Protocol I8H-MC-BDCX (b)

A Phase 3, Parallel-Design, Open-Label, Randomized Control Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Degludec in Insulin Naïve Adults With Type 2 Diabetes

NCT05362058

Approval Date: 13-May-2022

Title Page

Protocol Title:

A Phase 3, Parallel-Design, Open-Label, Randomized Control Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Degludec in Insulin Naïve Adults with Type 2 Diabetes

Protocol Number: I8H-MC-BDCX

Amendment Number: b

Compound: LY3209590

Brief Title:

Efficacy and Safety of LY3209590 Compared to Degludec in Adults with Type 2 Diabetes Who Are Starting Basal Insulin for the First Time

Study Phase: 3

Acronym: QWINT-2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

IND: 129390

EudraCT: 2021-005891-21

Document ID: VV-CLIN-040206

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)	*15 Feb 2022*
Original Protocol	*04 Feb 2022*

Amendment [b]

This amendment is considered to be nonsubstantial.

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.

Section no and Name	Description of Change	Brief Rationale
1.1. Synopsis	Edited the subsections 'Overall Design', 'Brief Summary', and 'Intervention Groups and Duration'	Correction
	Updated the section to align with the changes in the main body of the protocol	For consistency
1.2. Schema	Added a note below the schema as follows: During the safety follow-up period, CGM device will be worn for 4 weeks (52 to 56), but device return and data download will occur a week later (on Week 57).	For clarity
1.3.1. Screening Visit 1, Lead-In Visit 2, and Treatment Visits 3-18	In CGM sensor insertion line, added "Participants will be required to replace the sensor at designated intervals per the investigator instruction. Additional unscheduled visits may be needed for participants support" under comments column	For clarity
1.3.2. Treatment Visits 19 to 31, Early Discontinuation, Unscheduled Visits, and Safety Follow-up Visits 801 and 802	In CGM sensor insertion line, added "Participants will be required to replace the sensor at designated intervals per the investigator instruction. Additional unscheduled visits may be needed for participants support" under comments column	For clarity
1.3.2. Treatment Visits 19 to 31, Early Discontinuation, Unscheduled Visits, and Safety Follow-up Visits 801 and 802	In CGM device return and data download line, added "CGM device will be worn for 4 weeks (52 to 56), but device return and data download will occur a week later (on Week 57)."	For clarity
3. Objectives, Endpoints, and Estimands	Removed "Incidence" from the subgroup tertiary objective endpoint of Level 1 and composite of Level 2 and 3 hypoglycemia events during the treatment period	Correction

3. Objectives, Endpoints, and Estimands	Moved the "Evaluation of Immunogenicity - Incidence of positive LY3209590 treatment-emergent anti-drug antibodies" under Tertiary Safety Parameters	For consistency
3. Objectives, Endpoints, and Estimands	Removed "Potential intrinsic and extrinsic factors" under tertiary objective – Characterize the PK/PD of LY3209590	For consistency
3. Objectives, Endpoints, and Estimands	In Primary estimand subsection, United States registration, edited the text in primary clinical question of interest to clarify "study eligible" participants	For clarity
3. Objectives, Endpoints, and Estimands	Edited Treatment regimen estimand attributes table - Population: added cross reference to Section 9.2, and removed other cross references	For clarity
3. Objectives, Endpoints, and Estimands	In Primary estimand subsection, Registration for countries outside the United States, edited the text in primary clinical question of interest to clarify "study eligible" participants	For clarity
3. Objectives, Endpoints, and Estimands	Edited Efficacy estimand attributes table - Population: added cross reference to Section 9.2, and removed other cross references	For clarity
4.1. Overall Design	Updated CGM related items to the description of the visits	For clarity and consistency
4.2. Scientific Rationale for Study Design	Added "of 52 weeks" to Study Duration subsection	For clarity
5.1. Inclusion Criteria	In inclusion criterion 3, added "as determined by central laboratory"	For clarity
5.1. Inclusion Criteria	In inclusion criterion 4, updated the language	For clarity
5.1. Inclusion Criteria	In inclusion criterion 8, added a note "The use of personal, non-study CGM device will not be allowed	For clarity
5.2. Exclusion Criteria	In exclusion criterion 20, increased AST and ALT thresholds from 2.5x ULN to 3x ULN	To address regulatory feedback
5.2. Exclusion Criteria	In exclusion criterion 20, updated the language of non-alcoholic fatty liver disease	For consistency
5.2. Exclusion Criteria	In exclusion criterion 26, added "glimins"	For clarity
5.2. Exclusion Criteria	In exclusion criterion 29, added wording "after having signed the ICF" and "after receiving at least 1 dose of the study basal insulin"	For clarity

6.1.2. Rescue Medicine for Management of Severe or Persistent Hyperglycemia	Modified the rescue criteria (timing to initiate the rescue therapy) to match the program strategy	To address regulatory feedback
	Modified the language in paragraphs 1 and 3; moved paragraph 4; and included the last two paragraphs	To address regulatory feedback
6.3. Measures to minimize Bias: Randomization and Blinding	In the Randomization and stratification subsection, added "Yes/No" to the use of sulfonylurea and GLP-1 RA at randomization	For clarity
6.5.1.3. LY3209590 Dose Adjustment Based on Hypoglycemia Events	Added "over the previous week" to the second column heading of the table	For clarity
6.5.2.3 LY3209590 Dose Adjustment Based on Hypoglycemia Events	Added "over the previous week" to the second column heading of the table	For clarity
6.7. Treatment of Overdose	Added "consider holding sulfonylureas if clinically appropriate"	To optimize the overdose management guidance
6.8.3. Antihyperglycemic Medications	In the table showing the conditions for use of concomitant antihyperglycemic medications, replaced "N" with "See Note" in 'Rescue Therapy' column for 'Non-study basal insulins' and 'Insulin mixtures' rows; and added "Note: Participants who require a non-study basal insulin or insulin mixture as rescue therapy must discontinue study basal insulin therapy (LY3209590 or insulin degludec). The participant will remain in the study and follow procedures for the remaining study visits"	For clarity
6.8.4. Treatment after Study Completion	Added this new section	To address regulatory feedback
7.1.2. QTc Stopping Criteria	Removed the section	There is no specific QTc stopping criteria due to no known or suspected safety-related risk with insulins or LY3209590
8.1.1.2. Continuous Glucose Monitoring (CGM) Systems	Updated the section	To address regulatory feedback
9. Statistical Considerations	Replaced "Visit 31 (Week 52)" with "Week 52 (Visit 31)"	For clarity
9.2. Analyses Sets	Updated the analysis population/set.	To meet the anticipated requirement for excluding inadvertently enrolled participants in some countries.
9.3. Statistical Analyses	Made updates according to the changes in analyses sets.	As 9.2 and for clarity.

10.4.2. Contraception Guidance	Corrected the typo error and added “these forms of contraception must be used for the duration of the study.”	Correction
10.7. Appendix 7. Country-specific Requirements 10.7.3. Germany	Deleted “10.1.3. Informed Consent Process” as reference to “legally authorized representative,” “legal guardian,” “parents” is not mentioned in the protocol amendment.	Correction
	Updated the brief rationale in the table	
10.9. Appendix 9: Abbreviations and Definitions	Added CGM parameters.	To address regulatory feedback
	Removed ‘FAS’	Correction
Throughout protocol	Following glucose values in mg/dL, added corresponding values in mmol/L.	For clarity
Throughout protocol	Minor editorial and formatting changes	Minor, therefore, not detailed.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 3, Parallel-Design, Open-Label, Randomized Control Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Degludec in Insulin Naïve Adults with Type 2 Diabetes

Brief Title:

Efficacy and Safety of LY3209590 Compared to Degludec in Adults with Type 2 Diabetes Who Are Starting Basal Insulin for the First Time

Regulatory Agency Identifier Number(s):

IND: 129390

EudraCT: 2021-005891-21

Rationale:

This Phase 3 study will evaluate the efficacy and safety of once-weekly administration of LY3209590 on glycemic control compared with daily administration of insulin degludec in insulin naïve adult participants with Type 2 diabetes (T2D) who are starting basal insulin therapy for the first time. This study will inform the clinical development of LY3209590.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
Demonstrate noninferiority of LY3209590 compared to insulin degludec for the treatment of T2D in adults	Change in HbA1c from baseline to Week 52
Key Secondary (Multiplicity Adjusted)	
Demonstrate noninferiority of LY3209590 compared to insulin degludec for participants using GLP-1 receptor agonists	Change in HbA1c from baseline to Week 52
Demonstrate noninferiority of LY3209590 compared to insulin degludec for participants not using GLP-1 receptor agonists	Change in HbA1c from baseline to Week 52
Demonstrate superiority of LY3209590 compared to insulin degludec in selected parameters of glycemic control	• Change in HbA1c from baseline to Week 52 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, collected during the CGM session prior to Week 52

Other Secondary	
Compare the effect of LY3209590 to insulin degludec in parameters of glycemic control	• Change from baseline to Week 26 of HbA1c • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, collected during the CGM session prior to Week 26 • Change from baseline to Week 26 and Week 52 of fasting glucose measured by SMBG • Glucose variability measured during the CGM session prior to Weeks 26 and 52 • Insulin dose at Weeks 26 and 52
Compare the effect of LY3209590 to insulin degludec on safety endpoints	• Incidence and rate of composite of Level 2 and 3 hypoglycemia events during treatment period • Incidence and rate of composite of Level 2 and 3 nocturnal hypoglycemia events during treatment period • Change from baseline to Weeks 26 and 52 in body weight • Measurements collected during CGM sessions prior to Weeks 12, 26, and 52 of o Time in hypoglycemia with glucose <70 mg/dL (3.9 mmol/L) o Time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L), and o Time in hyperglycemia defined as glucose >180 mg/dL (10.0 mmol/L)
Compare the effect of LY3209590 to insulin degludec on patient-reported outcomes questionnaires	• Change from baseline to Weeks 26 and 52 of o TRIM-D o SF-36, and o EQ-5D-5L

Abbreviations: CGM = continuous glucose monitoring; SF-36 = Short Form-36; SMBG = self-monitoring of blood glucose; T2D = type 2 diabetes; TRIM-D = Treatment-Related Impact Measure – Diabetes.

Overall Design

This is a Phase 3, parallel-design, open-label, randomized control study to evaluate the efficacy and safety of LY3209590 administered once-weekly compared to insulin degludec administered daily, in insulin-naïve adults with T2D who are on stable treatment with 1 to 3 noninsulin diabetes medications prior to entering the study. Participants will continue prior stable therapy with 1 to 3 allowed noninsulin diabetes medications during the study.

The study includes a 3-week screening and lead-in period, a 52-week treatment period, and a safety follow-up period approximately 5 weeks after the last visit in the treatment period.

Brief Summary

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 52.

Study Population:

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

- are 18 years of age or older
- have a diagnosis of T2D
- are starting basal insulin for the first time
- have been taking 1 to 3 medication that lowers their blood glucose levels for at least 3 months prior to screening and are willing to maintain this stable treatment for the duration for the study, and
- are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required.

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

- have received these diabetes treatments within 30 days prior to screening
    - glinides
    - glimins
    - pramlintide, or
    - insulin or any insulin containing product.
- are women who are pregnant, lactating, or breastfeeding, or
- have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.

Number of Participants:

Approximately 888 participants will be randomly assigned to LY3209590 and insulin degludec in a 1:1 ratio. With the assumption of 15% dropout at Week 52, approximately 377 and 377 participants will complete 52 weeks of treatment on LY3209590 and insulin degludec, respectively.

Intervention Groups and Duration:

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

The study treatment period duration is 52 weeks.

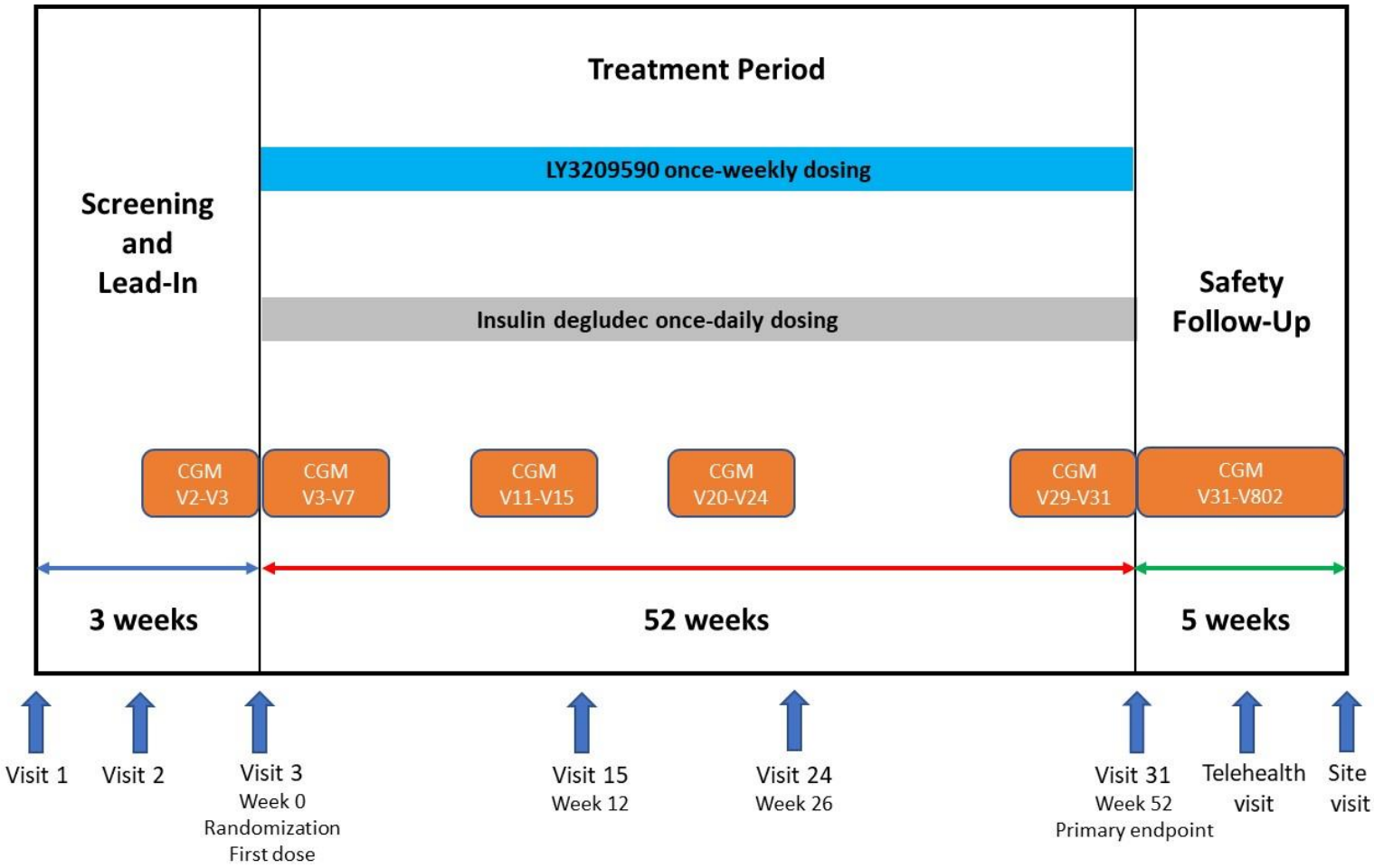
Both LY3209590 and insulin degludec will be administered by subcutaneous injection.

Ethical Considerations of Benefit or Risk:

Considering the data that are available to date from previous clinical studies, and the measures taken to ensure the safety of the participants in this study, the potential risks related with LY3209590 are justified by the anticipated benefits a participant with T2D may experience in the study.

Data Monitoring Committee: Yes

1.2. Schema



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

Note: During the safety follow-up period, CGM device will be worn for 4 weeks (52 to 56), but device return and data download will occur a week later (on Week 57).

1.3. Schedule of Activities (SoA)

Two tables describe the schedule of activities.

Table 1 (Section 1.3.1) describes procedures for Screening Visit 1, Lead-In Visit 2, and Treatment Visits 3 to 18.

Table 2 (Section 1.3.2) describes Treatment Visits 19 to 31, Early Discontinuation, Unscheduled Visits, and the Safety Follow-Up Visits 801 and 802.

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 tables represent telehealth visits.

Unscheduled visits

Unscheduled visits may occur as needed. The SoA reflects some of the procedures that may occur during these visits. Perform additional procedures per investigator's 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 samples should be collected as non-fasting and this will not be considered a protocol deviation.

1.3.1. Screening Visit 1, Lead-In Visit 2, and Treatment Visits 3-18

Study I8H-MC-BDCX Table 1	Screening and Lead-In		Treatment																Comments
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T = telehealth visit F = fasting visit
Informed consent	X																		The ICF must be signed before any protocol-specific tests or procedures are performed. See Section 10.1.3 for additional details.
Inclusion or exclusion criteria, review and confirm	X	X	X																Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.
Demographics	X																		Includes ethnicity (where permissible), year of birth, sex, and race.
Preexisting conditions and medical history, including relevant surgical history	X																		Collect all ongoing conditions and relevant past surgical and medical history.
Prespecified medical history (indication and history of interest)	X																		
Prior treatments for indication	X																		
Substance use such as recreational drugs, alcohol, caffeine, and tobacco use	X																		

Study I8H-MC-BDCX Table 1	**Screening and Lead-In**		**Treatment**															**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T = telehealth visit F = fasting visit
Concomitant medications	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	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	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		
Vital signs	X	X	X	X	X		X		X		X				X		X		Include blood pressure and pulse rate. Measure 3 times, using the same arm, after participant has been sitting at least 5 min and before ECG tracing and collection of blood samples for laboratory testing. Additional vital signs may be measured as necessary at investigator's discretion.
Physical examination	X																		Additional physical examinations may be completed as necessary at investigator's discretion.

Study I8H-MC-BDCX Table 1	Screening and Lead-In		Treatment															Comments
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T = telehealth visit F = fasting visit
12-lead ECG (local)	X																		Participants should be supine for approximately 5 to 10 min before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit. ECGs will be performed prior to collection of any blood samples.
Blinded Continuous Glucose Monitoring																			
Dispense CGM		X																	Dispense supplies as needed.
CGM sensor insertion		X	X								X								Participants will be required to replace the sensor at designated intervals per the investigator instruction. Additional unscheduled visits may be needed for participants support.
CGM device return and data download			X				X								X				
Participant Education																			
Diabetes counseling, training, and education		X	X																Includes SMBG, hypoglycemia (see Sections 5.3 and 8.3.6). After Visit 3, conduct as needed.
e-diary, glucometer, and CGM training		X	X																After Visit 3, conduct as needed.

Study I8H-MC-BDCX Table 1	Screening and Lead-In		Treatment															Comments
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T = telehealth visit F = fasting visit
Electronic Participant Diary and Blood Glucose Meter																			
Dispense e-diary and glucometer		X																	Dispense supplies as needed.
Diary compliance check			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.
Paper Patient-Reported Outcomes																			
Treatment-Related Impact Measure - Diabetes (TRIM-D)			X																
Electronic Patient-reported Outcomes																			
SF-36 v2 acute			X																
EQ-5D-5L			X																
Laboratory Tests and Sample Collections																			
Hematology	X		X												X				
Hemoglobin A1c (HbA1c)	X		X		X		X								X		X		
Clinical chemistry	X		X												X				

Study I8H-MC-BDCX Table 1	Screening and Lead-In		Treatment																Comments
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T = telehealth visit F = fasting visit
Glucose							X												
Lipid panel			X												X				
Urinalysis	X																		
Serum pregnancy	X		X																Collect for WOCBP only.
Urine pregnancy (local)			X																The result must be available prior to first dose of intervention. 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																
eGFR (CKD-EPI)	X		X												X				
UACR	X		X												X				
Pharmacokinetic (PK) samples			X		X		X								X				Visit 3: collect sample at least 15 min after dosing. For all other visits, collect at any time during the visit.

Study I8H-MC-BDCX Table 1	Screening and Lead-In		Treatment															Comments
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T = telehealth visit F = fasting visit
Immunogenicity (ADA) samples			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																Collect before dosing.
Randomization and Dosing Related Activities																			
Process visit using IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization using IWRS			X																
Insulin dose assessment or adjustment or documentation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense LY3209590 or insulin degludec, and related supplies			X				X				X				X		X		
Site administers LY3209590 or insulin degludec			X																
Dosing and injection training			X																After Visit 3, conduct as needed.

Study I8H-MC-BDCX Table 1	**Screening and Lead-In**		**Treatment**															**Comments**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	18	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit Detail			F			T	F	T		T		T	T	T	F	T		T	T = telehealth visit F = fasting visit
Observe participant administer LY3209590 and insulin degludec				X															
Assess dosing compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant returns unused LY3209590 or insulin degludec							X				X				X		X		

Abbreviations: ADA = antidrug antibody; BG = blood glucose; CGM = continuous glucose monitoring; eGFR (CKD-EPI) = estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration); ECG = electrocardiogram; FSH = follicle-stimulating hormone; ICF = informed consent form; IWRS = interactive web-response system; SF-36 v2 acute = Short Form-36 Version 2 Health Survey Acute Form; SMBG = self-monitoring of blood glucose; TRIM-D = Treatment-Related Impact Measure – Diabetes; UACR = urinary albumin/creatinine ratio; WOCBP = Women of childbearing potential.

1.3.2. Treatment Visits 19 to 31, Early Discontinuation, Unscheduled Visits, and Safety Follow-Up Visits 801 and 802

Study I8H-MC-BDCX Table 2	**Treatment**															**Safety Follow-Up**		**Comments**
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 10.3, Appendix 3.
Hypoglycemia events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Clinical assessment based on participant history and e-diary entries.
Physical Evaluation																		
Weight		X				X			X		X		X	X			X	

Study I8H-MC-BDCX Table 2	**Treatment**															**Safety Follow-Up**		**Comments**
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
Vital signs		X				X			X		X		X	X			X	Include blood pressure and pulse rate. Measure 3 times, using the same arm, after participant has been sitting at least 5 min and before ECG tracing and collection of blood samples for laboratory testing. Additional vital signs may be measured as necessary at investigator's discretion.
Physical examination						X							X	X			X	Additional physical examinations may be completed as necessary at investigator's discretion.

Study I8H-MC-BDCX Table 2	**Treatment**															**Safety Follow-Up**		**Comments**
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
12-lead ECG (local)													X	X				Participants should be supine for approximately 5 to 10 min before ECG collections and remain supine but awake during the ECG collection. ECGs may be repeated at the investigator's discretion at any visit. ECGs will be performed prior to collection of any blood samples.
Blinded Continuous Glucose Monitoring																		
CGM sensor insertion		X									X		X					Participants will be required to replace the sensor at designated intervals per the investigator instruction. Additional unscheduled visits may be needed for participants support.

Study I8H-MC-BDCX Table 2	**Treatment**															**Safety Follow-Up**		**Comments**
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
CGM device return and data download						X							X	X			X	ED visit: if the ED visit occurs during a CGM session, the device must be returned and data downloaded. CGM device will be worn for 4 weeks (52 to 56), but device return and data download will occur a week later (on Week 57).
Participant Education																		
Diabetes counseling, training, and education																		Conduct as needed.
e-diary, glucometer, and CGM training																		Conduct as needed.

Study I8H-MC-BDCX Table 2	**Treatment**															**Safety Follow-Up**		**Comments**
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
Electronic Participant Diary and Blood Glucose Meter																		
Diary compliance check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Review entries of BG, hypoglycemia events, and insulin dose. If participant is not compliant, study personnel will re-educate the participant on study requirements for continued study participation.
Dispense ancillary supplies		X				X			X		X							Dispense supplies as needed.
Required diary return														X			X	The diary must be returned on the last participant visit.
Electronic Patient-Reported Outcomes																		
Simplicity Questionnaire (SIM-Q) study intervention						X							X	X				
SF-36 v2® Health Survey						X							X	X				

Study I8H-MC-BDCX Table 2	**Treatment**															**Safety Follow-Up**		**Comments**
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
Basal Insulin Experience Likelihood of incorporating into routine													X	X				
EQ-5D-5L						X							X	X				
Paper Patient-Reported Outcomes																		
Treatment-Related Impact Measure - Diabetes (TRIM-D)						X							X	X				
Laboratory Tests and Sample Collections																		
Hematology						X							X	X			X	
Hemoglobin A1c (HbA1c)						X			X				X	X			X	
Clinical chemistry						X							X	X			X	
Glucose									X									
Lipid panel						X							X	X			X	
Urinalysis						X							X	X			X	

Study I8H-MC-BDCX Table 2	Treatment															Safety Follow-Up		Comments
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
Urine pregnancy (local)														X			X	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.
C-Peptide						X							X	X				
eGFR (CKD-EPI)						X							X	X			X	
UACR						X							X	X			X	
Pharmacokinetic (PK) samples						X							X	X			X	Collect sample at any time during the visit.
Immunogenicity (ADA) samples						X							X	X			X	If an immediate or nonimmediate systemic drug hypersensitivity reaction occurs, collect additional unscheduled samples as detailed in Section 10.2.1.

Study I8H-MC-BDCX Table 2	**Treatment**															**Safety Follow-Up**		**Comments**
Visit Number	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**ED**	**UV**	**801**	**802**	ED = early discontinuation UV = unscheduled visit 801, 802 = safety follow-up
Weeks from Randomization	20	22	23	24	25	26	28	32	36	42	48	50	52	—	—	54	57	
Visit Interval Tolerance (days)	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±3	±3	±3	—	—	+7	±7	
Visit Detail	T		T	T	T	F	T	T	F	T		T	F	F		T	F	T = telehealth visit F = fasting visit
Stored samples																		
Exploratory biomarker samples													X	X				
Dosing related activities																		
Process visit using IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
Insulin dose assessment or adjustment or documentation	X	X	X	X	X	X	X	X	X	X	X	X			X			
Dispense LY3209590 or insulin degludec, and related supplies		X				X			X		X							
Dosing and injection training																		After Visit 3, review conduct as needed.
Assess dosing compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Participant returns unused LY3209590 or insulin degludec		X				X			X		X		X	X				
Assessment for poststudy treatment													X	X		X	X	

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

2. Introduction

LY3209590 is a long-acting insulin receptor agonist in development for the once-weekly treatment of 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 on glycemic control compared with daily administration of insulin degludec in insulin naïve adult participants with T2D who are starting basal insulin therapy for the first time. 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 to overcome barriers to dose optimization with basal insulins that provide simple dosing algorithms, rapid achievement of glycemic targets, and a predictable profile with low likelihood of contributing to hypoglycemia.

Potential for improved treatment regimens and compliance

Once-weekly insulin with a simple titration regimen could result in earlier adoption of insulin therapy that may improve treatment compliance and lead to better real-world patient outcomes. Weekly insulins with a lower peak-to-trough profile during the week and a nearly flat 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, nonclinical and clinical efficacy, and safety of LY3209590 is provided in the IB.

Summary of clinical results

A total of 5 clinical studies, in healthy participants and participants with 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 BDCL preliminary results

Study BDCL is a randomized, open-label, comparator-controlled study evaluating the efficacy and safety of LY3209590 compared with insulin degludec. Study participants have T2D, are insulin naïve, and treated with a stable dose of metformin, alone or in combination with a stable dose of a DPP-4 inhibitor and/or an SGLT2 inhibitor, for at least 3 months prior to screening.

Safety data during 26 weeks of treatment in participants with T2D showed no increased risk of safety with LY3209590 compared to degludec.

LY3209590 was noninferior to degludec for glycemic control as measured by change in HbA1c after 26 weeks of treatment.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Potential risks for this study

The potential risks associated with LY3209590 include

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

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

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

Potential risks for the LY3209590-prefilled pen device are described in the "Instructions for Use".

Management of Risks

Sections 5.1, 5.2, 6.1.2, 6.8.1, 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 whenever hypoglycemia is experienced or suspected and check glucose values.

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 and rescue therapy

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).

Participants will be monitored for persistent, severe hyperglycemia and will receive rescue therapy if this should occur (see Section 6.1.2).

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.

Participants may also benefit from the improvement of glycemic control promoted by basal insulin. The weekly administration of LY3209590 has the potential to offer a 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 insulin naïve participants with T2D.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
Demonstrate noninferiority of LY3209590 compared to insulin degludec for the treatment of T2D in adults	Change in HbA1c from baseline to Week 52
Key Secondary (Multiplicity Adjusted)	
Demonstrate noninferiority of LY3209590 compared to insulin degludec for participants using GLP-1 receptor agonists	Change in HbA1c from baseline to Week 52
Demonstrate noninferiority of LY3209590 compared to insulin degludec for participants not using GLP-1 receptor agonists	Change in HbA1c from baseline to Week 52
Demonstrate superiority of LY3209590 compared to insulin degludec in selected parameters of glycemic control	• Change in HbA1c from baseline to Week 52 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, collected during the CGM session prior to Week 52
Other Secondary	
Compare the effect of LY3209590 to insulin degludec in parameters of glycemic control	• Change from baseline to Week 26 of HbA1c • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive, collected during the CGM session prior to Week 26 • Change from baseline to Weeks 26 and 52 of fasting glucose measured by SMBG • Glucose variability measured during the CGM session prior to Weeks 26 and 52 • Insulin dose at Weeks 26 and 52

Compare the effect of LY3209590 to insulin degludec on safety endpoints	• Incidence and rate of composite of Level 2 and 3 hypoglycemia events during the treatment period • Incidence and rate of composite of Level 2 and 3 nocturnal hypoglycemia events during the treatment period • Change from baseline to Weeks 26 and 52 in body weight • Measurements collected during CGM sessions prior to Weeks 12, 26, and 52 of o Time in hypoglycemia with glucose <70 mg/dL (3.9 mmol/L) o Time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L) o Time in hyperglycemia defined as glucose >180 mg/dL (10.0 mmol/L)
Compare the effect of LY3209590 to insulin degludec on patient-reported outcomes questionnaires	• Change from baseline to Weeks 26 and 52 of o TRIM-D o SF-36, and o EQ-5D-5L
Tertiary	
Compare the effect of LY3209590 to insulin degludec in participants using GLP-1 receptor agonists versus participants not using GLP-1 receptor agonists	• Rate of Level 1 and composite of Level 2 and 3 hypoglycemia events during the treatment period • Change from baseline to Weeks 26 and 52 in body weight • Insulin dose at Weeks 26 and 52 • Measurements collected during CGM sessions prior to Weeks 12, 26, and 52 of o Time in hypoglycemia with glucose <70 mg/dL (3.9 mmol/L) o Time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L) o Time in hyperglycemia defined as glucose >180 mg/dL (10.0 mmol/L), and o Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L), inclusive

Compare the effect of LY3209590 to insulin degludec for efficacy parameters	• Percentage of participants at Week 52 achieving o HbA1c <7% o HbA1c <7% without nocturnal hypoglycemia, and o HbA1c ≤6.5% without hypoglycemia • Change from baseline to Weeks 26 and 52 of fasting serum glucose
Compare the effect of LY3209590 to insulin degludec for safety parameters	• Incidence and rate of Level 2 hypoglycemia events during treatment period • Incidence and rate of Level 3 hypoglycemia events during treatment period • Evaluation of immunogenicity - incidence of positive LY3209590 treatment-emergent antidrug antibodies
Characterize the PK/PD of LY3209590	• LY3209590 PK and concentration-response relationships to key safety and efficacy measures
Compare the effect of LY3209590 to insulin degludec for patient-reported outcomes	• SIM-Q and • Frequency of responses to Basal Insulin Experience of "likelihood of incorporating into routine"

Abbreviations: CGM = continuous glucose monitoring; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; PK/PD = pharmacokinetics/pharmacodynamics; SMBG = self-monitoring of blood glucose; SF-36 = Short Form-36 Version 2 Health Survey Acute Form; SIM-Q = Simplicity Questionnaire; T2D = type 2 diabetes; TRIM-D = Treatment-Related Impact Measure – Diabetes.

Primary estimand

United States registration

The primary clinical question of interest is

> What is the treatment difference between LY3209590 and insulin degludec in HbA1c change from baseline after 52 weeks of treatment, in study eligible participants, regardless of treatment discontinuation for any reason and regardless of initiation of rescue medication?

Treatment regimen estimand attributes

This table describes the treatment regimen estimand attributes.

Treatment Regimen Estimand Attribute	Description
Population	Targeted study population. See Section 9.2 for details.
Endpoint	HbA1c change from baseline to Week 52.
Remaining intercurrent events	None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both addressed by the treatment condition of interest attribute.
Treatment condition	The randomized treatment regardless of treatment discontinuation and use of rescue medications.
Population-level summary	Difference in mean changes between treatment conditions.

Rationale for the treatment regimen estimand

The treatment regimen estimand estimates how participants with T2D are treated in clinical practice and considers both efficacy and safety.

Registration for countries outside the United States

The primary clinical question of interest is

> What is the treatment difference between LY3209590 and insulin degludec in HbA1c change from baseline after 52 weeks of treatment, in study eligible participants who adhere to the randomized treatment without intercurrent events during the study treatment period?

Efficacy estimand attributes

This table describes the efficacy estimand attributes.

Efficacy Regimen Estimand Attribute	**Description**
Population	Targeted study population. See Section 9.2 for details.
Endpoint	HbA1c change from baseline to Week 52.
Remaining intercurrent events	None. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both handled by the hypothetical strategy, for example, the potential outcome for those participants if the intercurrent events have not occurred will be estimated.
Treatment condition	The randomized treatment.
Population-level summary	Difference in mean changes between treatment conditions.

Rationale for the efficacy estimand

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

Secondary estimands for multiplicity-adjusted objectives

The superiority test in change from baseline to Visit 31 (Week 52) in HbA1c will also be based on the primary estimands described above.

The change from baseline to Visit 31 (Week 52) in HbA1c in the subpopulations of participants using or not using GLP-1 receptor agonists will use treatment regimen estimand for US registration and efficacy estimand for other countries.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured during CGM session prior to Visit 31 (Week 52) will use treatment regimen estimated for US registration and efficacy estimand for other countries.

4. Study Design

4.1. Overall Design

This is a Phase 3, parallel-design, open-label, randomized control study to evaluate the efficacy and safety of LY3209590 administered once-weekly compared to insulin degludec administered daily.

The study includes a 3-week screening and lead-in period, a 52-week treatment period, and a safety follow-up period approximately 5 weeks after the last visit in the treatment 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 and insert a new 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.

Participants will continue their current diabetes therapy until randomization.

Treatment period

Visit 3 (Week 0): Randomization

This is the general flow for Visit 3

- study personnel confirm enrollment criteria
- participants are randomly assigned to an intervention group
- study personnel complete baseline procedures and sample collection
- study personnel will provide dosing training and administer the first dose of LY3209590 or insulin degludec,
- study personnel will download the CGM

- participant will continue CGM wear per the SoA, and
- study personnel complete all visit procedures.

Participants assigned to insulin degludec will continue daily administration 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 administer their second dose of LY3209590, or insulin degludec.

Visit 5 through Visit 31 (Week 2 through Week 52)

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

The participant's median FBG will be used to titrate basal insulin dose adjustments throughout the study based on the study titration algorithm described in Section 6.5.1.

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
- 4 weeks prior to Visit 24, and the site will download the CGM data at Visit 24; and
- 4 weeks prior to Visit 31, and the site will download the CGM data at Visit 31.

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

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

Last study treatment visit: either Visit 31 (Week 52) 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 treatment to another non-study diabetic treatment.

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 31, 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 of 52 weeks is a reasonable time frame to observe the effects of LY3209590 compared to insulin degludec.

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

Comparator

Insulin degludec was chosen as the comparator because it is widely accepted as the best-in-class 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 degludec 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 degludec 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 significant titrations while reaching steady state.

Participants randomly assigned to LY3209590 will receive a single loading dose of 300 U of LY3209590, which equals 3 times the starting weekly dose of 100 U.

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

Starting weekly dose

The second dose is the starting weekly dose of 100 U, unless hypoglycemia is observed after the initial loading dose, requiring a dose reduction.

Dose Adjustments

Assessments for dose adjustment will occur from the third dose onwards. Dosing will be individualized based on FBG and hypoglycemia events, and adjustments should occur weekly from Visits 5 to 15 (Weeks 2 to 12) and then every 4 weeks thereafter.

Insulin degludec

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

Starting dose

The starting dose is 10 U, consistent with the insulin degludec label.

Dose Adjustments

Dosing will be individualized based on FBG and hypoglycemia events, and adjustments should occur weekly from Visits 4 to 15 (Weeks 1 to 12) and then every 4 weeks thereafter.

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 inclusive, at screening, or older per local regulations.

Type of Participant and Disease Characteristics

2. Have a diagnosis of T2D according to the World Health Organization criteria.
3. Have an HbA1c of 7.0%-10.5%, inclusive, as determined by central laboratory at screening.
4. Are on a stable treatment with 1 to 3 antihyperglycemic medication, for at least 3 months prior to screening, and willing to continue the stable treatment for the duration of the study. Therapies must be used in accordance with the corresponding local product label.

   These antihyperglycemic medications are accepted in the study

   - DPP-4 inhibitors
   - SGLT2 inhibitors
   - biguanides, such as metformin
   - alpha-glucosidase inhibitors
   - GLP-1 receptor agonists, oral or injectable
   - sulfonylureas, or
   - thiazolidinediones.
5. Are insulin naïve.

   Exceptions:

   - short-term insulin treatment for a maximum of 14 days, prior to screening, and
   - prior insulin treatment for gestational diabetes.

Weight

6. Have a body mass index ≤45 kg/m^2.

Contraceptive or barrier requirements

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

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

Study Procedures

8. Are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures as required, such as
    - self-inject intervention
    - store and take provided study interventions as directed
    - maintain an electronic study diary
    - use only the glucometer supplied for use in the study, and
    - wear the CGM device as directed, see Section 8.1.1.2.
      Note: The use of personal, non-study CGM device will not be allowed.

    Note: persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the intervention.

Informed Consent

9. Are 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.

Other Inclusions

10. Have usual wake and sleep patterns, such that midnight to 0600 hours will reliably reflect a usual sleeping pattern.

5.2. Exclusion Criteria

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

Medical conditions

11. Have a diagnosis of T1D, latent autoimmune diabetes, or specific type of diabetes other than T2D, for example, monogenic diabetes, diseases of the exocrine pancreas, or drug-induced or chemical-induced diabetes.
12. Have a history of >1 episode of ketoacidosis or hyperosmolar state or coma requiring hospitalization within 6 months prior to screening.
13. Have had severe hypoglycemia episodes within 6 months prior to screening.
14. Have a history of renal transplantation, are currently receiving renal dialysis, or have an estimated glomerular filtration rate <20 mL/min/1.73 m^2 as calculated by the Chronic Kidney Disease-Epidemiology equation, determined by central laboratory at screening.
15. Have had a blood transfusion or severe blood loss within 90 days prior to screening.
16. Have known hemoglobinopathy, hemolytic anemia or sickle cell anemia, or any other traits of hemoglobin abnormalities known to interfere with the measurement of HbA1c.
17. Have had New York Heart Association Class IV heart failure or any of these cardiovascular conditions within 3 months prior to screening
    - acute myocardial infarction
    - cerebrovascular accident (stroke), or
    - coronary bypass surgery.

18. Have had gastric bypass (bariatric) surgery, restrictive bariatric surgery, for example Lap-Band, or sleeve gastrectomy within 1 year prior to screening.
19. Have had a significant weight gain or loss within 3 months prior to screening, for example, ≥5%.
20. Have acute or chronic hepatitis, cirrhosis, or obvious clinical signs or symptoms of any other liver disease, except non-alcoholic fatty liver disease (that is, study participants with non-alcoholic fatty liver disease are eligible for participation), and/or have elevated liver enzyme measurements, as determined by the central laboratory at screening and as indicated below:
    a. Total bilirubin >2x ULN, with the exception of previously diagnosed Gilbert's disease
    b. ALT or serum glutamic pyruvic transaminase >3x ULN
    c. AST or serum glutamic oxaloacetic transaminase >3x ULN, or
    d. ALP >2.5x ULN.
21. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy within 5 years prior to screening.

    Exceptions:

    - Basal cell or squamous cell skin cancer.
22. Are at increased risk for developing cancer or a recurrence of cancer.
23. Have a history of or current significant psychiatric disorders considered clinically significant, in the opinion of the investigator.
24. Have a history or presence of an underlying disease, or surgical, physical, or medical condition that, in the opinion of the investigator, would potentially affect participant safety within the study or interfere with the interpretation of data.
25. Have a known hypersensitivity or allergy to any of the study interventions or their excipients.

Prior or Concomitant Therapy

26. Have received these diabetes treatments within 30 days prior to screening
    - glinides
    - glimins
    - pramlintide, or
    - insulin or any insulin containing product.
27. Are receiving or received systemic glucocorticoid therapy for >14 days within the month before screening.

    Exceptions:

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

Prior or Concurrent Clinical Study Experience

28. Are currently enrolled or have participated within the last 30 days in a clinical study involving an investigational intervention or any other type of medical research judged not to be scientifically or medically compatible with this study. If the previous investigational intervention has a long half-life, 3 months or 5 half-lives, whichever is longer, should have passed prior to Visit 1.
29. Have previously completed or withdrawn from this study after having signed the ICF or any other study investigating LY3209590 after receiving at least 1 dose of the study basal insulin.

Other Exclusions

30. Have hypoglycemia unawareness in the opinion of the investigator.
31. Are women who test positive for pregnancy or intend to become pregnant.
32. Are women who are lactating or breastfeeding.
33. Have evidence of any substance use disorder of any severity defined by the Diagnostic and Statistical Manual of Mental Disorders-5, within 6 months prior to screening.

    Exceptions: nicotine or caffeine.
34. Are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.
35. 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.
36. Are unsuitable for inclusion in the study in the opinion of the investigator.

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 may be reviewed throughout the study, as needed.

Dietary and exercise considerations

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

Dietary and exercise restrictions

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

Blood donation

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

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any 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 to 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 or 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 where that treatment would be in conflict with the protocol-provided treatment requirements. If there are no local or national standards of care for diabetes, the investigators should follow current published standards of care from the American Diabetes Association.

6.1. Study Intervention(s) Administered

LY3209590 and insulin degludec will be dispensed at the study visits summarized in SoA.

Returned LY3209590 or insulin degludec should not be re-dispensed to the participants.

This table lists the interventions used in this clinical study.

Intervention Name	LY3209590	Insulin degludec
IMP and NIMP/AxMP	IMP	IMP
Authorized as defined by EU Clinical Trial Regulation[a]	No	Yes
Use	Experimental	Active comparator
Type	Biologic	Biologic
Dose Formulation	Solution	Solution
Unit Dose Strength(s)	500 units/mL	100 units/mL
Dosage Level(s)	Individualized dosing (see Section 6.5.1)	Individualized dosing (see Section 6.5.2)
Frequency of Administration	Once weekly	Once daily
Route of Administration	Subcutaneous	Subcutaneous

Abbreviations: AxMP = auxiliary medicinal product; IMP = Investigational Medicinal Product; NIMP = non-investigational medicinal product.

[a] Study interventions identified as authorized are used in accordance with the terms of their marketing authorizations.

LY3209590 frequency of administration and guidance for missed doses

LY3209590 should be administered once weekly at approximately the same time and day each week. If a dose is missed, it should be administered as soon as possible if at least 3 days (72 hours) remain until the next scheduled dose. If less than 3 days remain before the next scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day.

In each case, participants can then resume their regular once-weekly dosing schedule.

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

Insulin degludec frequency of administration

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

Anatomical Location of Injections

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

Packaging and labeling

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

6.1.1. Medical Devices

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

Instructions for device use are provided in the "Instructions for Use."

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

6.1.2. Rescue Medicine for Management of Severe or Persistent Hyperglycemia

If a participant develops severe, persistent hyperglycemia after randomization, optimization of concomitant antihyperglycemic medication and/or the addition of an allowed agent for rescue therapy should be considered after investigator assessment, based on conditions described in this table.

Average of FBG over 2-week period	Timing of events
>270 mg/dL (15 mmol/L)	From Visit 15 until 17 (Week 12 to 16)
>240 mg/dL (13 mmol/L)	After Visit 17 until 19 (Week 16 to 20)
>200 mg/dL (11 mmol/L)	After Visit 19 until 31 (Week 20 to end of study treatment at Week 52)

First, investigators should confirm participant compliance with the assigned intervention and that they do not have an acute condition causing severe hyperglycemia.

Rescue therapy will begin with dose optimization of the participant's current concomitant antihyperglycemic medications. Then consider the addition of an allowed agent for rescue therapy (see Section 6.8.3), if applicable, so the participant is taking up to 3 antihyperglycemic medications at effective doses before considering prandial insulin rescue therapy.

If severe, persistent hyperglycemia is not improving in spite of compliance with the assigned therapeutic regimen and optimization of other concomitant glucose-lowering agents, the addition of prandial insulin may be considered.

Participants who receive rescue therapy for hyperglycemia management should also continue administering either LY3209590 or insulin degludec for the remaining period in the study.

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

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

6.2. Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

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

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

Participant responsibilities

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization and stratification

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

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

Participants will be stratified based on

- country
- HbA1c stratum at Visit 1 (<8% and ≥8%)
- sulfonylurea use at randomization (Yes/No), and
- GLP-1 RA use at randomization, regardless of oral or injectable administration (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.

An early PK/PD unblinded transfer may also be conducted. Only a small group of personnel can be unblinded to the data for the potential PK/PD analysis and must keep information confidential until the planned unblinding of the trial.

6.4. Study Intervention Compliance

Participants are responsible for entering the date of their daily or weekly insulin dose and dose amount in their e-diary.

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.

6.5. Dose Modification

Dosing 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).

The investigator is responsible for titrating the basal insulin dose using the guidance in Sections 6.5.1 and 6.5.2.

6.5.1. LY3209590 Dose Initiation and Adjustment

This section outlines the LY3209590

- general dosing information by visit
- dose adjustment guidance based on FBG, and
- dose adjustment guidance based on hypoglycemia.

6.5.1.1. LY3209590 General Dosing Information by Visit

This table provides general dosing information across visits for all participants randomly assigned to LY3209590.

LY3209590 General Dosing Information		
Visit (Week)	**Dose**	**Additional dosing instruction**
Visit 3 (Week 0) initial loading dose	300 U	*CAUTION:* Do NOT repeat administration of the loading dose.
Visit 4 (Week 1) starting weekly dose	100 U	If a participant experiences hypoglycemia in the previous week, then reduce the starting weekly dose to 60 U, a 40 U reduction based on adjustments for hypoglycemia (see Section 6.5.1.3).
Visits 5-15 (Weeks 2-12)	Doses will be individualized based on FBG and hypoglycemia events	Dose modifications may occur weekly.
After Visit 15	Doses will be individualized based on FBG and hypoglycemia events	Dose modifications may occur every 4 weeks.

6.5.1.2. LY3209590 Dose Adjustment Based on FBG

This table provides guidance for dose adjustments based on median FBG from the 3 most recently recorded FBG data from the previous week.

If the participant experienced any documented BG ≤70 mg/dL (≤3.9 mmol/L) in the previous week, the dose should not be increased.

If the median FBG is…		**Then…**
mg/dL	**mmol/L**	
<80	<4.4	reduce the LY3209590 dose by 20 U.
80-120	4.4-6.6	do not change the dose.
121-140	6.7-7.7	increase the LY3209590 dose by 20 U.
>140	>7.7	increase the LY3209590 dose by 40 U.

6.5.1.3. LY3209590 Dose Adjustment Based on Hypoglycemia Events

This table provides guidance when hypoglycemia events occur.

If a participant reports…	**with a blood glucose value of... over the previous week**	**then…**
≥3 hypoglycemic events	≤70 mg/dL (3.9 mmol/L)	reduce the LY3209590 dose by 40 U.
≥1 hypoglycemic event	<54 mg/dL (3.0 mmol/L)	
≥1 nocturnal hypoglycemic event	≤70 mg/dL (3.9 mmol/L)	
Any confirmed severe hypoglycemia (neurological impairment confirmed by investigator)	___	

6.5.2. Insulin Degludec Dose Initiation and Adjustment

This section outlines the insulin degludec

- general dosing information by visit
- dose adjustment guidance based on FBG, and
- dose adjustment guidance based on hypoglycemia.

6.5.2.1. Insulin Degludec General Dosing Information by Visit

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

Insulin degludec General Dosing Information		
Visit	**Dose**	**Additional dosing instruction**
Visit 3 (Week 0) starting dose	10 U/day	
Visits 4-15 (Weeks 1-12)	Doses will be individualized based on FBG and hypoglycemia events	Dose modifications may occur weekly
After Visit 15 (Week 12)	Doses will be individualized based on FBG and hypoglycemia events	Dose modifications may occur every 4 weeks

6.5.2.2. Insulin Degludec Dose Adjustment Based on FBG

This table provides guidance for dose adjustments based on median FBG from the 3 most recently recorded FBG data from the previous week.

If the participant experienced any documented hypoglycemia (BG ≤70 mg/dL) (≤3.9 mmol/L) in the previous week, the dose should not be increased.

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.

6.5.2.3. Insulin Degludec Dose Adjustment Based on Hypoglycemia Events

This table provides guidance when hypoglycemia events occur.

If a participant reports…	with a blood glucose value of… over the previous week	then…
≥3 hypoglycemic events	≤70 mg/dL (≤3.9 mmol/L)	reduce the dose by 2 to 6 U. Dose reductions of 2 or 4 units may occur every 3 days to achieve a weekly 6 U reduction as clinically indicated
≥1 hypoglycemic event	<54 mg/dL (3.0 mmol/L)	
≥1 nocturnal hypoglycemic event	≤70 mg/dL (3.9 mmol/L)	
Any confirmed severe hypoglycemia	___	

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.

6.7. Treatment of Overdose

An overdose of LY3209590 or insulin degludec, 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 degludec 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 sulfonylureas if clinically appropriate
- closely monitor the participant for any AE or SAE and laboratory abnormality until study intervention no longer has a clinical effect, and
- obtain a plasma sample for PK analysis if the participant is assigned to LY3209590.

6.8. Concomitant Therapy

Concomitant therapy regimens

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

Participants taking concomitant medications should be on stable dosages at the time of screening and should remain at stable dosages throughout the study, unless changes need to be made because of an AE or rescue therapy (see Section 6.1.2).

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.

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
- lorcaserin
- phentermine or topiramate combination
- naltrexone or bupropion, or
- semaglutide injection 2.4 mg.

Prohibited usage of weight loss medication during the study

After screening, 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 two 14-consecutive day periods during study treatment period. Each period must be at least 30 days apart.

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 concomitant 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**
GLP-1 RAs	Y	Yes, if on stable therapy 90 days prior to screening	N/A	Y	Y
DPP-4 inhibitors	Y		N/A	Y	Y
SGLT2 inhibitors	Y		N/A	Y	Y
Non-study basal insulins	N	N	Yes, only if study basal insulin is temporarily discontinued	See Note	Y
Insulin mixtures	N	N	Yes, only if study basal insulin is discontinued	See Note	Y
Prandial insulin	N	N	Y	Y	Y
Meglitinides	N	N	N/A	N	Y
Alpha-glucosidase inhibitors	Y	Yes, if on stable therapy 90 days prior to screening	N/A	Y	Y
Sulfonylureas	Y	Yes, if on stable therapy 90 days prior to screening	N/A	Y	Y
Thiazolidinediones	Y	Yes, if on stable therapy 90 days prior to screening	N/A	Y	Y
Metformin[a]	Y	Yes, if on stable therapy 90 days prior to screening	N/A	Yes, if the dose is below maximum approved dose per country-specific label	Y

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.

Note: Participants who require a non-study basal insulin or insulin mixture as rescue therapy must discontinue study basal insulin therapy (LY3209590 or insulin degludec). The participant will remain in the study and follow procedures for the remaining study visits

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)
- a dose increases as part of rescue therapy, and
- for safety reasons at the discretion of the investigator.

Any changes in dose should be documented.

6.8.4. Treatment after Study Completion

Study interventions will not be made available to study participants after Visit 31 (Week 52) or after the participant's early discontinuation from study treatment.

At the last treatment visit (Visit 31 [Week 52] or ED visit), the investigator will determine participant's transition from study treatment to another non-study diabetic treatment. The investigator may prescribe a non-study basal insulin for use during the safety follow-up period. Participants will continue their concomitant non-insulin antihyperglycemic medications at the discretion of the investigator and continue to monitor their FBG and complete the e-diary.

Study participants treated with LY3209590 transitioning to a non-study basal insulin: Study participants will receive the last injection of LY3209590 at Week 52 of the study and can begin the transition to the non-study insulin after Visit 31 (Week 52). At Visit 31 (Week 52), the investigator will review the instructions for transitioning to the non-study insulin. During this transition period, the participant's FBG should be used to guide dose initiation and adjustment for the insulin prescribed for the safety follow-up period.

No daily basal insulin will be required until the FBG is above 120 mg/dL (6.6 mmol/L) for 2 consecutive measurements. The prescribed non-study daily basal insulin should be started at a dose of 10 units/day and adjusted based on FBG and the investigator judgement in accordance with any country-specific label. The initial prescribed dose and any dose adjustments made for the non-study insulin during the safety follow-up period should be documented in the eCRF. An unscheduled visit in addition to Visit 801 may occur during this time to facilitate the transition to the non-study daily basal insulin.

Since LY3209590 has a half-life of approximately 17 days, a careful titration of the daily basal insulin is necessary to prevent hypoglycemia due to overlapping insulin action. Therefore, the investigator should consider titrating the daily insulin to reach 50% of the required daily dose at approximately 2-weeks and 80% at approximately 4-weeks.

Study Participants treated with insulin degludec transitioning to a non-study basal insulin: Study participants assigned to the insulin degludec treatment arm may transition to a non-study basal insulin after Visit 31 (Week 52). The investigator will prescribe the non-study insulin and titrate the dose based on FBG and clinical judgement in accordance with the country-specific label for the basal insulin. The initial prescribed dose and any dose adjustments made during the safety follow-up period will be documented in the eCRF.

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 study intervention. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA.

Participants who stop the study intervention permanently may receive another glucose-lowering medication. The new glucose-lowering medication will be recorded on the CRF for antihyperglycemic medications.

A participant should be **permanently discontinued** from study intervention if

- the participant becomes pregnant during the study
- the participant requests to discontinue study intervention
- 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 degludec 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 the study intervention for safety reasons.

7.1.1. Liver Chemistry Stopping Criteria

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

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

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

7.1.2. Hypersensitivity Reactions

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

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

7.1.3. Temporary Discontinuation of Study Intervention

Criteria for temporary discontinuation of LY3209590 or insulin degludec

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

This will be allowed for up to 21 consecutive days for insulin degludec 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 study intervention occurs

Every effort should be made by the investigator to maintain participants in the study and to restart study intervention 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 study intervention

The dates of study intervention interruption and restart must be documented in source documents and entered on the CRF.

Participant noncompliance should not be recorded as interruption of study intervention 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 the participant is diagnosed with any type of diabetes mellitus other than T2D
- 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, and
- 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.

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 study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

7.3. Lost to Follow up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are 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
- fasting blood glucose measured by SMBG
- Level 2 and 3 nocturnal hypoglycemia
- Level 2 and 3 hypoglycemia events
- body weight
- insulin dose
- CGM measurements
    - time in range between 70 and 180 mg/dL (3.9 and 10 mmol/L), inclusive
    - glucose variability, and
    - time in hyperglycemia or hypoglycemia, and
- patient-reported outcomes questionnaires
    - TRIM-D
    - SIM-Q
    - SF-36 v2 Health Survey
    - Basal Insulin Experience, and
    - EQ-5D-5L.

See Section 3 for specific efficacy endpoints.

See Section 8.3.6 for information related to hypoglycemia and hyperglycemia.

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
- to check for hyperglycemic events, or
- as directed by the investigator.

When to measure fasting blood glucose (FBG) 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.

Glucometer data transfer

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

8.1.1.2. Continuous Glucose Monitoring (CGM) Systems

The study-provided CGM system or alternative sponsor-approved glucose monitoring device 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.

Participants are not allowed to use a personal, non-study CGM device during the study.

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.

Participants are not allowed to connect the transmitter and/or sensor of the CGM 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 or used sensors 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 and/or site monitor when sessions do not meet the compliance thresholds. CGM compliance

reports will also be provided to the Sponsor during the study for review and to determine if further mitigation is necessary.

8.1.2. Patient-Reported Outcomes

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

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. TRIM-D
2. SIM-Q
3. SF-36 v2 Health Survey Acute Form
4. Basal Insulin Experience: Likelihood of incorporating into routine, and
5. EQ-5D-5L.

8.1.2.1. Treatment-Related Impact Measure – Diabetes (TRIM-D)

Description of TRIM-D

The TRIM-D is a participant self-administered instrument, which assesses the impact of diabetes treatment on participants' functioning and well-being across available diabetes treatments. Participants assess their experience "over the past 2 weeks."

The TRIM-D assesses 5 domains of impact.

Domain	Number of items per domain
Treatment Burden	6
Daily Life	5
Diabetes Management	5
Compliance	4
Psychological Health	8

Scoring

Each of the 28 items is assessed on a 5-point scale, where higher scores indicate a better health state.

8.1.2.2. Simplicity of Diabetes Treatment Questionnaire (SIM-Q) Single Medication Status Version

Description of SIM-Q

The SIM-Q is a brief 10-item measure developed to assess the simplicity and complexity of treatment for T2D. This version of the instrument assesses the simplicity and complexity of a single medication. The participant responses should consider only the assigned study intervention.

In this study, only the last 2 questions of the SIM-Q will be completed

"How simple or complex is your medication treatment for diabetes?" and

"Overall, how simple or complex is it to manage your diabetes, including medication, checking your blood glucose levels, diet, and any other aspects of diabetes treatment?"

Scoring

Each item is scored on a 5-point scale ranging from "Very complex" to "Very simple."

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

Description of SF-36 v2

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

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

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

Scoring

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

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

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

8.1.2.4. Basal Insulin Experience: Likelihood of Incorporating into Routine

Description of questionnaire

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

Scoring

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

8.1.2.5. EQ-5D-5L

Description of EQ-5D-5L

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

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

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

The 5L version scores each dimension at 5 levels

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

A total of 3125 health states are possible.

Scoring

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

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

EQ Visual Analog Scale

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

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Physical examination at screening

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

- cardiovascular
- respiratory
- gastrointestinal, and
- neurologic.

Height and weight will be measured and recorded.

Additional assessments include clinical signs and symptoms related to T2D, T2D-related illnesses, and injection site reactions.

8.2.2. Vital Signs

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

8.2.3. Electrocardiograms

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

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

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

8.2.4. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE.

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

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 weeks after the last dose of intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE or AE or dose modification, then report the information as an AE.

8.2.5. Hepatic Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur. This table shows when to repeat laboratory tests.

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

What to do if the abnormal condition persists or worsens

If the abnormal liver test result persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including

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

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

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

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in this table occur.

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs or symptoms[a], or 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)

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

What a comprehensive evaluation should include

At a minimum, this evaluation should include

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

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels

- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

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

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

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

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

See Section 10.5 for hepatic laboratory tests.

8.2.6. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA.

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

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

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

- adverse events (AEs)
- serious adverse events (SAEs), 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 or 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)					
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)					
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 study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Product Complaints (PC)					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3209590 or insulin degludec.

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 poststudy 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, they may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Cardiovascular Events

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

Events include

- death
- myocardial infarction
- coronary revascularization procedure
- hospitalization for unstable angina
- hospitalization for heart failure, and
- stroke or Transient Ischemic Attack.

8.3.4. Systemic Hypersensitivity Reactions

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

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

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

8.3.5. Injection Site Reactions

Symptoms and signs of a local injection site reaction may include erythema, induration, pain, pruritus, 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, 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 ADAs are defined in Section 9.3.6.2.

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

Sample retention is described in Section 10.1.12.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The first version of the SAP will be finalized prior to the 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 not inferior to insulin degludec on glycemic control as measured by change in HbA1c from baseline to Week 52 (Visit 31) in participants with T2D who are starting basal insulin for the first time.

The null hypothesis (H_0) is the difference between LY3209590 versus insulin degludec in the change from baseline to Week 52 (Visit 31) in HbA1c is greater than the NIM.

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

Secondary Hypotheses

The key secondary objectives (multiplicity adjusted) are to test the hypotheses that LY3209590 is

- not inferior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31) for the subpopulation of participants using GLP-1 receptor agonists
  H_0: the difference (LY3209590-insulin degludec) >0.4%
- not inferior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31) for the subpopulation of participants not using GLP-1 receptor agonists
  H_0: the difference (LY3209590-insulin degludec) >0.4%
- superior to insulin degludec for change in HbA1c from baseline to Week 52 (Visit 31)
  H_0: the difference (LY3209590-insulin degludec) ≥0.0, and
- superior to insulin degludec with respect to time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive, collected during the CGM collected session prior to Week 52 (Visit 31)
  H_0: the difference (LY3209590-insulin degludec) ≤0.0.

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 ICF.
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 study treatment. 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 medication.
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 analyses will be conducted on either EAS1 or EAS2, and the safety analyses will be conducted on the SS. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and 2-sided 95% confidence intervals will be calculated.

Unless otherwise stated, 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 medication, whichever is earlier.

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

9.3.2. Primary Endpoint or Estimand Analysis

The primary objective is to compare the HbA1c change from baseline to Week 52 between LY3209590 and insulin degludec and will be based on either of these 2 estimands

treatment regimen estimand for registration in the United States and

efficacy estimand for registration in other countries.

The 2-sided 95% CI of the LS mean for individual treatment groups, treatment LS mean difference (LY3209590 – insulin degludec) in the HbA1c change from baseline to Week 52 (Visit 31) will be estimated.

For both estimands, LY3209590 will be declared noninferior to insulin degludec if the upper limit of the 2-side 95% CI for the LS mean difference in the HbA1c change from baseline is below NIM (+0.4% or +0.3% for different regulatory requirements).

The HbA1c is reported in 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 (http://www.ngsp.org/ifccngsp.asp).

Treatment regimen estimand

The treatment regimen estimand will be based on the HbA1c data at baseline and Week 52 (Visit 31) from the EAS1, regardless of the use of study intervention or rescue medications.

Missing measures

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 study intervention prior to Week 52 (Visit 31) but have non-missing measures at Week 52 (Visit 31).

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 52 (Visit 31) will be imputed by return-to-baseline multiple imputations.

Analysis model

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

The model will include treatment, strata (country, GLP-1 RA treatment at randomization, and SU use at randomization), and baseline value of the dependent variable. The statistical inference will be based on the multiple imputation framework by Rubin (1987).

Efficacy estimand

The efficacy estimand is the treatment difference in the change of HbA1c from baseline to Week 52 (Visit 31) if all participants 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 medication.

Analysis model

The MMRM model will be used, and the missing values will be handled implicitly in the MMRM analysis under the assumption of missing at random. The MMRM model will include treatment, strata (country, GLP-1 RA treatment at randomization and SU use at randomization), visit and treatment-by-visit interaction as fixed effects, and baseline of the dependent variable 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
6. compound symmetry without heterogeneous variances.

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 of key secondary objectives as described in Section 9.1.

Noninferiority test

The noninferiority test in change from baseline to Week 52 (Visit 31) in HbA1c for the subpopulations will be based on the ANCOVA model for treatment regimen estimand (using data from the EAS1) and an MMRM model for efficacy estimand (using data from the EAS2)

In the ANCOVA model, treatment, strata (country and SU use at randomization), and baseline of the dependent variable will be used as covariates.

The MMRM model will include treatment, strata (country and SU use at randomization), visit and treatment-by-visit interaction as fixed effects, and baseline of the dependent variable as a covariate.

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

Superiority test

The superiority test in change from baseline to Week 52 (Visit 31) in HbA1c will be based on the same primary endpoint analysis described above.

The time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive, measured by CGM, will be analyzed using an ANCOVA model for treatment regimen estimand and an MMRM model for efficacy estimand. In the ANCOVA model, treatment, strata (country, baseline HbA1c stratum [<8.0%, ≥8.0%], GLP-1 RA treatment at randomization, and SU use at randomization), and baseline of the dependent variable will be used as covariates. The MMRM model will include treatment, strata (country, baseline HbA1c stratum [<8.0%, ≥8.0%], GLP-1 RA treatment at randomization, and SU use at randomization), visit and treatment-by-visit interaction as fixed effects, and baseline of the dependent variable as a covariate. For treatment regimen estimand, the missing data will be imputed by multiple imputation with the approach similar to the imputation used for the primary endpoint.

9.3.3.2. Other Secondary Endpoints

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

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

Safety measures will be analyzed using the SS regardless of treatment discontinuation and use of rescue medications.

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

Summary statistics will be provided for incidence of

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

Hypoglycemia analysis

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

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

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

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

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

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, and 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 Analysis

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

9.3.6.2. Evaluation of Immunogenicity

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

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

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

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

Definition of TEADA+

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

Treatment-induced ADA is defined as the participant having a 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 having a 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.

9.3.7. Subgroup Analyses

The following outcomes will be analyzed by the subgroups of GLP-1 RA use at randomization:

- rate of Level 1 hypoglycemia events during Weeks 0 to 26, Weeks 26 to 52, and Weeks 0 to 52
- rate of composite of Level 2 and 3 hypoglycemia events during Weeks 0 to 26, Weeks 26 to 52, and Weeks 0 to 52
- change from baseline to Week 26 and Week 52 in body weight
- insulin dose at Week 26 and Week 52
- measurements collected during CGM sessions collected prior to Weeks 12, 26, and 52 of
    - time in hypoglycemia with glucose <70 mg/dL (3.9 mmol/L)
    - time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L)
    - time in hyperglycemia defined as glucose >180 mg/dL (10.0 mmol/L), and
    - time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L, respectively), inclusive.

The analyses will evaluate whether the treatment impact is different by the subgroups. The models used for these analyses will vary depending on the outcome. Other subgroup analyses may be performed as deemed appropriate.

Details of the modeling 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 are specified in the DMC charter or a separate unblinding plan document.

9.5. Sample Size Determination

Approximately 888 participants will be randomly assigned to LY3209590 and insulin degludec in a 1:1 ratio. With the assumption of 15% dropout at Week 52, approximately 377 and 377 participants will complete 52 weeks of treatment on LY3209590 and insulin degludec, respectively.

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control as measured by change from baseline to Visit 31 (Week 52) in HbA1c in participants with T2D who are starting basal insulin for the first time. 754 completers (377 on LY3209590 and 377 on insulin degludec) will provide an at least 99% statistical power to show noninferiority between LY3209590 and insulin degludec using the upper limit of a 2-sided 95% confidence interval (LY3209590 – insulin degludec) and these assumptions

- NIM of 0.4%
- no true difference between treatment groups, and
- an SD of 1.1%.

This sample size also has at least 95% statistical power to show noninferiority between LY3209590 and insulin degludec using a 0.3% NIM at Week 52.

The number of participants in each subpopulation of background treatment will be approximately 50% of the study population with balanced treatment assignment to support the following secondary objectives, controlled for Type 1 error:

To demonstrate noninferiority of LY3209590 to insulin degludec in HbA1c change from baseline to Week 52 for the subpopulation of participants using GLP-1 RAs

To demonstrate noninferiority of LY3209590 to insulin degludec in HbA1c change from baseline to Week 52 for the subpopulation of participants not using GLP-1 RAs.

In each subpopulation, 188 completers for each study intervention will provide an approximately 90% statistical power to show noninferiority between LY3209590 and insulin degludec using the upper limit of a 2-sided 95% confidence interval (LY3209590 – insulin degludec) and these assumptions

- a NIM of 0.4%
- no true difference between treatment groups, and
- an SD of 1.1%.

The 754 completers will provide 95% statistical power to demonstrate the superiority of LY3209590 versus insulin degludec, of change in HbA1c from baseline to 52 weeks, assuming an SD of 1.1% and true mean difference is -0.3%, using the alpha of 0.05.

The 754 completers will provide at least 95% statistical power to show the superiority of the percentage of time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive during the CGM session prior to Week 52 between LY3209590 and insulin degludec, assuming an SD of 18% and true mean difference is 5%, using the alpha of 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, and
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents, for example, advertisements, must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, if applicable, and all other applicable local regulations, and
- Reporting significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 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 safety review team, which includes safety signal detection at any time during the study.

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

10.1.5.2. Clinical Event Committee for Adjudication of Events

A blinded Clinical Event Committee, external to Lilly, will adjudicate 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 dataset 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 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 quality tolerance limits 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 system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data, participant-focused outcome instrument, and other data will be collected by the participant, caregiver, or authorized study personnel, using a paper source document and will be transcribed by the authorized study personnel into the EDC system via direct data captured in the EDC system and will serve as the source documentation.

Additionally, electronic clinical outcome assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant 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]
Exploratory biomarkers	Sponsor or designee	15 years
Pharmacokinetic	Sponsor or designee	1 year
Immunogenicity	Sponsor or designee	15 years

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the Lilly-designated laboratory or 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	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 International Organization for Standardization 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, and 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 or disorder being studied or expected progression, signs or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy and 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, and 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. Results 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:
  o deficiencies in labeling information, and
  o 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 they have 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 pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship/
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB for LY3209590 and the Product Information for degludec in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have 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) 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 toward 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, IRB/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

Women of childbearing potential (WOCBP)

Females are considered women of childbearing potential if

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

Any amount of spotting should be considered menarche.

Women not of childbearing potential

Females are considered women not of childbearing potential if

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

Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, and tubal ligation.

Postmenopausal

The postmenopausal state should be defined as

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

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

10.4.2. Contraception Guidance

Guidance for women of childbearing potential

This outlines the rules for WOCBP to ensure they do not become pregnant during the study.

If, as part of their preferred and usual lifestyle, WOCBP…	**Then…**
are in a same-sex relationship	• they must stay in same-sex relationships without sexual relationships with males, and • take pregnancy tests.
are completely abstinent	• they must agree to remain completely abstinent
are not completely abstinent	• they must agree to o use 1 highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception. o take pregnancy tests. • these forms of contraception must be used for the duration of the study.
Note on forms of contraception: At least 1 form of contraception must be highly effective, meaning that it has a less than 1% failure rate.	

Guidance for all men

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

Methods of contraception for women of childbearing potential

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and 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	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide.
	
	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, and female condom with spermicide) to be considered effective.

Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post coital douche, and • lactational amenorrhea.

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

Hepatic Evaluation Testing

See Section 8.2.5 for guidance on appropriate test selection.

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

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

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

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]
HBV DNA[b]	Anti-actin antibody[c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver kidney microsomal Type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

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

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

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

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

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

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

10.7. Appendix 7: Country-specific Requirements

10.7.1. Canada

This section describes protocol changes applicable to adult participants at study sites in Canada.

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

Protocol Section Number and Name	Description of the Change	Brief Rationale
Inadvertently Enrolled Participants	New section specific to Canada.	Information on inadvertently enrolled participants added per Canadian local requirements.

The revised text described below shows the changes applicable to adult participants at study sites in Canada. Deletions are identified by ~~strikethrough format~~ and additions by underlined text.

Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study intervention and safety follow-up should be performed as outlined in the SoA and Section 8.3 of the protocol.

10.7.2. Brazil

This section describes protocol changes applicable to adult participants at study sites in Brazil.

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

Protocol Section Number and Name	Description of the Change	Brief Rationale
Section 5.2. Exclusion Criteria	Exclusion criterion 28 30 days is changed to 1 year.	Resolution No. 251 (Brazil 1997). The National ERB Brazil recommends not having a participant enter a new clinical study if less than 1 year has elapsed since participation in another clinical study of an investigational drug or device unless there is a direct benefit to the research participant.
Section 10.1.12. Sample Retention	Biological samples will be stored for up to 10 years.	Compliance with Brazilian regulation applicable to sample storage, resolution CNS 441 (Brazil 2011).
Patient Access to Project Benefits	New section specific to Brazil.	Clarifies the sponsor responsibilities to comply with Resolution CNS 466 (Brazil 2012) and RDC 38 (Brazil 2013).
Section 11. References	Addition of Brazil-specific references	The references are specific to the Brazil-specific requirements.

The revised text described below shows the changes applicable to adult participants at study sites in Brazil. Deletions are identified by ~~strikethrough format~~ and additions by underlined text.

5.2. Exclusion Criteria

28. ~~Are currently enrolled or have participated within the last 30 days in a clinical study involving an investigational intervention or any other type of medical research judged not to be scientifically or medically compatible with this study. If the previous investigational intervention has a long half-life, 3 months or 5 half-lives, whichever is longer, should have passed prior to Visit 1.~~

Are currently enrolled in, discontinued, or completed within a period of 1 year, before inclusion, from a clinical study involving an investigational intervention or nonapproved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study unless there is direct benefit to the research subject. A time period of 30 days, as indicated by the protocol, must still be followed if a direct benefit to the research participant is identified.

10.1.12. Sample Retention

In Brazil, the biological samples obtained within this study will be stored for up to 10 years, with possibility of renewal under request, followed by appropriate justification and a report with all activities developed with the biological samples (CNS 441/2011). The sample and any data generated from it can be linked back to the participant only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study intervention.

Patient Access to the Project Benefits

In Brazil, at the end of their participation in the study, all participants must have assured access to the best proven prophylactic, diagnostic, and therapeutic methods, which may include LY3209590 or insulin degludec, identified through the study (CNS 466/2012 and RDC 38/2013).

11. References

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 251/1997 do Conselho Nacional de Saúde/MS: Normas de Pesquisa com Novos Fármacos, Medicamentos, Vacinas e Testes Diagnósticos Envolvendo Seres Humanos.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 466/2012 do Conselho Nacional da Saúde / MS: Diretrizes e Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos. Publicado no Diário Oficial da União em 13 de junho, 2013.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 340/2004 do Conselho Nacional da Saúde/MS: Diretrizes para Análise Ética e Tramitação dos Projetos de Pesquisa da Área Temática Especial de Genética Humana.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 441/2011 do Conselho Nacional da Saúde / MS: Diretrizes para análise ética de projetos de pesquisas que envolvam armazenamento de material biológico humano ou uso de material armazenado em pesquisas anteriores.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução-RDC 38/2013
da Agência Nacional deVigilância Sanitária/MS: Aprova o regulamento para os programas de acesso expandido, usocompassivo e fornecimento de medicamento pós-estudo.

10.7.3. Germany

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

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/Withdraw from the Study 8.3. Adverse Events, Serious Adverse Events, and Product Complaints	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.
10.8 Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances	Replaced references to "exceptional circumstances" with the "COVID-19 pandemic".	Temporary measures may only be used in response to the COVID-19 pandemic.

The revised text described below shows the changes applicable to adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~ and additions by <u>underlined text</u>.

7.2. Participant Discontinuation/Withdraw from the Study

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 enrollment in any other clinical study involving an investigational product or enrollment 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 another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

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

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

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

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

Section 10.8. Appendix 8: Provisions for Changes in Study Conduct ~~During Exceptional Circumstances~~ due to the COVID-19 Pandemic

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~~ Study disruptions due to the COVID-19 pandemic

Individual, site, or regional restrictions due to the COVID-19 pandemic ~~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~~ during the COVID-19 pandemic

~~In an exceptional circumstance, a~~ 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~~ the COVID-19 pandemic

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.

To ensure the quality of data and the well-being of participants, it will be ensured that the investigator sites and their staff are following GCP principles and are meeting the sponsor responsibilities of Section 5 of ICH GCP. Throughout these activities the participant remains under the care of the primary investigator.

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~~ the COVID-19 pandemic if written approval is provided by the sponsor.

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

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

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

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

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

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

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

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

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

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening or the lead-in visits are valid for a maximum of 24 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to ~~exceptional circumstances~~ the COVID-19 pandemic:

- 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~~ the COVID-19 pandemic. 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 31 (Week 52), 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~~ the COVID-19 pandemic. 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.

Section 10.10. Appendix 10: 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 eCRF.

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

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken.

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

Screening period guidance

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

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

Adjustments to visit windows

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

The primary endpoint visit, Visit 31 (Week 52), 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	antidrug antibody
AE	adverse event
ANCOVA	analysis of covariance
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
CGM	continuous glucose monitoring; can refer to study procedure or analysis of representative CGM derived variables including but not limited to: • time in range from 70 to 180 mg/dL (3.9-10 mmol/L) and 70 to 140 mg/dL (3.9-7.7 mmol/L) • time below range from ≥54 mg/dL (3 mmol/L) to <70 mg/dL (3.9 mmol/L), <70 mg/dl (3.9 mmol/L), and <54 mg/dL (3 mmol/L) • time above range from >180 mg/dL (10 mmol/L) to ≤250 mg/dL (13.9 mmol/L) and >250 mg/dL (13.9 mmol/L) • daily average glucose • glucose management indicator • between- and within-day glucose variability • low blood glucose index, high blood glucose index; blood glucose risk indicator; and • ambulatory glucose profiles with interquartile ranges.
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, 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
DMC	data monitoring committee; a data-monitoring committee 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
DPP-4	dipeptidyl peptidase-4
Device deficiencies	equivalent to product complaint
EDC	electronic data capture
eGFR (CKD-EPI)	estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration)
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
ERB	Ethical Review Board
FBG	fasting blood glucose
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IMP	investigational medicinal product A medicinal product, which is being tested or used as a reference, including as a placebo, in a clinical trial. See also "investigational product."
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form

interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created or locked
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form
IRB	Institutional Review Boards
IWRS	interactive web-response system
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, and at the right time. In addition to the core 5 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, and 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
MMRM	mixed-model repeated measures
NIM	noninferiority margin
NIMP	non-investigational medicinal product A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. See AxMP.
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

PT-INR	prothrombin time, INR
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study
SGLT2	sodium-glucose cotransporter 2
SIM-Q	Simplicity of Diabetes Treatment Questionnaire
SMBG	self-monitoring of blood glucose
SU	sulphonylureas
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TEADA	treatment-emergent ADA
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
TRIM-D	Treatment-Related Impact Measure – Diabetes

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]: (15 Feb 2022)

This amendment is considered to be nonsubstantial.**Overall Rationale for the Amendment**

The overall rationale for the changes implemented in the protocol amendment is to update the insulin degludec dose adjustments so that it will more closely reflect those for LY3209590.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Visit and Week numbers were changed and an additional row was added to the table to indicate that insulin degludec dose adjustments may occur every 4 weeks after Week 12 (Visit 15)	Table was modified to reflect the changes in insulin degludec dose adjustments
Section 1.2 Schema	Added "CGM Visits" to Safety Follow-Up section	Correction-this section was missing in original schema
Section 1.3.1 Schedule of Activities	Demographics comment-replaced "gender" with "sex"	Preferred terminology
Section 1.3.1 and 1.3.2 Schedule of Activities	Added the following text to ECG comment-"ECGs will be performed prior to collection of any blood samples"	For clarification
Section 4.3 Justification for Dose	Text was changed to indicate that insulin degludec dose adjustments should occur weekly from Visits 4 to 15 (Weeks 1 to 12) and then every 4 weeks thereafter.	The text was modified to be consistent with LY3209590 dose adjustments
Section 6.1 Study Intervention(s) Administered	Added the following text to Anatomical Location of Injections –" Injections may be administered in the abdomen, thigh, arm, or buttock. Refer to the IFU for complete instructions on dose administration.	Anatomical location of insulin injections added to address FDA feedback to include acceptable anatomical locations for insulin administration in the protocol
Section 6.5.1.2 LY3209590 Dose Adjustment Based on FBG	Addition of the following sentence: "If the participant experienced any documented BG ≤70 mg/dL (≤3.9 mmol/L) in the previous	To emphasize that, in the occurrence of a hypoglycemia event <70, insulin doses should not increase

	week, the dose should not be increased"	
Section 6.5.2.1 Insulin Degludec General Dosing Information by Visit	Visit and Week numbers were changed and an additional row was added to the table to indicate that insulin degludec dose adjustments may occur every 4 weeks after Week 12 (Visit 15)	Table was modified to reflect the changes in insulin degludec dose adjustments
Section 6.5.2.2 Insulin Degludec Dose Adjustment Based on FBG	Addition of the following sentence: "If the participant experienced any documented BG ≤70 mg/dL (≤3.9 mmol/L) in the previous week, the dose should not be increased"	To emphasize that, in the occurrence of a hypoglycemia event <70, insulin doses should not increase
Section 9.3.6.1 Pharmacokinetic and Pharmacodynamic Analyses	Replaced "gender" with "sex"	Preferred terminology
Throughout	Minor editorial revisions	Minor, therefore, have not been summarized

11. References

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Approval	PPD Medical Director 13-May-2022 16:16:50 GMT+0000

Approval	PPD Statistician 13-May-2022 16:19:47 GMT+0000

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