of LY3209590. Insulin glargine can be taken at the site or after the visit depending upon whether the study visit timing coincides with the participant's usual time to administer basal insulin. Administered insulin doses will be entered into the e-diary
- Study personnel train participants on administering insulin lispro at mealtimes
- Study personnel will download the CGM
- Participant will continue CGM wear per the SoA, and
- Study personnel complete all visit procedures.

All participants will be treated with insulin lispro as prandial insulin throughout the treatment period as described in Section 6.5.3. Participants assigned to insulin glargine will administer glargine daily after Visit 3.

Visit 4 (Week 1)

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

Study personnel will provide dosing training and observe participants administering their second dose of LY3209590. Participants assigned to insulin glargine can continue routine daily administration.

Visit 5 through Visit 23 (Week 2 through Week 26)

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

The participant's median FBG from the 3 most recent FBGs in the prior week will be used to titrate basal insulin dose adjustments throughout the study based on the study titration algorithm described in Section 6.5.1. Prandial insulin doses should be adjusted as needed.

Participants will collect blinded CGM for

- 4 weeks prior to Visit 7, and the site will download the CGM data at Visit 7
- 4 weeks prior to Visit 15, and the site will download the CGM data at Visit 15, and
- 4 weeks prior to Visit 23, and the site will download the CGM data at Visit 23.

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

- SMBGs
- hypoglycemia events including related signs and symptoms, and
- dosing information, including date and time of doses.

Last study treatment visit: either Visit 23 (Week 26) or ED visit

Participants should complete all visit procedures in a fasting state.

Participants will return unused study intervention to the investigative site.

Assessments for the transition to non-study diabetic treatment after the participant's last dose.

- The investigator will determine a participant's transition from study basal insulin to another basal insulin. Investigators will also start the participant on a non-study prandial insulin (see Section 6.6.1).
- Participants will continue their concomitant antihyperglycemic medications at the discretion of the investigator.

Safety follow-up visits 801 and 802

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

Participants will collect blinded CGM for 4 weeks following Visit 23, and the site will download the CGM data at Visit 802.

The investigator will follow-up on the participant's transition from study treatment to another non-study diabetic 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 glargine. The primary endpoint at Visit 23 (Week 26) is based on participants reaching a stable insulin dose in order to achieve glycemic stability approximately 12 weeks in advance of the 26-week primary endpoint. HbA1c is the primary endpoint and reflects glycemic control from the prior 8 to 12 weeks.

The follow-up visits after the last dose are designed to capture any additional safety signals and to monitor the transition from study basal insulin to non-study basal insulin.

Comparator

Insulin glargine was chosen as the comparator because it is a widely used basal insulin.

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 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 glargine are derived based on findings from Phase 2 studies and model-based simulations. These data informed the development of a titration algorithm to safely and efficiently initiate and guide LY3209590 and insulin glargine dose adjustments to achieve the same glycemic goals of FBG between 80 and 120 mg/dL (4.4 and 6.6 mmol/L) while minimizing hypoglycemia risk.

See Section 6.5 for dose modification and titration details.

LY3209590

Initial loading dose

The initial loading dose aims to optimize and accelerate glycemic control by allowing participants to reach a steady-state concentration faster. The use of a single one-time-only loading dose enables participants to achieve concentrations close to steady state within a few days rather than a period of weeks. This approach minimizes the risk for hyperglycemia during transition to LY3209590 while reaching steady state. In all cases, starting doses will be based upon existing total daily basal insulin doses.

This approach is supported by the Phase 2 Study BDCM and PK model-based simulations.

Details on deriving the loading dose are described in Section 6.5.

Starting weekly dose

The second dose is the starting weekly dose which is equal to the pre-study total daily basal insulin dose multiplied by 7. The dose will be equivalent to pre-study basal insulin doses, with further adjustment for participants who used insulin glargine U-300 or NPH as their pre-study basal insulin. Details on deriving the starting weekly dose are described in Section 6.5.

Dose adjustments

Dosing will be individualized based on FBG and hypoglycemia events in the prior week, and adjustments may occur weekly from Visit 5 to 15 (Week 2 to 12) and then every 4 weeks thereafter, or more often as clinically indicated.

Insulin glargine

Insulin glargine will be titrated to achieve the FBG target using an algorithm that is patterned after the well-established Riddle algorithm (Riddle et al. 2003) but modified to balance efficacy and hypoglycemia risk for the same FBG targets as LY3209590.

Starting dose

The starting dose of insulin glargine is designed to be equivalent to the pre-study basal insulin dose, with further adjustment for participants who used insulin glargine U-300 or NPH as their pre-study basal insulin. Details on deriving the starting weekly dose are described in Section 6.5.

Dose adjustments

Dosing will be individualized based on FBG and hypoglycemia events in the prior week and adjustments may occur weekly from Visit 4 to 15 (Week 1 to 12) and then every 4 weeks thereafter, or more often as clinically indicated.

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 18 years of age or older, at screening (Visit 1), per local regulations.

Type of participant and disease characteristics

2. Have a diagnosis of T2D according to the WHO criteria, currently treated with basal insulin and at least 2 injections of prandial insulin per day.
3. Are receiving ≥10 units of total basal insulin per day at screening (Visit 1).
4. Are receiving ≤2 units/kg/day of total daily insulin at screening (Visit 1).
5. Have an HbA1c value of 7.0% to 10%, inclusive, as determined by the central laboratory at screening (Visit 1).
6. Have been treated with a stable regimen of one of the following basal insulins used according to local product label with or without noninsulin diabetes therapy for at least 90 days prior to screening (Visit 1).
    - once daily U-100 or U-200 insulin degludec
    - once daily U-100 or U-300 insulin glargine
    - once or twice daily U-100 insulin detemir (Levemir® [Novo Nordisk A/S., Bagsvaerd, Denmark]), or
    - once or twice daily human insulin Neutral Protamine Hagedorn.
7. Have been treated with at least twice daily dosing of any of the following insulins used according to local product label for at least 90 days prior to screening (Visit 1). One dose of prandial insulin must occur at the evening meal.
    - Insulin lispro (U-100 and U-200)
    - Insulin lispro-aabc (Lyumjev™ [Eli Lilly and Co., Indianapolis, IN], U-100 or U-200)
    - Insulin aspart (U-100; including Fiasp® and NovoLog® [Novo Nordisk A/S., Bagsvaerd, Denmark])
    - Insulin glulisine (U-100), or
    - Regular insulin (U-100).
8. Acceptable noninsulin diabetes therapies may include 0 to up to 3 of the following with a stable dose for at least 90 days prior to screening (Visit 1).
    - dipeptidyl peptidase IV inhibitors

- sodium-glucose co-transporter-2 inhibitors
- biguanides (for example, metformin), or
- glucagon-like peptide-1 receptor agonists.

Note: All noninsulin diabetes therapies must be used in accordance with the corresponding local product label at the time of screening (Visit 1), and participants should be willing to continue stable dosing throughout the study according to the protocol.

Weight

9. Have a body mass index ≤45 kg/m^2.

Sex and contraceptive/barrier requirements

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

10. Male study participants: No male contraception required except in compliance with specific local government study requirements.
    Female study participants: For the contraception requirements of this protocol, see Section 10.4.

Study procedures

11. In the investigator's opinion, are well-motivated, capable, and willing to

    - self-inject treatment, as required for this protocol; visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the IP; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the IP
    - adhere to the study basal-bolus insulin MDI regimen and use of study insulins according to injection instructions and protocol
    - use LY3209590 or insulin glargine, and insulin lispro
    - use the glucometer supplied for this study for glucose monitoring, diabetes management, and data collection per protocol
    - wear blinded CGM during specified periods
    - maintain an electronic study diary 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.

Informed consent

12. Capable of giving signed informed consent as described in Section 10.1.3, 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

13. Have a diagnosis of type 1 diabetes mellitus or latent autoimmune diabetes, or specific type of diabetes other than T2D (for example, monogenic diabetes, diseases of the exocrine pancreas, drug-induced or chemical-induced diabetes).
14. Are currently receiving any of the following insulin therapies anytime in the past 90 days:
    - insulin mixtures
    - Afrezza® (insulin human) inhalation powder (MannKind Corporation, Danbury, CT), or
    - continuous subcutaneous insulin infusion therapy
    - regular insulin U-500
15. Have a history of greater than 1 episode of ketoacidosis or hyperosmolar state/coma requiring hospitalization in the 6 months prior to screening (Visit 1).
16. Have had any episodes of severe hypoglycemia, defined as requiring assistance due to neurologically disabling hypoglycemia, within the 6 months prior to screening (Visit 1).
17. Have hypoglycemia unawareness in the opinion of the investigator.
18. Anticipate making changes in personal CGM or FGM use (for example, initiation, stopping, or changing device) during the study.

Cardiovascular

19. Have had New York Heart Association Class IV heart failure or any of the following cardiovascular conditions in the past 3 months prior to screening (Visit 1): acute myocardial infarction, cerebrovascular accident (stroke), or coronary bypass surgery.

Gastrointestinal

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

Hepatic

22. Have acute or chronic hepatitis, cirrhosis, or obvious clinical signs or symptoms of any other liver disease, except NAFLD (that is, persons with NAFLD are eligible for participation), or have elevated liver enzyme measurements, as determined by the central laboratory at screening (Visit 1):
    - Total bilirubin >2x ULN, with the exception of previously diagnosed Gilbert's syndrome
    - ALT or serum glutamic pyruvic transaminase (SGPT) >3x ULN, or
    - AST or serum glutamic oxaloacetic transaminase (SGOT) >3x ULN, or
    - ALP >2.5x ULN.

Renal

23. 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 (Visit 1).

Hematologic

24. Have had a blood transfusion or severe blood loss within 90 days prior to screening (Visit 1).
25. Have known hemoglobinopathy, hemolytic anemia or sickle cell anemia, or any other traits of hemoglobin abnormalities known to interfere with the measurement of HbA1c in the opinion of the investigator.

Malignancy

26. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy within 5 years prior to screening (Visit 1).

    Exceptions:
    - Basal cell or squamous cell skin cancer.

27. Are at increased risk for developing cancer or a recurrence of cancer.

General

28. Have known hypersensitivity or allergy to any of the study medications or their excipients.
29. Have any other serious disease or condition (for example, known drug or alcohol abuse or psychiatric disorder) 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.
30. Have evidence of current or recent, within 6 months timeframe, history of any substance use disorder(s) of any severity as defined by the DSM-5 in the opinion of the investigator, excepting disorders of nicotine or caffeine use.
31. Have had a significant weight gain or loss in the past 3 months in the investigator's opinion (for example, ≥5%).
32. Persons of childbearing potential who

    - are pregnant or intend to become pregnant
    - are lactating/breastfeeding (including the use of a breast pump)
    - are unwilling to remain abstinent or use birth control, or
    - test positive for pregnancy at the time of screening.

Prior or concomitant therapy

33. Have received any of the following nonallowed diabetes medication within prior 90 days including

- meglitinides (glinides)
- sulfonylureas
- pramlintide
- alpha-glucosidase inhibitors, or
- thiazolidinediones.

34. Are receiving chronic or received systemic glucocorticoid therapy for >14 days within the 30 days before screening (Visit 1).

    Exceptions:
    - replacement therapy for adrenal insufficiency
    - topical, intraocular, intranasal, or inhaled preparations, or
    - intra-articular injection.

Prior or concurrent clinical study experience

35. Are currently enrolled in any other clinical study involving an IP or any other type of medical research, judged not to be scientifically or medically compatible with this study.
36. Have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.
37. 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.
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, should it occur. Diabetes self-management counseling should 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/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 LY3209590 or insulin glargine. 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 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.

Investigators and other study personnel are expected to treat participants according to the nationally established standards of care for diabetes management in respective participating countries, except when that treatment would be in conflict with the protocol-provided treatment requirements. If there are no local/national standards of care for diabetes, the investigators should follow current published standards of care from the American Diabetes Association (ADA 2022).

6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3209590	Insulin glargine	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 6.5.1)	Individualized dosing (see Section 6.5.2)	Individualized dosing (see Section 6.5.3)
Route of Administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Frequency of Administration	Once-weekly study basal insulin	Once-daily study basal insulin	Background prandial insulin therapy with meals and as needed
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and used according to authorization	Authorized and used according to authorization

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 glargine frequency of administration

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

Anatomical location of injections

For both LY3209590 and insulin glargine, 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.

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 or insulin glargine, and insulin lispro will be provided in prefilled pen injectors.

Instructions for device use will be provided.

All Product Complaints, including malfunction, use error and inadequate labeling, shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3) and appropriately managed by the sponsor.

6.1.2. Background Therapy

For patients with type 2 diabetes requiring MDI therapy, standard of care stipulates treatment with both basal and prandial bolus insulin. In this study, participants will be treated with LY3209590 or insulin glargine as study basal insulin intervention and insulin lispro as prandial bolus 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 glargine, both in combination with prandial insulin lispro. Correction doses of insulin lispro can also be used.

An additional antihyperglycemic medication should be considered as rescue therapy 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.

Average Fasting Glucose over 2-week Period	Timing of Events
>270 mg/dL (15 mmol/L)	From Visit 15 until Visit 17 (Weeks 12 to 16)
>240 mg/dL (13 mmol/L)	After Visit 17 until Visit 19 (Weeks 16 to 20)
>200 mg/dL (11 mmol/L)	After Visit 19 until Visit 23 (Weeks 20 to 26)

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 are fully optimized, the investigator will decide, in consultation with the participant, on an appropriate intensification of therapy after considering relevant clinical criteria. Therapy intensification may include adjustment of concomitant antihyperglycemic medication, addition of a concomitant antihyperglycemic medication if taking <3 concomitant medications as per Section 6.8.3, or addition of a non-study insulin. Participants who receive a new intervention for hyperglycemia management should also continue administering study insulin therapy for the remaining period in the trial.

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 glargine). 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 randomized and assigned to LY3209590 or insulin glargine using an IWRS. Before the study is initiated, the login 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 glargine.

Participants will be stratified based on

- country
- HbA1c stratum (<8% and ≥8%) at Visit 1
- Routine use of personal CGM or FGM at randomization (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

The investigator or trained designee will assess treatment compliance at each visit based on review of the participant 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 or specific diagnostic tests, they will be retrained as needed by designated study personnel.

Study personnel will ensure participants enter in their e-diary

- the dose amount and date of their basal insulin, and
- prandial insulin dose amount and date, and
    - additional recording of insulin dosing can be requested throughout the study as clinically indicated.

The insulin dose e-diary entries differ by study period as described in this table.

During study period…	**participants will record their dose for…**	**during…**	**at a frequency of…**
Screening and Lead-in	pre-study basal insulin	Week -1 to 0	≥2 days per week.
	Pre-study prandial insulin	Week -1 to 0	≥2 days per week.
Treatment	LY3209590 or insulin glargine	Week 0 to 26	1 day per week
	prandial insulin lispro	the week prior to the visits at Week 0-12, 16, 20, 24, and 26	≥2 days per week.
Safety Follow-up	basal insulin	Week 26 to 31	≥2 days per week.
	Prandial insulin	Week 26 to 31	≥2 days per week.

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

Study personnel will ensure participants perform

- FBGs daily when possible or a minimum of 3 days per week
- 4-point SMBG profiles strongly encouraged to be at least 3 days per week (see Section 8.1.1.1 for further information), and
- SMBG to assess hypoglycemia and hyperglycemia as needed.

6.5. Dose Modification

The overall glycemic targets for study participants during the study treatment period are similar to those recommended by clinical guidelines (ADA 2022). The glycemic targets should be balanced with minimizing the risk of significant hypoglycemia.

Glycemic target	**Target value**
Fasting glucose	80 to 120 mg/dL or 4.4 to 6.6 mmol/L
Nonfasting preprandial glucose	80 to 130 mg/dL or 4.4 to 7.2 mmol/L
Peak postprandial glucose	<180 mg/dL or ≤10.0 mmol/L

Dosing of basal insulin will be individualized based on FBG and hypoglycemia events. The FBG target is 80 to 120 mg/dL (4.4 to 6.6 mmol/L). Additional SMBG values, including 4-point

glucose profiles and the change from bedtime to fasting glucose values, should also be considered.

Titration of the study basal insulin (LY3209590 or glargine) dose should be made at weekly intervals from Week 0 to 12 (titration period, Visit 3 to 15), and every 4 weeks thereafter (Visits 17, 19, and 21) 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 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.

> Note: If the participant has only 2 FBG readings for the week, then the lower 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.

6.5.1. LY3209590 Dose Initiation and Adjustment

This section outlines the LY3209590

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

6.5.1.1. LY3209590 General Dosing Information by Visit

LY3209590 General Dosing Information		
Visit (Week)	**Dose**	**Additional dosing instruction**
Visit 3 (Week 0) Initial loading dose	• FBG >120 mg/dL (6.6 mmol/dL): usual daily basal dose (U) × 7 × 3 • FBG ≤120 mg/dL (6.6 mmol/dL): usual daily basal dose (U) × 7 • Doses should be rounded to the nearest 10	• If the participant's pre-study basal insulin is glargine U-300 or twice daily NPH, the prior daily basal insulin dose should be reduced by 20% when determining usual daily basal dose.
Visit 4 (Week 1) Starting weekly dose	• Usual daily basal dose (U) × 7 • Doses should be rounded to the nearest 10	• If the participant's pre-study basal insulin is glargine U-300 or twice daily NPH, the prior daily basal insulin dose should be reduced by 20% when determining usual daily basal dose. • If a participant experiences nocturnal or fasting hypoglycemia in the previous week, then reduce the starting weekly dose by 10% or as clinically indicated (see Section 6.5.1.2). • ***CAUTION***: Do NOT repeat administration of the loading dose.
Visits 5-15 (Weeks 2-12)	• Doses will be individualized based on FBG and hypoglycemia events (Section 6.5.1.2) • Doses should be rounded to the nearest 10	• **Dose modifications may occur weekly**. • Investigators should factor in 4-point SMBG profile and changes to prandial insulin doses as indicated.
After Visit 15 (Week 12)	• Doses will be individualized based on FBG and hypoglycemia events (Section 6.5.1.2) • Doses should be rounded to the nearest 10	• **Dose modifications may occur every 4 weeks** (Visits 17, 19, and 21) or as clinically indicated. • Investigators should factor in 4-point SMBG profile and changes to prandial insulin doses as indicated. • Dose may be adjusted at any time in response to hypoglycemia.

Abbreviations: FBG = fasting blood glucose; NPH = Neutral Protamine Hagedorn; SMBG = self-monitoring blood glucose.

Visit 3 (Week 0 – Randomization) loading dose

At Visit 3 (Week 0), participants will stop their pre-study basal and prandial insulin therapy and initiate study basal and prandial 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 most recent 3 FBGs in the week prior to randomization (Visit 3 [Week 0]).

6.5.1.2. LY3209590 Dose Adjustment

From Visit 5 until the end of treatment (Week 26), assess hypoglycemia events over the previous week, and reduce the LY3209590 dose if the participant meets a criterion for hypoglycemia dose reduction according to the table below.

Hypoglycemia Dose Reduction Criteria	Decrease the LY3209590 dose:
1 nocturnal hypoglycemia event ≤70 mg/dL (3.9 mmol/L) [a]	to previous lower dose [b]
1 fasting hypoglycemia event ≤70 mg/dL (3.9 mmol/L) [a]	
Any confirmed severe hypoglycemia event	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 and round dose to the nearest 10 units.

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

This table provides guidance for dose adjustments based on median FBG from the 3 most recently recorded FBG data from the previous week. Subject with lead-in FBG values ≤120 mg/dL or ≤6.6 mmol/L may be titrated with the more gentle titration algorithm throughout the study.

LY3209590 Dose Adjustment		
Median FBG mg/dL (mmol/L)	**Median Lead-In FBG ≤120 mg/dL (6.6 mmol/L)[a]**	**Median Lead-In FBG >120 mg/dL (6.6 mmol/L)**
<80 (4.4)	-10 to -20 units	-20 units
80–120 (4.4-6.6)	No change	No change
121–140 (6.7-7.7)	+10 units	+20 units
>140 (7.7)	+20 units	+40 units

Abbreviations: FBG = fasting blood glucose.

[a] Investigators may choose the more gentle titration algorithm for subjects with a pre-study basal insulin dose <20 units and median FBG >120 mg/dL (6.6 mmol/L)

Note: 120 mg/dL is rounded to 6.6 mmol/L and 121 mg/dL is rounded to 6.7 mmol/L to allow for distinct thresholds in consideration of glucose meters only displaying 1 significant digit after the decimal point.

6.5.2. Insulin Glargine Dose Initiation and Adjustment

This section outlines the insulin glargine

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

6.5.2.1. Insulin Glargine General Dosing Information by Visit

At Visit 3 (Week 0), participants will stop their pre-study basal and prandial insulin therapy and initiate study basal and prandial insulin therapy.

The first glargine dose is based on the participant's prior daily basal insulin dose from the week prior to randomization (Visit 3 [Week 0]). If participant's usual basal insulin dosing time overlaps with the visit, they should take the first dose at the site. If participant's usual basal insulin dosing time does not coincide with the visit, they are not required to administer at the site.

This table provides general dosing information across visits for all participants randomized to insulin glargine.

Insulin Glargine General Dosing Information		
Visit	**Dose**	**Additional dosing instruction**
Visit 3 (Week 0) starting dose	Equivalent to pre-study usual daily basal insulin dose	**Note:** If the participant's pre-study basal insulin is glargine U-300 or twice daily NPH, the prior daily basal insulin dose should be reduced by 20% when determining usual daily basal insulin dose.
Visits 4-15 (Weeks 1-12)	Doses will be individualized based on FBG and hypoglycemia events	**Dose modifications may occur weekly**. Investigators should factor in 4-point SMBG profile and changes to prandial insulin doses as indicated. Dose may be adjusted at any time in response to hypoglycemia.
After Visit 15 (Week 12)	Doses will be individualized based on FBG and hypoglycemia events	• **Dose modifications may occur every 4 weeks** (Visits 17, 19, and 21) or as clinically indicated. Investigators should factor in 4-point SMBG profile and changes to prandial insulin doses as indicated. • Dose may be adjusted at any time in response to hypoglycemia.

Abbreviations: FBG = fasting blood glucose; NPH = neutral protamine Hagedorn; SMBG = self-monitoring blood glucose.

6.5.2.2. Insulin Glargine Dose Adjustment

For Visit 4 until end of treatment (Week 26), assess hypoglycemia events over the previous week, and reduce the insulin glargine dose if the participant meets criterion for hypoglycemia dose reduction according to this table.

Hypoglycemia Dose Reduction Criteria	Decrease the glargine dose:
1 nocturnal hypoglycemia event ≤70 mg/dL (3.9 mmol/L) [a]	to previous lower dose [b]
1 fasting hypoglycemia event ≤70 mg/dL (3.9 mmol/L) [a]	
Any confirmed severe hypoglycemia	by 3 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 glargine dose according to this table. This table provides guidance for dose adjustments based on median FBG from the 3 most recently recorded FBG data from the previous week.

Insulin Glargine Dose Adjustment		
If the median FBG is…		Then…
mg/dL	mmol/L	
<80	<4.4	reduce the dose by 3 U.
80-120	4.4-6.6	do not change the dose.
121-140	6.7-7.7	increase the dose by 3 U.
>140	>7.7	increase the dose by 6 U.

Abbreviations: FBG = fasting blood glucose; U = units.
Note: 120 mg/dL is rounded to 6.6 mmol/L and 121 mg/dL is rounded to 6.7 mmol/L to allow for distinct thresholds in consideration of glucose meters only displaying 1 significant digit after the decimal point.

6.5.3. Prandial Insulin Lispro Dose Initiation and Adjustment

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

During the treatment period (Visit 3 to 23), all participants will be treated with insulin lispro. The initial insulin lispro doses may be converted unit-for-unit from the pre-study prandial insulin regimen.

Prandial insulin is titrated based on glucose and hypoglycemia data and other clinical factors. 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.

To facilitate prandial insulin dose titration, subjects should be strongly encouraged to check 4-point glucose profiles for at least 3 days each week.

- fasting
- pre-midday meal
- pre-evening meal, and
- bedtime.

See Section 8.1.1.1 for further information about 4-point SMBG.

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. If participants enter the study not covering all meals with prandial insulin, investigators can choose to increase the numbers of meals covered by prandial insulin as needed to reach glycemic targets.

Participants must remain on at least 2 injections of prandial insulin per day with one at the evening meal except if safety concerns require a decrease in the number of prandial insulin injections per day.

A 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. Implementation of the correction factor (for example, via an equation or a sliding scale) is per investigator discretion in consultation with the participant.

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 SMBG, hypoglycemia data, and other clinical factors at clinic and telephone visits and as clinically indicated.

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 SMBG, hypoglycemia data and other clinical factors at clinic and telephone visits and as clinically indicated.

Assessment of the prandial insulin dose includes review of the SMBG levels in the previous week 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 glucose values from the pre-midday meal.

Prandial Insulin Dose Assessed	Corresponding SMBG for Review
Fasting or morning premeal	Pre-midday meal glucose values[a]
Midday premeal	Pre-evening meal glucose values[a]
Evening premeal	Bedtime glucose values[a]

Abbreviation: SMBG = self-monitored blood glucose.
[a] Investigators can request 2-hour post-meal glucose values or other additional glucose values from participants to aid titration.

The median SMBG profile from premeal or bedtime is used as the "adjustment value" and the change in insulin lispro dose (either increase or decrease) is based upon this value as described in the table below.

If Mealtime Dose of Insulin Lispro is:	Glucose Below Target Range	Glucose at Target Range	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 with previous/current insulin regimen and recent glucose profiles. Alternatively, the correction factor may initially be calculated as follows:

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

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

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

The sponsor will not provide participants with any 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 23 [Week 26] or ED 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 25 of the study and can begin the transition to the non-study insulin after Visit 23 (Week 26). At Visit 23 (Week 26), the investigator will review instructions for transitioning to the non-study insulin 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 120 mg/dL (6.6 mmol/L), and then daily basal insulin would be initiated and adjusted based on fasting glucose, other SMBGs, hypoglycemia evaluation, and other clinical factors. 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. In addition to Visit 801, unscheduled visits may occur during this time to facilitate the transition to non-study daily basal insulin.

Study participants treated with insulin glargine

Participants assigned to the insulin glargine treatment arm will transition to their non-study basal insulin after Visit 23 (Week 26) with dose adjustment per investigator discretion based on fasting glucose, other SMBGs, and hypoglycemia evaluation and in accordance with the local product label for the basal insulin.

6.7. Treatment of Overdose

An overdose of LY3209590 or insulin glargine, defined as a 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 glargine depending on the participant treatment assignment.

In the event of an overdose, the investigator or 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
- consider holding non-insulin diabetes medications, if clinically appropriate
- closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect, and
- if the participant is assigned to LY3209590, a plasma sample for PK analysis may be obtained.

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 (see Section 5.2).

Acceptable non-insulin diabetes treatments are described in Section 6.8.3

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.

For diabetes and lipid-modifying medications, collect dosage information including dose and frequency.

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

6.8.1. Medications with Approved Weight Loss Indication

Allowed usage of weight loss medication during the study

A participant may use a medication that promotes weight loss if they are on stable therapy 90 days prior to screening (Visit 1).

Allowed medications include, but are not limited to

- over-the-counter medications, including food supplements that promote weight loss
- liraglutide 3.0 mg
- orlistat
- sibutramine
- mazindol
- phentermine
- phentermine and topiramate combination
- naltrexone and bupropion combination, or
- semaglutide injection 2.4 mg.

Prohibited usage of weight loss medication during the study

After screening (Visit 1), no prescription or over-the-counter medications that promote weight loss may be initiated or changes in dosage allowed.

6.8.2. Chronic Systemic Glucocorticoid Medication

Chronic systemic glucocorticoid therapy is allowed for no more than one 14-consecutive day period during study treatment period.

This restriction does not apply to glucocorticoid therapy used as replacement therapy for adrenal insufficiency, or topical, intraocular, intranasal, inhaled preparations, and intra-articular injections.

6.8.3. Antihyperglycemic Medications

This table shows the conditions for use of other antihyperglycemic medications.

Drug Class	Use during Screening or Lead-In	Conditions for Use after Randomization			
	Y = yes, if on stable therapy 90 days prior to screening. **N** = No	During Treatment Period	Acute Therapy Treatment for up to 14 days	Rescue Therapy	During Safety Follow-Up Period
Metformin[a]	Y	Yes, if on stable therapy 90 days prior to screening	N/A	Y[b]	Y[c]
GLP-1 Ras	Y		N/A	Y[b]	Y[c]
DPP-4 inhibitors	Y		N/A	Y[b]	Y[c]
SGLT2 inhibitors	Y		N/A	Y[b]	Y[c]
Non-study daily basal insulins	Y	N	Yes, only if study basal insulin is temporarily discontinued	See Note[d]	Y
Non-study prandial insulin	Y	N	Yes, only if study prandial insulin is temporarily discontinued	Y	Y
Insulin mixtures	N	N	N	N	N
Meglitinides	N	N	N/A	N	N
Alpha-glucosidase inhibitors	N	N	N/A	N	N
Sulfonylureas	N	N	N/A	N	N
Thiazolidinediones	N	N	N/A	N	N

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = no; N/A = not applicable; SGLT2 = sodium-glucose cotransporter 2; Y = yes.

[a] Switching metformin manufacturer is allowed if the dosage is the same. Changing to a metformin formulation with a different action profile (that is, from short-acting to long-acting metformin) is not permitted.

[b] For rescue therapy, concomitant antihyperglycemic medication doses may be increased if the dose is below maximum approved dose per country-specific label.

[c] Participants can continue on these therapies but should not start a new class of therapy during the 5-week safety follow-up period.

[d] Participants who require a non-study basal insulin as rescue therapy must discontinue study basal insulin therapy (LY3209590 or insulin glargine). The participant will remain in the study and follow procedures for the remaining study visits.

Dose adjustments of allowable non-insulin antihyperglycemic medications are permitted after randomization under the following circumstances:

- situations that require short-term treatment interruption consistent with the product labeling for each respective country
- situations that require dose adjustment or discontinuation per country-specific label, for example, in the case of reduced estimated glomerular filtration rate
- in the case of increased hypoglycemia risk during the treatment period (as described in Section 8.3.6), and
- for safety reasons at the discretion of the investigator.

Any changes in dose should be documented.

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 glargine. 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 glargine permanently may receive another glucose-lowering medication. The new glucose-lowering medication will be recorded on the appropriate CRF.

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

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

7.1.1. Liver Chemistry Stopping Criteria

The study drug should be interrupted or discontinued if one 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 LY3209590 or insulin glargine 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 LY3209590 or insulin glargine 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%)	

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

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-drug 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

Criteria for temporary discontinuation of LY3209590 or insulin glargine

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 21 consecutive days for insulin glargine or 3 consecutive doses for LY3209590 at any time during the study. This information should be documented by the investigator.

Guidance when temporary discontinuation of LY3209590 or insulin glargine occurs

Every effort should be made by the investigator to maintain participants in the study and to restart LY3209590 or insulin glargine 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 glargine

The dates of LY3209590 or insulin glargine 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 glargine 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 T2D.

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

If the participant has not already discontinued the LY3209590 or insulin glargine, the participant will be permanently discontinued from the LY3209590 or insulin glargine 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 glucose ranges measured during the CGM session prior to Week 26
- Fasting glucose, and
- Patient-reported outcomes questionnaires
    - EQ-5D-5L
    - DID-EQ
    - Basal Insulin Experience: Preference
    - Basal Insulin Experience: Likelihood of incorporating into routine

See Section 3 for specific efficacy endpoints.

This section will outline glucose monitoring and PRO.

8.1.1. Glucose Monitoring

Participants **must** use only the study-provided glucometer during the study.

8.1.1.1. Self-Monitoring of Blood Glucose (SMBG)

Glucometer for participant use during the study

Participants will receive a sponsor-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.

Participants should use the glucometer

- whenever hypoglycemia is experienced or suspected
- when there is awareness of increased risk related to changes in dietary intake, physical activity, or inadvertent or atypical insulin dosing

- at meals in order to aid in prandial insulin dosing
- to check for hyperglycemic events
- at their own discretion, or
- as directed by the investigator.

When to measure fasting blood glucose during the study

Site personnel will train the participant to measure FBG daily when possible, and a minimum of 3 times per week using the study-provided glucometer.

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

When to measure 4-point self-monitored blood glucose profile during the study

Site personnel will train the participant to measure a 4-point SMBG profile using the study-provided glucometer.

The 4-point SMBG profile should be measured

- upon waking in the morning, prior to food or caloric beverage intake (FBG)
- ahead of the midday meal
- ahead of the evening meal, and
- at bedtime.

Subjects are strongly encouraged to perform 4-point SMBG ≥3 days per week. Subjects should be encouraged to perform 4-point SMBG profiles on consecutive days of the week so that the change from bedtime glucose to fasting glucose can be assessed by the investigator. In addition, subjects should be encouraged to measure an SMBG ahead of administration of all prandial insulin and at bedtime to assist in insulin dosing decisions throughout the study. Investigators may request 2-hour postprandial glucose readings, overnight glucose readings, or other additional glucose readings at their discretion.

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 Systems

The Dexcom G6 Continuous Glucose Monitoring System will be used in blinded mode during the study. The blinded CGM will not display the sensor glucose readings to the participant or investigator, and high and low glucose alerts will not be available to the participant.

Training and initiation

Site personnel will dispense CGM supplies and initiate blinded CGM sessions at the times specified according to the SoA. Participants will be trained on the CGM system before use and will be required to replace the sensor at designated intervals per the investigator instruction. A CGM Participant User Guide that provides an overview of device components and study specific instructions is available for at-home use.

Participants are not allowed to connect the transmitter of the Dexcom G6 system to a personal smartphone, smartphone application, or other system.

CGM data compliance

At the end of each CGM session, participants will return the CGM system to the site. Site personnel will upload the CGM data to a vendor-hosted online portal to view data capture compliance using the available reports and visualization tools. The compliance threshold of 80% for each session is defined as the percentage of actual data versus expected data collected during a session. Site personnel will re-educate participants on CGM operation and requirements when session compliance is <80%.

To minimize data loss, the CGM service vendor will review site uploads 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.

Participants may continue to use their personal CGM in addition to the study provided CGM if they were using CGM before screening (Visit 1). Participants who use a personal CGM must also check FBGs, 4-point SMBGs, and BGs for hypoglycemia events as specified in the protocol. Subjects must check a BG prior to treatment for hypoglycemia even if personal CGM values indicate hypoglycemia unless it would be unsafe to do so.

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.

Order of administering the questionnaires during the visit

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

Preferred administration order of these questionnaires is

1. EQ-5D-5L
2. Diabetes Injection Device Experience Questionnaire
3. Basal Insulin Experience: Preference, and
4. Basal Insulin Experience: Likelihood of incorporating into routine.

8.1.2.1. 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 profile and a single index value for health status 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. In addition to the health profile, a 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 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. The participant rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health). In conjunction with the health state data, it provides a composite picture of the respondent's health status.

8.1.2.2. Diabetes Injection Device Experience Questionnaire

Description of DID-EQ

The DID-EQ (Matza et al. 2018) is a self-administered, 10-item questionnaire designed to assess participants' perceptions of diabetes injection delivery systems for T2D.

Scoring for DID-EQ

Each item is rated on a 4-point scale with higher scores indicating more positive perceptions of the injection device.

Items 1 to 7 focus on specific characteristics of diabetes injection device, and these 7 items comprise the Device Characteristics subscale.

In addition, there are 3 global items:

- Item 8 assessing overall satisfaction
- Item 9 ease of use, and
- Item 10 convenience of diabetes injection devices.

These 3 global items are each scored separately.

8.1.2.3. 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.

8.1.2.4. Basal Insulin Experience: Likelihood of Incorporating into Routine

The Basal Insulin Experience: Likelihood of Incorporating into Routine is a self-report scale consisting of a single question to understand the participant's likelihood of incorporating their study insulin into their diabetes management routine. 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 (Section 1.3).

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 T2D, T2D-related illnesses, and injection-site reactions.

8.2.2. Vital Signs

Blood pressure and pulse rate will be measured as 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 study 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 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 (Section 10.5), 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.

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)

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

What to do if the abnormal condition persists or worsens

If the abnormality 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

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

Frequency of monitoring

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

Comprehensive hepatic evaluation

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 these conditions occur:

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

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

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

What a comprehensive evaluation should include

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

Based on the 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 (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), 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
- discontinues study intervention due to a hepatic event, or
- has changes in laboratory results described in this table.

If a participant with baseline	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 ≥2x baseline on 2 or more consecutive blood tests	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; CRF = case report form; TBL = total bilirubin; ULN = upper limit of normal.

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 Section 10.3, Appendix 3:

- Adverse events (AEs)
- Serious adverse events (SAEs), and
- 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
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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed PC 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	PC form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; PC = product complaint; SAE = serious adverse event.

[a] SAEs 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 LY3209590 or insulin glargine.

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. Adjudicated Events: Cerebrocardiovascular 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, lipodystrophy, 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.

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 (Section 1.3), 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 in Section 10.2, 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 T2D, mechanisms of action of LY3209590 or research methods, or in validating diagnostic tools or assay(s) related to T2D.

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, venous blood samples from all study participants will be collected 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 anti-drug antibody (TE ADA) is 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 glargine on glycemic control as measured by change in HbA1c from baseline at Week 26 in participants with T2D currently on basal insulin and at least 2 injections per day of prandial insulin.

The null hypothesis (H_0) to be tested is the difference in the change in HbA1c (LY3209590 – insulin glargine) from baseline at Week 26 is greater than the noninferiority margin (NIM).

The NIMs of 0.4% and 0.3% will both be tested to meet different regulatory requirements. Each NIM will have its own familywise error rate. The upper bound of the 2-sided 95% CI will be used for testing the noninferiority hypothesis.

Secondary hypotheses

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

- change from baseline in HbA1c at Week 26
  H_0: the difference (LY3209590 – insulin glargine) ≥0.0
- The percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 26
  H_0: the odds ratio (LY3209590 vs insulin glargine) ≤1
- the event rate of nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment period up to Week 26
  H_0: the relative event rates (LY3209590 vs insulin glargine) ≥1

These hypotheses and the primary hypothesis will be tested using a strategy to control the overall type 1 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 other 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

This table defines the populations for the purpose of analysis.

Analysis Populations or Datasets	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 glargine. Participants will be analyzed according to the treatment they were assigned.
Efficacy Analysis Set 1 (EAS1) for treatment regimen estimand	The data will include • mITT Population excluding participants discontinuing the study treatment due to inadvertent enrollment • all measurement regardless of the use of study treatment or rescue medications.
Efficacy Analysis Set 2 (EAS2) for efficacy estimand	The data will include • mITT Population excluding participants discontinuing the study treatment due to inadvertent enrollment • measurement up to the discontinuation of study treatment or the initiation of rescue medications.
Safety Analysis Set (SS)	The data will include • mITT Population • all measurement 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 and safety analyses will be conducted on either EAS1 or EAS2, and the safety analyses 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 specified, the other secondary and tertiary efficacy measures will be analyzed using the data up to the discontinuation of study treatment (EAS2), defined by the date of last study dose + 10 days or the initiation of rescue therapy, 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 demonstrate noninferiority of LY3209590 compared to insulin glargine on the HbA1c change from baseline at Week 26 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 for the EAS1 regardless of the use of study treatment or rescue therapy.

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 glargine prior to Week 26 but have non-missing measures at Week 26.

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 will be imputed by return-to-baseline approach.

Analysis model

After the imputation, the observed and imputed data will be analyzed by the analysis of covariance (ANCOVA).

The model will include treatment, strata (country and use of personal CGM or FGM), and baseline HbA1c value. 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 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 study treatment or use of rescue therapy.

The mixed-model for repeated measures (MMRM) will be used, and the missing values will be handled in the MMRM analysis under the assumption of missing at random.

Analysis model

The MMRM model will include treatment, strata (country and use of personal CGM or FGM), visit and treatment-by-visit interaction as fixed effects, and baseline HbA1c value 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, treatment LS mean difference (LY3209590 – insulin glargine) in the HbA1c change from baseline to Week 26 will be estimated. For both estimands, LY3209590 will be declared noninferior to insulin glargine if the upper limit of the 2-sided 95% CI for the LS mean difference in the HbA1c change from baseline is below the NIM (+0.4% or +0.3% depending on regulatory requirements).

The HbA1c is reported in unit of % and will be converted to the unit of mmol/mol using the following 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 glargine for

1) change in HbA1c from baseline at Week 26
2) the percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 26
3) the event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment period up to Week 26

The superiority test in change from baseline at Week 26 in HbA1c will be based on the same primary endpoint analysis described above.

The percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) will be analyzed by logistic regression model including treatment, strata (country and use of personal CGM or FGM), baseline HbA1c value, and baseline incidence of nocturnal hypoglycemia as independent variables.

The rate of nocturnal hypoglycemia will be analyzed by a negative binomial regression with treatment, baseline HbA1c, baseline incidence of nocturnal hypoglycemia as independent variables, and log (exposure in year) as the offset.

9.3.3.2. Other Secondary Endpoints

Other secondary endpoints include various measures for efficacy, patient-reported outcome measures and safety. Efficacy and patient-reported outcome measures will be analyzed using EAS2 unless otherwise noted. Safety measures will be analyzed using the SS regardless of treatment discontinuation and use of rescue therapy.

Analysis details will be provided in the SAP.

9.3.4. Tertiary Endpoint(s) 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 glargine, or reported to worsen in severity from baseline, will be considered as TEAEs. The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity.

Summary statistics will be provided for incidence of

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

Hypoglycemia analysis

The participant-reported hypoglycemia will be analyzed using data from 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 Level 2 and Level 3.

The analysis periods of 0-6, 0-12, 0-26, 12-26 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.

For continuous safety variables (for example, laboratory measures, vital signs and weight), MMRM or ANCOVA models will be used. For categorical safety variables (for example, AEs, incidence of hypoglycemia, treatment-emergent abnormal laboratory measurements), either Fisher's exact test or logistic regression will be used for treatment comparison.

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

The number and percentage of participants who are TE ADA positive (TE ADA+) will be summarized by treatment group.

The frequency of cross-reactive binding to endogenous insulin may also be summarized for the participants with TE ADA+.

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

Definition of TE ADA+

A participant is considered TE ADA+ 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.

9.3.6.3. Subgroup Analysis

Detailed description of the subgroup variables will be provided in the SAP.

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 is specified in the DMC Charter or a separate unblinding plan document.

9.5. Sample Size Determination

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

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin glargine on glycemic control as measured by change from baseline at Week 26 in HbA1c in participants with T2D currently on basal insulin and at least 2 injections per day of prandial insulin.

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

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

The 568 completers will provide 90% statistical power to demonstrate the superiority (LY3209590 vs insulin glargine) on percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 26 using a Fisher's Exact test assuming 28.7% of insulin glargine patients achieve this target and 42% of LY3209590 patients achieve this target.

The 568 participants will provide approximately 83% 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 26 (assuming event rate of 0.55 [SD = 2.6] and 1.1 [SD = 2.6] events per participant per year for LY3209590 and insulin glargine, respectively, representing a 50% decrease in event rate for LY3209590 over insulin glargine) 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 GCP Guidelines
  - International Organization for Standardization (ISO) 14155
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, 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
  - 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 Code of Federal Regulations 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 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 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 all deaths and 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 analyses.

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

Additionally, electronic clinical outcome assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant, caregiver, or study personnel, into an instrument, for example, hand-held smart phone or tablet. The eCOA 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 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

- study termination
    - discontinuation of further study intervention development
- 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, or
    - 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]
Pharmacokinetic	Sponsor or designee	1 year
Exploratory biomarker	Sponsor or designee	15 years
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 by 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 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 LY3209590 concentration	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites
Additional Testing	Assayed by Lilly-designated laboratory
C-Peptide	
HbA1c	
Glucose	Fasting per SoA
Exploratory Biomarker Storage Samples	Assayed by Lilly-designated laboratory Results will not be provided to the investigative sites
Serum	
Plasma (EDTA)	
Immunogenicity Samples	Assayed by Lilly-designated laboratory 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 test 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. Note: The optimal collection time is from 1 to 2 hr 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. If samples were already collected per the SoA on the same day as the event, then duplicate samples are not collected. Note: The optimal collection time is up to 12 hr after the start of the event.	Serum	LY3209590 ADAs
	Plasma	LY3209590 concentration

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

[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.

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.
- 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).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. See definitions in Section 10.9.

- 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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 preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

- 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 an 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 Product Information for insulin glargine and insulin lispro 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 an 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 an 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 an 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 an 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

Females 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.

Females not of childbearing potential

Females are considered women not of childbearing potential if

- absence of a uterus including having a congenital condition 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 state
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 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, selective estrogen receptor modulators (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
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• 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. 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.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives

	• contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• barrier method with use of a spermicide o male condom with spermicide o diaphragm with spermicide or cervical sponge, or o female condom with spermicide 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 whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

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

Hepatic evaluation testing

See protocol 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/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 Section 10.3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.7. Appendix 7: Country-specific Requirements

10.7.1. Germany

This section describes protocol changes applicable for adult participants in study sites in Germany.

10.7.1.1. Provisions for Changes in Study Conduct During Exceptional Circumstances

In Germany, the temporary measures described in the "Provisions for Changes in Study Conduct During Exceptional Circumstances" (Section 10.8, Appendix 8) are applicable only to "the COVID-19 pandemic."

10.7.1.2. Changes Related to "Legally Authorized Representative," "Legal Guardian," "Parents"

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
7.2. Participant Discontinuation/Withdrawal from the Study 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.9. Appendix 9: Abbreviations and Definitions	Deleted references to "legally authorized representative," "legal guardian," "parents"	The German Drug Law (Arzneimittelgesetz – AMG) with reference to EU Regulation 536/2014 requires that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.

The revised text in the following sections show the changes applicable to adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~.

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 T2D.

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

The definitions of the following events can be found in Section 10.3, 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~~).

10.9. Appendix 9: Abbreviations and Definitions

enter	Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~

10.8. Appendix 8: 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 ERBs, 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 GCP, 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 CRF.

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 23 (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.

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
blinding	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CGM	continuous glucose monitoring: can refer to study procedure or analysis of representative CGM derived variables including but not limited to: • 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 with interquartile ranges
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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.
CT	computed tomography
CV	cardiovascular
Device deficiencies	equivalent to product complaint
DID-EQ	Diabetes Injection Device Experience Questionnaire
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.
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EAS	Efficacy Analysis Set
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
ED	Early Discontinuation
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	EuroQol 5 dimensions 5 levels
FBG	fasting blood glucose
FGM	Flash glucose monitoring
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c

IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (see also "investigational product") 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/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."
IP	investigational product
IRB	Institutional Review Board
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
LLT	lowest level term
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 involve a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • 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
mITT	Modified Intent-to-Treat
MMRM	mixed-model for repeated measures
NAFLD	nonalcoholic fatty liver disease
NIM	noninferiority margin
NIMP	Non-investigational Medicinal Product
NPH	neutral protamine Hagedorn
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
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT-INR	prothrombin time, INR
QTLs	quality tolerance limits
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.

SMBG	self-monitoring of blood glucose
SoA	schedule of activities
SS	Safety Analysis Set
T1D	type 1 diabetes
T2D	type 2 diabetes
TBL	total bilirubin
TE	treatment emergent
TE ADA	treatment-emergent anti-drug 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
WHO	World Health Organization
WOCBP	women of childbearing potential

10.10. Appendix 10: Protocol Amendment History

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

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 and rescue medication. These 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
3. Objectives, Endpoints, and Estimands	Added initiation of rescue therapy to primary and secondary estimands. Added "2" intercurrent events in the description for remaining intercurrent events under efficacy regimen estimand attribute. Replaced "targeted study" with "study eligible" participants in the primary clinical question of interest for United States registration.	Addressing regulator feedback. For clarity.
5.1. Inclusion Criteria	In inclusion criterion 5, added "as determined by the central laboratory".	For clarity.
	In inclusion criterion 7, removed "stable regimen" and added "any"	
5.2. Exclusion Criteria	In exclusion criterion 22, added cirrhosis as a liver disease. ALT and AST thresholds were increased from 2.5x ULN to 3x ULN.	For clarity. Addressing regulator feedback.
	In exclusion criterion 37, added wording "after having signed the informed consent form (ICF)" and "after receiving at least 1 dose of the study basal insulin".	For clarity.
6.1. Study Intervention(s) Administered	Added dose formulation and unit dose strength for study interventions used in this study.	For clarity.
6.1.3. Rescue Therapy for Management of Participants with Severe, Persistent Hyperglycemia	Added new subsection and content for rescue therapy.	Addressing regulator feedback.

Section # and Name	Description of Change	Brief Rationale
during the Treatment Period		
6.3. Measures to Minimize Bias: Randomization and Blinding	Revised “use of personal CGM or FGM” to “Routine use of personal CGM or FGM at randomization (yes/no)”.	For clarity.
6.8.3. Antihyperglycemic Medications	Added rescue therapy in the table for use of other antihyperglycemic medications and a footnote.	Related to addition of rescue therapy.
8.1.1.2. Continuous Glucose Monitoring Systems	Updated the type of continuous glucose monitoring (CGM) to be utilized in the study along with training and initiation and CGM data compliance.	For clarity.
9.2. Analyses Sets	Updated the analysis populations or datasets for anticipated requirement for some countries.	To meet the anticipated requirement for excluding inadvertently enrolled participants in some countries.
9.3. Statistical Analyses	Updated according to the changes made in analyses sets. Added use of rescue therapy	Aligned with analyses sets and for clarity.
10.9. Appendix 9: Abbreviations and Definitions	Added CGM parameters.	To address regulator feedback.
	Added Modified Intent-to-Treat (mITT), Efficacy Analysis Set (EAS) and Safety Analysis Set (SS).	Editorial consistency.

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