Protocol I8H-MC-BDCU (b)

A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Trial to Evaluate the Efficacy and Safety of LY3209590 Compared With Insulin Degludec in Participants With Type 2 Diabetes Currently Treated With Basal Insulin (QWINT-3)

NCT05275400

Approval Date: 13-May-2022

Title Page

Protocol Title:

A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Trial to Evaluate the Efficacy and Safety of LY3209590 Compared with Insulin Degludec in Participants with Type 2 Diabetes Currently Treated with Basal Insulin (QWINT-3)

Protocol Number: I8H-MC-BDCU(b)

Amendment Number: b

Compound: LY3209590

Brief Title:

Efficacy and Safety of the Once-Weekly Basal Insulin LY3209590 Therapy Compared with Daily Insulin Degludec in Adults with Type 2 Diabetes Treated with Basal Insulin

Study Phase: Phase 3

Acronym: QWINT-3 (Once-Weekly Insulin Therapy)

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers

IND: 129390

EudraCT: 2021-002569-16

Document ID: VV-CLIN-045582

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	28-JAN-2022
Original Protocol	08-NOV-2021

Amendment [b]

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or the rights of the study participants

Overall Rationale for the Amendment:

The primary rationale for the current amendment is to address regulatory feedback regarding exclusionary ALT and AST thresholds and include specific details for participants who enter the study and use personal CGM. These changes are detailed in the table below.

Section # and Name	Description of Change	Brief Rationale
1.3.2. SoA for the Treatment Period (V23-V37), ET, UV, and Safety Follow-Up Period (801-802)	Added a Note "Visit 3 (Week 0) should occur 11-17 days after Visit 2."	For clarity
	Edited the footnote of CGM Visits: removed "to ensure adequate data collection" and added "During the study blinded CGM sessions, only the study CGM device may be worn. Participants who routinely use personal CGM/FGM at study entry may not wear a personal CGM/FGM during the study required blinded CGM sessions."	To address regulatory feedback
3. Objectives, Endpoints, and Estimands	In Primary estimand subsection, US registration, edited the text in primary clinical question of interest to clarify "study-eligible" participants	For clarity
	Edited treatment regimen estimand attributes - Population: added cross reference to Section 9.2	
	In Primary estimand subsection, Registration for other countries, edited the text in primary clinical question of interest to clarify "study-eligible" participants	
	Edited efficacy estimand attributes - Population: added cross reference to Section 9.2	
5.1. Inclusion Criteria	In inclusion criterion 4, added "as determined by central laboratory"	For clarity

Section # and Name	Description of Change	Brief Rationale
	In inclusion criterion 5, added trademark name for insulin detemir	
	In inclusion criterion 8, added "Note: Participants who are already using CGM or FGM at study entry will be allowed to continue to use their personal CGM/FGM during the study when not wearing the study CGM. Participants must use the study-provided glucometer for all FBG values and any other BG values reported during the study"	For clarity and to address regulatory feedback
	In inclusion criterion 8, added "not wear a personal CGM/FGM during the study blinded CGM assessments" and "not initiate the use of personal CGM/FGM if not already routinely using CGM/FGM at study entry"	
5.2. Exclusion Criteria	In exclusion criterion 20, added wording "after having signed the ICF" and "after receiving at least 1 dose of the study basal insulin"	For clarity
	In exclusion criterion 25, increased AST and ALT thresholds from 2.5x ULN to 3x ULN	To address regulatory request
6.1.3. General Insulin Dose Considerations for Both Treatment Groups	Under "Insulin Dose Titration and Dose Maintenance", modified "Visit 6 (Week 3)" to "Visit 5 (Week 2)"	Correction
6.8. Concomitant Therapy	Under "Criteria for Use of Concomitant Medications" table, replaced "N/A" 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
	Removed all the trademark names from footnote "a"	For consistency
6.8.1. Rescue Therapy for Management of Participants with Severe / Persistent Hyperglycemia during the Treatment Period	Removed paragraph 2 and added "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"	To address regulatory feedback
	Removed the last paragraph and added "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"	

Section # and Name	Description of Change	Brief Rationale
8.1.5.2. CGM Monitoring	Updated the section	To address regulatory feedback
8.4. Pharmacokinetics	Added "Bioanalytical" subsection	Correction
8.7. Biomarkers	Removed the last paragraph	Correction
9. Statistical Considerations	Replaced "Visit 22 (Week 26)" with "Week 26 (Visit 22)"; "Visit 37 (Week 78)" with "Week 78 (Visit 37)	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
10.2. Appendix 2: Clinical Laboratory Tests	In Glucose line of Clinical Chemistry, added "Fasting or random (refer to SoA)"; and deleted in Glucose line of Urinalysis.	Correction
	Added Glucose under Additional Testing	For clarity
10.4.2. Females	Corrected the typographical error and added "These forms of contraception must be used for the duration of the study."	Correction
10.8. Appendix 8: Abbreviations and Definitions	Added CGM parameters.	To address regulatory feedback
	Added "EAS – efficacy analysis set," "FGM – flash glucose monitoring", "IFU – instructions for Use," and "SS – safety analysis set".	To provide definition of terms
	Moved FSH abbreviation as per the alphabetical order	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, Multicenter, Randomized, Parallel-Design, Open-Label Trial to Evaluate the Efficacy and Safety of LY3209590 Compared with Insulin Degludec in Participants with Type 2 Diabetes Currently Treated with Basal Insulin (QWINT-3).

Brief Title:

Efficacy and Safety of the Once-Weekly Basal Insulin LY3209590 Therapy Compared with Daily Insulin Degludec in Adults with Type 2 Diabetes Treated with Basal Insulin

Rationale:

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. It was designed as a divalent (dimer) insulin receptor agonist consisting of a single-chain insulin analog (comprised of an insulin B-chain analog, a short peptide linker, and an insulin A-chain analog) fused to a second peptide linker that is fused to an unmodified human IgG2 Fc domain. LY3209590 has a mean half-life of approximately 17 days and a peak-to-trough PK profile of 1.14. The low peak-to-trough ratio and extended half-life of LY3209590 support once-weekly dosing and have the potential to decrease patient burden, overcome barriers to initiation of basal insulin therapy, and may improve glycemic control and quality of life for patients with T2D compared to other basal insulins that require daily administration.

The Phase 2 Study I8H-MC-BDCM (BDCM) demonstrated that following 32 weeks of treatment, LY3209590 effectively and safely improved glycemic control, comparable to insulin degludec, in participants with T2D treated with basal insulin with or without other allowed non-insulin lowering medications. The risk of all documented and nocturnal hypoglycemia (with blood glucose ≤70 mg/dL [3.9 mmol/L]) was statistically significantly lower (20% to 40%) for both LY groups compared to insulin degludec consistent with higher fasting glucose values observed with LY3209590. The reported treatment-emergent SAEs were balanced across the 3 treatment groups. Results of Study BDCM therefore support continued development of LY3209590 as a treatment for diabetes mellitus.

The objective of this Phase 3 study (I8H-MC-BDCU [BDCU]) is to evaluate the efficacy and safety of LY3209590 as a weekly basal insulin compared to insulin degludec (daily basal insulin) using target FBG values of 80–120 mg/dL (4.4-6.6 mmol/L) in participants with T2D currently treated with basal insulin.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To investigate the hypothesis that LY3209590 is noninferior to the comparator (insulin degludec) on glycemic control in study participants with T2D currently on basal insulin	• Change from baseline in HbA1c at Week 26
Key Secondary (Multiplicity Adjusted)	
• To demonstrate LY3209590 is superior to insulin degludec in the selected parameters of glycemic control	• Change from baseline in HbA1c at Week 26 • The event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 78 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured during the CGM session prior to Week 26

Abbreviations: CGM = continuous glucose monitoring; dL = deciliter; HbA1c = hemoglobin A1c; mg = milligrams; T2D = Type 2 Diabetes.

Note: Other Secondary Objectives and Endpoints are listed in Section 3.

Overall Design

Brief Summary:

Study BDCU is a Phase 3, multicenter, randomized, open-label, comparator-controlled study to evaluate the efficacy and safety of once-weekly basal insulin (LY3209590) compared to insulin degludec in participants with T2D treated with basal insulin. The study consists of a 3-week screening/lead-in period, a 78-week treatment period, and a 5-week safety follow-up period. The primary outcome is the change from baseline in HbA1c at Week 26.

Study details include

- The study duration will be up to 86 weeks.
- The treatment duration will be up to 78 weeks.

Number of Participants:

Approximately 1341 participants will enter the study such that 939 evaluable participants will be randomly assigned in a 2:1 ratio to study drug with 626 participants in the LY3209590 group and 313 participants in the insulin degludec group.

Intervention Groups and Duration:

Participants who meet entry criteria will be randomly assigned in a 2:1 (LY3209590:insulin degludec) ratio to the following treatment groups:

- LY3209590: once-weekly administration, and

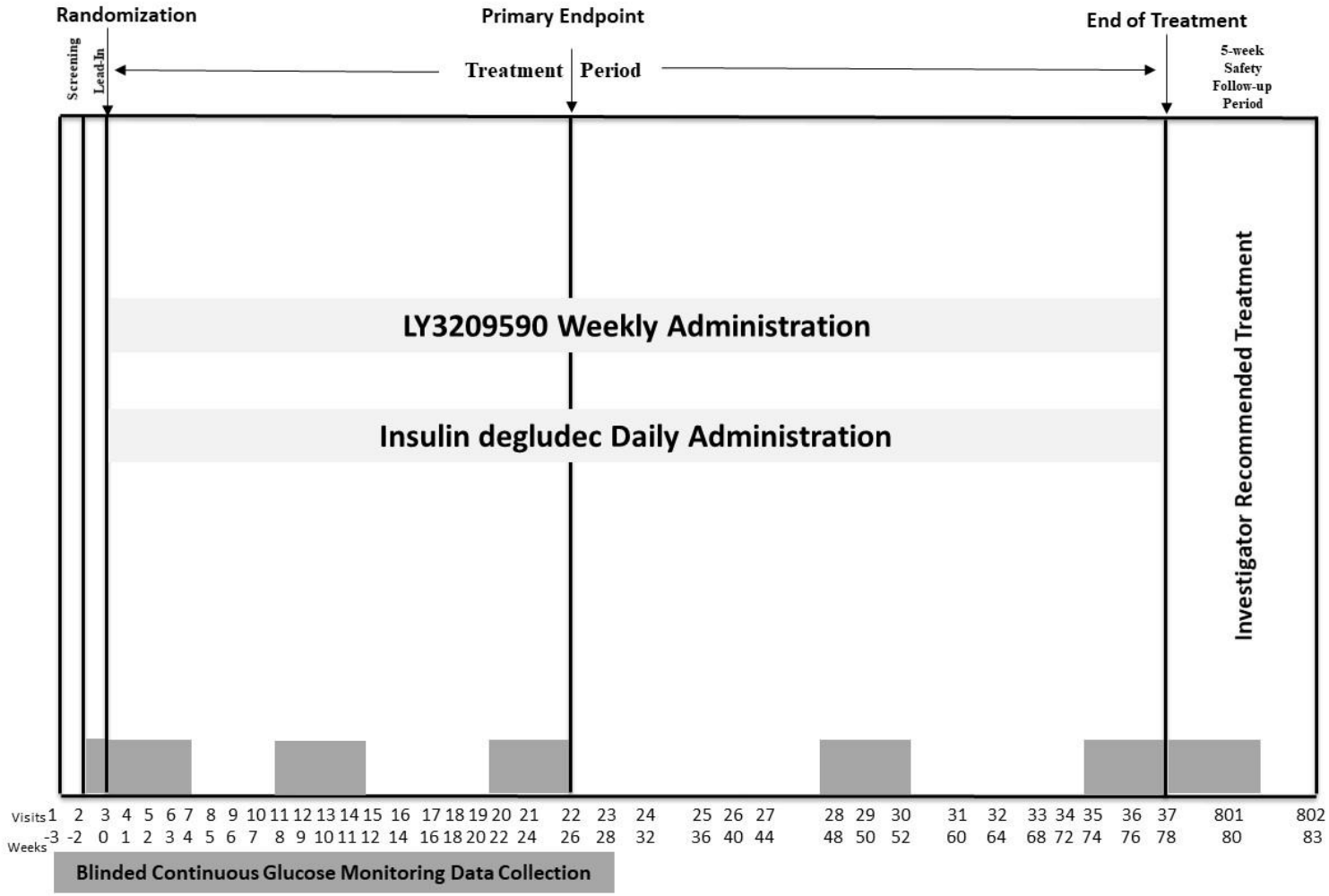
- Insulin degludec: once-daily administration.

The total duration of study participation for each participant, including screening and the posttreatment follow-up periods, is approximately 86 weeks, across the following study periods:

- Study Period I: Screening and Lead-In Period, 3 weeks
- Study Period II: Treatment Period, 78 weeks, and
- Study Period III: Safety Follow-Up Period, 5 weeks.

Data Monitoring Committee: Yes

1.2. Schema


Randomization
Primary Endpoint
End of Treatment
Screening
Lead-In
Treatment Period
5-week Safety Follow-up Period
LY3209590 Weekly Administration
Insulin degludec Daily Administration
Investigator Recommended Treatment
Visits 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 801 802
Weeks -3 -2 0 1 2 3 4 5 6 7 8 9 10 11 12 14 16 18 20 22 24 26 28 32 36 40 44 48 50 52 60 64 68 72 74 76 78 80 83
Blinded Continuous Glucose Monitoring Data Collection

1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in Study BDCU. However, for those participants whose participation in this study is affected by exceptional circumstances, such as pandemics or natural disasters, please refer to Section 10.7 for additional guidance.

1.3.1. SoA for the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22)

For procedures at the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22) **For procedures at Visit 23 to Visit 37, ET, UV, 801 and 802 (Study Period III) Safety F/u Period, please see Section 1.3.2**																				
Study Period I – Screening/Lead-In			**Study Period II - Treatment Period**																	**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 13 14	15	16	17	18 19	20	21	22	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9 10 11	12	14	16	18 20	22	24	26	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Fasting or Telehealth Visit			F			T	F	T	[a]	T		T	F	T		T		T	F	T = telehealth visit; F = fasting visit; [a]see notes below
Informed consent	X																			
Inclusion/exclusion criteria, review and confirm	X	X	X																	Review lab results and confirm I/E criteria
Demographics	X																			
Preexisting conditions and medical history, including relevant surgical history	X																			
Prespecified medical history (indication and history of interest)	X																			

For procedures at the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22) For procedures at Visit 23 to Visit 37, ET, UV, 801 and 802 (Study Period III) Safety F/u Period, please see Section 1.3.2																				
Study Period I – Screening/Lead-In			**Study Period II - Treatment Period**																	**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 13 14	15	16	17	18 19	20	21	22	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9 10 11	12	14	16	18 20	22	24	26	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Fasting or Telehealth Visit			F			T	F	T	[a]	T		T	F	T		T		T	F	T = telehealth visit; F = fasting visit; [a]see notes below
Prior treatments for indication	X																			
Substance use (recreational drugs, alcohol, caffeine, tobacco use)	X																			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 10.3
Physical Evaluation																				
Height	X																			
Weight	X	X	X	X	X		X		X		X		X		X		X		X	
Vital signs	X	X	X	X	X		X		X		X		X		X		X		X	See Section 8.2.2
Physical examination	X																		X	Additional physical examinations may be completed as necessary at PI discretion

For procedures at the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22) For procedures at Visit 23 to Visit 37, ET, UV, 801 and 802 (Study Period III) Safety F/u Period, please see Section 1.3.2																			
Study Period I – Screening/Lead-In			**Study Period II - Treatment Period**																**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 13 14	15	16	17	18 19	20	21	22	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9 10 11	12	14	16	18 20	22	24	26	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Fasting or Telehealth Visit			F			T	F	T	[a]	T		T	F	T		T		T	F	T = telehealth visit; F = fasting visit; [a]see notes below
Hypoglycemia events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (local)	X																			See Section 8.2.3
Blinded Continuous Glucose Monitoring																				
CGM sensor insertion and training		X	X								X						X			Dispense CGM supplies as needed
CGM device return and data download			X				X						X						X	
Participant Education																				
Diabetes counseling, SMBG, hypoglycemia training/education		X	X																	Includes diabetes counseling, SMBG, hypoglycemia (see Sections 5.3, 8.3.3). After V3, review as needed
Participant Diary (Electronic) and BG Meter																				
Dispense e-diary, glucometer, complete training		X																		
Dispense ancillary supplies as needed		X	X	X	X		X				X		X				X		X	

For procedures at the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22) For procedures at Visit 23 to Visit 37, ET, UV, 801 and 802 (Study Period III) Safety F/u Period, please see Section 1.3.2																			
Study Period I – Screening/Lead-In			**Study Period II - Treatment Period**																**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 13 14	15	16	17	18 19	20	21	22	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9 10 11	12	14	16	18 20	22	24	26	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Fasting or Telehealth Visit			F			T	F	T	[a]	T		T	F	T		T		T	F	T = telehealth visit; F = fasting visit; [a]see notes below
Diary compliance check			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Review FBG, hypoglycemia events, insulin dose
Patient-Reported Outcomes (Paper)																				
Treatment-Related Impact Measure - Diabetes (TRIM-D)			X																X	
Patient-Reported Outcomes (Electronic)																				
Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs)			X																	
Diabetes Treatment Satisfaction Questionnaire-Change (DTSQc)																			X	
EQ-5D-5L			X																X	
Simplicity Questionnaire (SIM-Q) – Daily Basal Insulin			X																	

For procedures at the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22) For procedures at Visit 23 to Visit 37, ET, UV, 801 and 802 (Study Period III) Safety F/u Period, please see Section 1.3.2																			
Study Period I – Screening/Lead-In			**Study Period II - Treatment Period**																**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 13 14	15	16	17	18 19	20	21	22	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9 10 11	12	14	16	18 20	22	24	26	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Fasting or Telehealth Visit			F			T	F	T	[a]	T		T	F	T		T		T	F	T = telehealth visit; F = fasting visit; [a]see notes below
Simplicity Questionnaire (SIM-Q) study intervention																			X	
Basal Insulin Experience: Preference																			X	
Basal Insulin Experience: Likelihood of Incorporating into Routine																			X	
Laboratory Tests and Sample Collections																				
Hematology	X		X										X						X	
Hemoglobin A1c (HbA1c)	X		X		X		X						X		X				X	
Clinical chemistry	X		X										X						X	
Glucose							X													
Lipid panel			X																X	
Urinalysis	X																		X	
Serum pregnancy	X		X																	Collect for WOCBP only

For procedures at the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22) For procedures at Visit 23 to Visit 37, ET, UV, 801 and 802 (Study Period III) Safety F/u Period, please see Section 1.3.2																			
Study Period I – Screening/Lead-In			**Study Period II - Treatment Period**																**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 13 14	15	16	17	18 19	20	21	22	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9 10 11	12	14	16	18 20	22	24	26	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Fasting or Telehealth Visit			F			T	F	T	[a]	T		T	F	T		T		T	F	T = telehealth visit; F = fasting visit; [a]see notes below
Urine pregnancy (local)			X																	Additional pregnancy testing may be performed if required by local regulations
Follicle-stimulating hormone (FSH)	X																			
C-Peptide			X																X	
eGFR (CKD-EPI)	X		X										X						X	
UACR	X		X										X						X	
Pharmacokinetic (PK) samples			X		X		X						X						X	All randomized participants
Immunogenicity (ADA) samples			X		X		X						X						X	All randomized participants
Stored Samples																				
Exploratory biomarker samples			X																X	
Randomization and Dosing																				
Randomization			X																	

For procedures at the Screening/Lead In Period I (V1-V2) and Treatment Period II (V3-V22) For procedures at Visit 23 to Visit 37, ET, UV, 801 and 802 (Study Period III) Safety F/u Period, please see Section 1.3.2																			
Study Period I – Screening/Lead-In			**Study Period II - Treatment Period**																**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 13 14	15	16	17	18 19	20	21	22	
Weeks from Randomization	-3	-2	0	1	2	3	4	5	6	7	8	9 10 11	12	14	16	18 20	22	24	26	
Visit Interval Tolerance (days)		±3	—	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	
Fasting or Telehealth Visit			F			T	F	T	[a]	T		T	F	T		T		T	F	T = telehealth visit; F = fasting visit; [a]see notes below
Insulin dose assessment/adjustment/ documentation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study intervention and related supplies			X				X						X						X	
Site administers study intervention and trains participant			X																	
Observe patient administer LY3209590 study intervention				X																Dose documented in e-diary immediately
Assess study intervention and storage compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant returns unused study drug							X						X						X	

1.3.2. SoA for the Treatment Period (V23-V37), ET, UV, and Safety Follow-Up Period (801-802)

For Treatment Period (V23-V37), ET, UV, and Safety F/u Period (801-802) For procedures at Screening Period I (V1-V2) and Treatment Period II (V3-V22), please see Section 1.3.1																
	Study Period II - Treatment Period													Study Period III Safety F/u		Comments
Visit Number	23 24	25	26 27	28	29	30	31	32	33 34	35	36	37	ET	UV	801	802	
Weeks from Randomization	28 32	36	40 44	48	50	52	60	64	68 72	74	76	78	—	—	80	83	
Visit Interval Tolerance (days)	±7	±7	±7	±3	±7	±3	±7	±7	±7	±3	±7	±3	—	—	+7	±7	
Fasting or Telehealth Visit	T	F	T	[a]	T	F	T	F	T	[a]	T	F	F		T	F	T = telehealth visit; F = fasting visit; [a]see below notes
Concomitant medications	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	See Section 10.3
Physical Evaluation																	
Weight		X		X		X		X		X		X	X			X	See Section 5.3
Vital signs		X		X		X		X		X		X	X			X	See Section 8.2.2
Physical examination												X	X			X	Additional physical examinations may be completed as necessary at PI discretion
Hypoglycemia events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (local)												X	X				See Section 8.2.3

For Treatment Period (V23-V37), ET, UV, and Safety F/u Period (801-802) For procedures at Screening Period I (V1-V2) and Treatment Period II (V3-V22), please see Section 1.3.1																
	Study Period II - Treatment Period													Study Period III Safety F/u		Comments
Visit Number	23 24	25	26 27	28	29	30	31	32	33 34	35	36	37	ET	UV	801	802	
Weeks from Randomization	28 32	36	40 44	48	50	52	60	64	68 72	74	76	78	—	—	80	83	
Visit Interval Tolerance (days)	±7	±7	±7	±3	±7	±3	±7	±7	±7	±3	±7	±3	—	—	+7	±7	
Fasting or Telehealth Visit	T	F	T	[a]	T	F	T	F	T	[a]	T	F	F		T	F	T = telehealth visit; F = fasting visit; [a]see below notes
Blinded Continuous Glucose Monitoring																	
CGM sensor insertion and training				X						X		X					Dispense CGM supplies as needed.
CGM device return and data download						X						X	X			X	
Participant Education																	
Diabetes counseling, SMBG, hypoglycemia training/education																	Includes diabetes counseling, SMBG, hypoglycemia (see Section 5.4, 8.3.3 respectively). After V3, review as needed

For Treatment Period (V23-V37), ET, UV, and Safety F/u Period (801-802) For procedures at Screening Period I (V1-V2) and Treatment Period II (V3-V22), please see Section 1.3.1																
	Study Period II - Treatment Period													Study Period III Safety F/u		Comments
Visit Number	23 24	25	26 27	28	29	30	31	32	33 34	35	36	37	ET	UV	801	802	
Weeks from Randomization	28 32	36	40 44	48	50	52	60	64	68 72	74	76	78	—	—	80	83	
Visit Interval Tolerance (days)	±7	±7	±7	±3	±7	±3	±7	±7	±7	±3	±7	±3	—	—	+7	±7	
Fasting or Telehealth Visit	T	F	T	[a]	T	F	T	F	T	[a]	T	F	F		T	F	T = telehealth visit; F = fasting visit; [a]see below notes
Participant Diary (Electronic) and BG Meter																	
Dispense ancillary supplies		X				X		X				X		X			
Diary compliance check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Review FBG, hypoglycemia events, insulin dose
Diary return													X			X	Participants will be required to return the e-diary to the investigative site at the last study visit
Patient-Reported Outcomes (Paper)																	
Treatment-Related Impact Measure – Diabetes (TRIM-D)						X						X	X				

For Treatment Period (V23-V37), ET, UV, and Safety F/u Period (801-802) For procedures at Screening Period I (V1-V2) and Treatment Period II (V3-V22), please see Section 1.3.1																
	Study Period II - Treatment Period													Study Period III Safety F/u		Comments
Visit Number	23 24	25	26 27	28	29	30	31	32	33 34	35	36	37	ET	UV	801	802	
Weeks from Randomization	28 32	36	40 44	48	50	52	60	64	68 72	74	76	78	—	—	80	83	
Visit Interval Tolerance (days)	±7	±7	±7	±3	±7	±3	±7	±7	±7	±3	±7	±3	—	—	+7	±7	
Fasting or Telehealth Visit	T	F	T	[a]	T	F	T	F	T	[a]	T	F	F		T	F	T = telehealth visit; F = fasting visit; [a]see below notes
Patient-Reported Outcomes (Electronic)																	
Diabetes Treatment Satisfaction Questionnaire - Change						X						X					
EQ-5D-5L						X						X	X				
Simplicity Questionnaire – Study Drug (SIM-Q)													X				Administered only if ET occurs before Visit 26
Basal Insulin Experience: Preference												X	X				
Basal Insulin Experience: Likelihood of Incorporating into Routine												X	X				
Laboratory Tests and Sample Collections																	
Hematology						X						X	X			X	
Hemoglobin A1c (HbA1c)		X				X		X				X	X			X	

For Treatment Period (V23-V37), ET, UV, and Safety F/u Period (801-802) For procedures at Screening Period I (V1-V2) and Treatment Period II (V3-V22), please see Section 1.3.1																
	Study Period II - Treatment Period													Study Period III Safety F/u		Comments
Visit Number	23 24	25	26 27	28	29	30	31	32	33 34	35	36	37	ET	UV	801	802	
Weeks from Randomization	28 32	36	40 44	48	50	52	60	64	68 72	74	76	78	—	—	80	83	
Visit Interval Tolerance (days)	±7	±7	±7	±3	±7	±3	±7	±7	±7	±3	±7	±3	—	—	+7	±7	
Fasting or Telehealth Visit	T	F	T	[a]	T	F	T	F	T	[a]	T	F	F		T	F	T = telehealth visit; F = fasting visit; [a]see below notes
Clinical chemistry						X						X	X			X	
Glucose		X						X									
Lipid panel						X						X	X			X	
Urinalysis												X	X			X	
Urine pregnancy													X			X	Additional pregnancy testing may be performed as necessary or if required by local regulations
C-Peptide												X	X				
eGFR (CKD-EPI)						X						X	X			X	
UACR						X						X	X			X	
Pharmacokinetic (PK) samples						X						X	X			X	All randomized participants

For Treatment Period (V23-V37), ET, UV, and Safety F/u Period (801-802) For procedures at Screening Period I (V1-V2) and Treatment Period II (V3-V22), please see Section 1.3.1																
	Study Period II - Treatment Period													Study Period III Safety F/u		Comments
Visit Number	23 24	25	26 27	28	29	30	31	32	33 34	35	36	37	ET	UV	801	802	
Weeks from Randomization	28 32	36	40 44	48	50	52	60	64	68 72	74	76	78	—	—	80	83	
Visit Interval Tolerance (days)	±7	±7	±7	±3	±7	±3	±7	±7	±7	±3	±7	±3	—	—	+7	±7	
Fasting or Telehealth Visit	T	F	T	[a]	T	F	T	F	T	[a]	T	F	F		T	F	T = telehealth visit; F = fasting visit; [a]see below notes
Immunogenicity (ADA) samples						X						X	X			X	All randomized participants.
Stored Samples																	
Exploratory biomarker samples												X	X				
Randomization and Dosing																	
Insulin dose assessment /adjustment/documentation	X	X	X	X	X	X	X	X	X	X	X	X	X	X			See Section 6.5.
Study participant may resume nonstudy insulin as clinically indicated												X	X				
Nonstudy insulin dose assessment/adjustment/ Documentation (eCRF)												X	X		X	X	See Section 6.8.5.
IWRS	X	X	X	X	X	X	X	X	X	X	X	X			X	X	
Dispense study intervention and related supplies		X				X		X									
Dispense ancillary supplies to participant		X				X		X				X		X			

For Treatment Period (V23-V37), ET, UV, and Safety F/u Period (801-802) For procedures at Screening Period I (V1-V2) and Treatment Period II (V3-V22), please see Section 1.3.1																
	Study Period II - Treatment Period													Study Period III Safety F/u		Comments
Visit Number	23 24	25	26 27	28	29	30	31	32	33 34	35	36	37	ET	UV	801	802	
Weeks from Randomization	28 32	36	40 44	48	50	52	60	64	68 72	74	76	78	—	—	80	83	
Visit Interval Tolerance (days)	±7	±7	±7	±3	±7	±3	±7	±7	±7	±3	±7	±3	—	—	+7	±7	
Fasting or Telehealth Visit	T	F	T	[a]	T	F	T	F	T	[a]	T	F	F		T	F	T = telehealth visit; F = fasting visit; [a]see below notes
Assess study intervention compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Participant returns unused study drug		X				X		X				X	X				

Abbreviations: ADA = antidrug antibody; BG = blood glucose; CGM = continuous glucose monitoring; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration equation; CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FBG = fasting blood glucose; FGM = flash glucose monitoring; F/u = follow-up; IWRS = interactive web-response system; PI = Principal Investigator; SMBG = self-monitoring of blood glucose; UACR = urinary albumin/creatine ratio; UV = unscheduled visit: V = visit; WOCBP = women of childbearing potential.

Notes:

- Visit 1 (Week -3) procedures may be conducted over more than 1 day if all activities are completed within 3 days.
- Visit Interval - The visit intervals including the allowable visit window should be scheduled relative to randomization.
- Visit 3 (Week 0) should occur 11-17 days after Visit 2.
- A local urine pregnancy test must be performed at Visit 3 (Week 0) with the result available prior to randomization and first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests (beyond those required per

SoA) should be performed at any time during the trial if a menstrual period is missed, there is clinical suspicion of pregnancy, or as required by local law or regulation.

- Visit 3 (Week 0) - ADA sample should be collected pre-dose administration for all randomly assigned participants.
- Visit 3 (Week 0) (randomization) - LY3209590 or insulin degludec will be administered during the study visit by site personnel.
- Visit 3 (Week 0) – PK sample should be collected at least 15 minutes post-dose. Dose amount and time should be recorded immediately after dose administration in the participant's e-diary.
- Visit 4 (Week 1) - weekly dose of LY3209590 will be administered by the participant during the study visit under observation of site personnel. The insulin dose amount and time is recorded for all doses.
- PK sampling– after Visit 3 may be collected at any time during the visit
- [a]Visit 9 (Week 6), Visit 28 (Week 48), and Visit 35 (Week 74) are eligible to be conducted remotely (that is, by telehealth visit in combination with mobile healthcare), as directed by the sponsor and allowed by local laws and regulations.
- Fasting "Visits" - participants should not eat or drink anything but water for a minimum of 8 hours before the visit. If a participant attends these visits in a non-fasting state, the sample should still be collected as non-fasting. This will not be considered a protocol deviation.
- CGM Visits – CGM collection should allow an interval of approximately14 days during the lead-in period and approximately 28 days for subsequent sessions post randomization. During the study blinded CGM sessions, only the study CGM device may be worn. Participants who routinely use personal CGM/FGM at study entry may not wear a personal CGM/FGM during the study required blinded CGM sessions. Refer to Section 8.1.5.2.
- Telehealth visit – may be telephone or other technology.
- Unscheduled visits may occur at any time during the study.
- Grey shaded columns denote Telehealth Visits.

2. Introduction

2.1. Study Rationale

LY3209590 is a long-acting insulin receptor agonist in development for the treatment of hyperglycemia in patients with T2D and T1D. It has an extended half-life of 17 days, enabling once-weekly dosing.

This Phase 3 study of LY3209590 will evaluate the effects of once-weekly administration of LY3209590 on glycemic control compared with daily administration of insulin degludec (U100) in adult participants with T2D treated with basal insulin with or without allowed non-insulin antihyperglycemic therapies.

2.2. Background

More than 50% of patients with T2D on basal insulin do not meet the target HbA1c (<7%) and clinical inertia, a failure to intensify titration to achieve an optimal basal insulin dose, contributes to poor glycemic control (Berard et al. 2018, Mocarski et al. 2018). Clinical inertia may result from physician concerns about managing the complex care needs of the patient with T2D or limited understanding of treatment algorithms (Berard et al. 2018). Additionally, optimizing basal insulin therapy doses may be negatively influenced by provider considerations of patient fears of side effects such as hypoglycemia, weight gain, or complex treatment regimens, as well as poor adherence by patients (Mocarski et al. 2018). A delay in treatment intensification has been shown to significantly increase the risk for cardiovascular events and diabetes-related complications, yet studies indicate that treatment intensification in T2D patients with poor glycemic control may take several years (Okemah et al. 2018). Therefore, 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.

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. It was designed as a divalent (dimer) insulin receptor agonist consisting of a single-chain insulin analog (comprised of an insulin B-chain analog, a short peptide linker, and an insulin A-chain analog) fused to a second peptide linker that is fused to an unmodified human IgG2 Fc domain. LY3209590 has a mean half-life of approximately 17 days and a peak-to-trough PK profile of 1.14. The low peak-to-trough ratio and extended half-life of LY3209590 support once-weekly dosing and have the potential to decrease patient burden, overcome barriers to initiation of insulin therapy, and may improve glycemic control and quality of life for patients with T2D compared to other daily basal insulins that require daily administration.

Phase 1 and Phase 2 studies have been completed to assess the PK/PD, safety, and efficacy of LY3209590. The PK of LY3209590 was characterized in Phase 1 with a single-ascending dose study that demonstrated clear evidence of glucose-lowering with prolonged time-action profile, that supports once-weekly administration. The multiple-ascending study used a single loading dose that was 3 times the initial weekly dose and demonstrated comparable exposure in 1 week to that observed at Week 6 with once-weekly dosing (1/3 of the loading dose, delivered once

weekly). The first Phase 2 Study BDCM has completed and evaluated the efficacy and safety of LY3209590 compared with insulin degludec (U100) in participants with T2D previously treated with basal insulin with or without other allowed non-insulin-lowering medications. Participants were randomly assigned (N = 399) to 1 of 2 dosing algorithms for LY3209590 or to daily administration of insulin degludec in a 1:1:1 ratio.

As Study BDCM was the first Phase 2 study of LY3209590, 2 dosing algorithms for LY3209590 were evaluated: Algorithm 1, with a titration target of FBG ≤140 mg/dL (7.7 mmol/L) with titration every 2 weeks and Algorithm 2 with an FBG target of 120 mg/dL (6.6 mmol/L) and titration every 4 weeks. For both dosing algorithms, a one-time loading dose of approximately 3 times the weekly dose was given, in order to reach steady-state insulin concentrations during the first week and avoid breakthrough hyperglycemia during transition from previous daily insulin to weekly basal insulin. Titration was based on median FBG values from the previous week and any occurrence of hypoglycemic events. Participants assigned to insulin degludec were dosed daily per a modified Riddle algorithm (Riddle et al. 2003) with titration target of FBG ≤100 mg/dL (5.5 mmol/L).

Results of Study BDCM demonstrated that following 32 weeks of treatment, LY3209590 effectively and safely improved glycemic control, comparable to insulin degludec. LY3209590 was non-inferior to insulin degludec with change in HbA1c from baseline to Week 32 for both Algorithms 1 and 2 with significant improvement in HbA1c in all treatment groups. The risk of all documented and nocturnal hypoglycemia (with blood glucose ≤70 mg/dL [3.9 mmol/L]) was statistically significantly lower (20% to 40%) for both LY groups compared to insulin degludec consistent with higher fasting glucose values observed with LY3209590. The reported TEAEs were balanced across the 3 treatment groups. Other safety measures including cardiovascular events, hepatic disorder events, injection-site and hypersensitivity reactions, immunogenicity, and treatment-emergent SAEs did not indicate an increased risk of safety with LY3209590 treatment compared to insulin degludec. Thus, the findings in Study BDCM support continued development of LY3209590 as a treatment for diabetes mellitus.

The objective of this Phase 3 study (BDCU) is to evaluate the efficacy and safety of LY3209590 as a weekly basal insulin compared to insulin degludec (daily basal insulin) using target FBG values of 80–120 mg/dL (4.4–6.6 mmol/L) in participants with T2D currently treated with basal insulin.

2.3. Benefit/Risk Assessment

The potential risks associated with LY3209590 include hypoglycemia, systemic allergic 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 of LY3209590 would be similar to those of other insulins' actions. Safety data available to date in Study BDCM suggest that there is no increased risk to participants' safety LY3209590 treatment compared to insulin degludec.

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with LY3209590 are justified by the benefits that may be offered to participants with T2D, which includes weekly administration, more consistent glycemic control,

and frequent engagement with health care providers during the study which provide opportunities for coaching and support.

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

Instructions for the transition from prestudy daily insulin doses and the titration algorithms (see Section 6.1) were developed to safely and efficiently initiate and guide LY3209590 and insulin degludec dose adjustments to achieve the same glycemic goals (FBG between 80 and 120 mg/dL [4.4 and 6.6 mmol/L]) while minimizing hypoglycemia risk.

2.3.1. Protocol Risk Mitigation Factors

An important feature of the study is the provision of an e-diary to each participant. The study-provided glucometer will wirelessly transfer participant SMBG to the e-diary. In addition, participants will record insulin dosing information and details related to any occurrence of hypoglycemia in the e-diary.

At Visit 2 (Week -2), 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 BG samples collected between study visits.

A web-interface and reporting system will be available for use by site personnel to view participant electronic diary (e-diary), 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 (requiring assistance due to neurological impairment) in the e-diary. The dosing algorithm used in the study requires consideration and adjustment of insulin dosing by the investigator based on participant FBG and hypoglycemia events. As modifications of the basal insulin dose may be influenced by other clinical circumstances or safety considerations known to the investigator, the investigator may prescribe a dose other than the algorithm recommended dose. If the investigator prescribes a dose other than the algorithm recommended dose, the investigator is responsible for documenting the clinical rationale for the prescribed dose.

Investigative site personnel will be thoroughly trained on the protocol design elements, inclusion/exclusion criteria, and study conduct. Any alerts received, for patient-reported events requiring assistance or treatment/outcomes that may be indicative of severe hypoglycemia will be reviewed and reported (Section 8.3.3).

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To investigate the hypothesis that LY3209590 is noninferior to the comparator (insulin degludec) on glycemic control in study participants with T2D currently on basal insulin	• Change from baseline in HbA1c at Week 26
Key Secondary (Multiplicity Adjusted)	
• To demonstrate LY3209590 is superior to insulin degludec in the selected parameters of glycemic control	• Change from baseline in HbA1c at Week 26 • The event rate of participant-reported clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 78 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured during the CGM session prior to Week 26
Other Secondary	
• To investigate the efficacy of LY3209590 compared with insulin degludec in additional parameters of glycemic control	• Change from baseline in HbA1c at Weeks 52 and 78 • Change from baseline in fasting glucose measured by SMBG at Weeks 26, 52, and 78 • Glucose variability measured during the CGM session prior to Weeks 26, 52, and 78 • Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured during the CGM session prior to Weeks 52 and 78 • Insulin dose at Weeks 26, 52, and 78
• To investigate the safety of LY3209590 compared with insulin degludec	• Incidence and rate of composite of Level 2 and 3 hypoglycemia events during treatment period • Body weight change from baseline to Weeks 26, 52, and 78 • Time in hypoglycemia with glucose <54 mg/dL (3.0 mmol/L) measured during the CGM session prior to Weeks 26, 52, and 78 • Time in hyperglycemia range defined as glucose >180 mg/dL (10.0 mmol/L) measured during the CGM session prior to Weeks 26, 52, and 78
• To evaluate treatment impact between LY3209590 and insulin degludec based on patient-reported outcomes questionnaires	• Change from baseline in TRIM-D at Weeks 26, 52, and 78 • DTSQ change from baseline at Weeks 26, 52, and 78

Tertiary	
• To investigate the treatment impact of LY3209590 compared with insulin degludec on other measures of efficacy, safety, PK/PD, and patient-reported outcomes	Efficacy • Percentage of participants achieving HbA1c <7% at Weeks 26, 52, and 78 • Percentage of participants achieving HbA1c <7% at Week 26 without nocturnal hypoglycemia during treatment phase up to Week 26 • Percentage of participants achieving HbA1c ≤6.5% at Weeks 26, 52, and 78 • Change from baseline in fasting serum glucose at Weeks 26, 52, and 78
	Safety • Incidence and rate of Level 2 hypoglycemia events during treatment period • Incidence and rate of Level 3 hypoglycemia events during treatment period • Incidence of positive treatment-emergent antibody of LY3209590
	PK/PD • LY3209590 PK and concentration-response relationships to key safety and efficacy measures • Potential intrinsic and extrinsic factors
	Patient-Reported Outcomes • Change from baseline in SIM-Q at Week 26 • Frequency of responses to "Basal Insulin Experience: Likelihood of incorporating into routine" at Weeks 26 and 78 • Frequency of responses to "Basal Insulin Experience: Preference" at Weeks 26 and 78 • Change from baseline in EQ-5D-5L at Weeks 26, 52, and 78

Abbreviations: DTSQ = Diabetes Treatment Satisfaction Questionnaire – change version; CGM = continuous glucose monitoring; HbA1c = Hemoglobin A1c; SMBG = self-monitoring of blood glucose; SIM-Q = Simplicity Questionnaire; T2D = type 2 diabetes; TRIM-D = Treatment-Related Impact Measure – Diabetes

Primary Estimand (for primary objective)

US registration

The *primary* clinical question of interest is: What is the treatment difference between LY3209590 and insulin degludec in change from baseline to Week 26 in HbA1c in the study-eligible participants with T2D currently on basal insulin regardless of treatment discontinuation for any reason and regardless of initiation of rescue medication?

The ***treatment regimen estimand*** will be used for the primary objective and is described by the following attributes:

- Treatment condition: randomized treatment regardless of treatment discontinuation and use of rescue medications

- Population: targeted study population (see Section 9.2 for details)
- Endpoint: change from baseline to Week 26 in HbA1c
- Remaining intercurrent events: none. The 2 intercurrent events, treatment discontinuation for any reason and initiation of rescue medication, are both addressed by the treatment condition of interest attribute
- Population-level summary: difference in mean changes between treatment conditions

Rationale for estimand: The treatment regimen estimand estimates how participants with T2D are treated in clinical practice and takes into account both efficacy and safety.

Registration for other countries

The *primary* clinical question of interest is: What is the treatment difference between LY3209590 and insulin degludec in change from baseline to Visit 22 (Week 26) in HbA1c in the study-eligible participants with T2D currently on basal insulin and adherent to the randomized treatment without intercurrent events during the study treatment period?

The ***efficacy estimand*** will be used for the primary objective and is described by the following attributes:

- Treatment condition: randomized treatment
- Population: targeted study population (see Section 9.2 for details)
- Endpoint: change from baseline to Visit 22 (Week 26) in HbA1c
- 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
- Population-level summary: difference in mean changes between treatment conditions

Rationale for estimand: The treatment 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 22 (Week 26) in HbA1c will also be based on the primary estimands described above.

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

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

4. Study Design

4.1. Overall Design

Study BDCU is a Phase 3, multicenter, randomized, open-label, comparator-controlled study to evaluate the efficacy and safety of once-weekly basal insulin (LY3209590) compared to insulin degludec in participants with T2D treated with basal insulin.

The study includes a 3-week screening/lead-in period, a 78-week treatment period, and a 5-week safety follow-up period.

Participants will continue prior stable diabetes therapy with 0 to 3 allowed non-insulin antihyperglycemic medications during the study.

Participants will discontinue their previous basal insulin doses at randomization and will be assigned to either LY3209590 or insulin degludec U100. The initial dose for the study treatment will be determined as described in Section 6.1.

4.1.1. Design Outline

Study Period I: Screening and Lead-In

Visit 1 (Week -3): Screening

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

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

Visit 2 (Week -2): Lead-In

Participants will receive their e-diary, BGM, and the Dexcom G6® CGM system.

Participants will receive training on

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

Eligibility for the study will be based on participant medical history, physical examination, laboratory values, and results of procedures as listed in the SoA. Participant eligibility to participate in the study must be confirmed prior to inclusion in the study (see Sections 5.1 and 5.2). A participant e-diary and BGM will be dispensed at Visit 2 (Week -2), and e-diary compliance checks will occur for future visits as specified in the SoA (Section 1.3). Concomitant Meds, AEs, including hypoglycemia events, required questionnaires, and other study procedures are to be performed and recorded as outlined in the SoA. Participants will continue their current insulin therapy until randomization and record the insulin doses in the e-diary. The Dexcom G6 CGM sensor will be inserted at Visit 2 (Week -2), and participants will be required to wear the

sensor and insert a new sensor when indicated and keep the receiver within 20 feet to minimize data loss until Visit 3 (Week 0). The CGM will be blinded to both participants and the investigator (Section 8.1.5.2).

Study Period II Treatment Period

Visit 3 (Week 0): Randomization

Entry criteria for study enrollment (Sections 5.1 and 5.2) will be confirmed before randomization. Participants meeting enrollment criteria will be randomly assigned to one of these treatments

- LY3209590: once-weekly administration, or
- insulin degludec: once-daily administration.

All measures except PK, to be performed at Visit 3 (Week 0) (see SoA, Section 1.3) should be done prior to injection of the study participant's assigned IP to ensure that appropriate baseline measurements are obtained. PK will be performed postdose. A local urine and serum pregnancy test will be done before IP administration. If the local urine pregnancy test is negative, the study participant will begin IP. If the result of the local urine pregnancy test is positive, the study participant will be considered a screen failure (see SoA Section 1.3).

Blinded CGM will continue at Visit 3 (Week 0) for an additional four-week period and periodically as described in the SoA. Please see Section 8.1.5.2 for specific details on CGM.

The first dose of both LY3209590 and insulin degludec U100 will be administered by site personnel. Participants assigned to insulin degludec will continue daily administration after Visit 3 (Week 0). Participants will continue to record their insulin doses in the e-diary throughout the study.

Visit 4 (Week 1)

Participants assigned to LY3209590 will administer their second dose at Visit 4 (Week 1), at the site, under observation of site personnel and document the dose administered in the e-diary before leaving the site.

Visit 5 (Week 2) - Visit 37 (Week 78)

Participants assigned to LY3209590 will administer their weekly doses during the remaining treatment period. Non-insulin antihyperglycemic medications will be continued after randomization. Study participants must measure their FBG levels each day when possible or at a minimum 3 times per week. The participant's FBG will be used to titrate basal insulin dose adjustments throughout the study based on the study titration algorithm (Section 6.1.3). Blinded CGM will be worn by participants at designated weeks (SoA Section 1.3, Section 8.1.5.2). Concomitant Meds, AEs, including hypoglycemia events, required questionnaires, diary compliance, and other study procedures will be recorded and completed as outlined in the SoA. The last dose of LY3209590 will be administered in the week prior to Visit 37 (Week 78), and the last dose of insulin degludec will be administered a day prior to Visit 37 (Week 78). Comprehensive efficacy and safety evaluations will be conducted through the end of the treatment period.

Randomly assigned participants who are discontinued from IP before the end of the treatment period at Visit 37 (Week 78) are encouraged to remain in the study for continued monitoring. Both efficacy and safety data will be collected as indicated in the SoA after the early discontinuation of IP.

Study Period III: Safety Follow-up Period

After the completion of the treatment period, study participants will begin their prestudy basal insulin, or a non-study basal insulin as specified by the investigator based on the instructions for transitioning to a non-study basal insulin (see Section 6.8.5.1). Current non-insulin antihyperglycemic medications will be continued. Investigators will prescribe and document the prescribed insulin dose during the safety follow up-period in the eCRF.

Study participants must measure their FBG levels each day when possible or at a minimum 3 times per week. Participants will collect blinded CGM for 4-weeks, and the site will download the CGM data at Visit 802.

Study participants will return unused study drug and study devices to the investigative site at the final study visit.

ET Visit

An ET visit is conducted when the participant discontinues treatment and will not continue the remaining visits in the treatment period. Participants should complete an ET visit in a fasting state. If a participant is wearing a CGM at the time of ET, the CGM data will be uploaded at the ET visit. Following an ET visit, the participant can continue to the safety follow-up period for participant safety monitoring.

4.2. Scientific Rationale for Study Design

This study will evaluate the efficacy and safety of once-weekly basal insulin LY3209590 compared to once-daily insulin degludec in adult participants with T2D already treated with basal insulin. A 2:1 randomization ratio of LY3209590: insulin degludec will allocate more participants for safety and exposure information to the LY3209590 treatment group. The 78-week treatment period provides collection of more efficacy and safety information for the experimental treatment. Insulin doses will be titrated to the same FBG targets of 80–120 mg/dL (4.4–6.6 mmol/L) for both treatment groups.

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.

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. The primary endpoint at Visit 22 (Week 26) is based on participants reaching stable insulin dose by 8 to 12 weeks and achieve glycemic stability in advance of the 26-week primary endpoint. The secondary objectives provide complementary information about glycemic control. Hypoglycemia, AEs, and immunogenicity will be assessed to characterize safety.

Race and Ethnicity

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity.

4.3. Justification for Dose

The IP used in this Phase 3 study will be in insulin units delivered via prefilled pens using the dosing algorithm provided in Section 6.1. The dosing guidance for starting doses and dose titrations of LY3209590 is derived based on findings from Phase 2 studies and model-based simulations. These data informed dosing increments designed to balance the goal of achieving a balanced FBG target range and minimize occurrence of hypoglycemia.

Justification for the LY3209590 single loading dose

Following a once-weekly subcutaneous administration of LY3209590, the time to reach steady-state PK without a loading dose is estimated to be between 8 and 10 weeks based on the long half-life of LY3209590. With a loading dose, the estimated time to reach steady state is within 2-3-weeks. Participants randomly assigned to LY3209590 with median FBG >120 mg/dL (6.6 mmol/L) will receive a single loading dose of LY3209590 that is 3-times the weekly dose calculated from their previous daily basal insulin dose multiplied by 7 (see Section 6.1). This strategy was designed to minimize loss of glycemic control when transitioning from the shorter duration once-daily basal insulins to a weekly insulin. This approach is supported by findings in the multiple-ascending dose Study BDCB, the Phase 2 Study BDCM, and model-based simulations.

For participants who are entering the study in good glycemic control (FBG ≤120 mg/dL [6.6 mmol/L]), a loading dose is not recommended. In such cases, treatment should be started using the weekly dose calculated from their previous daily basal insulin dose multiplied by 7 (see Section 6.1).

Directions for conversion of the prior daily basal insulin dose to the LY3209590 weekly dose are described in Section 6.1. The method to calculate the one-time loading dose and the titration rules to be used beginning at Visit 5 (Week 2) are also described in Section 6.1.

Justification for the insulin degludec starting dose

The starting dose for insulin degludec (U100) is the same as the daily dose of basal insulin the participant was taking prior to Visit 3 (Week 0). Insulin degludec will be titrated to achieve FBG target of 80-120 mg/dL (4.4-6.6 mmol/L) using an algorithm that is patterned after the well-established Riddle algorithm and other published algorithms (Meneghini et al. 2007, Kadowaki et al. 2017) but modified to balance efficacy and hypoglycemia for the same FBG targets as LY3209590 (Section 6.1).

Safety of study participants will be closely monitored during the early stages of dose titration to determine whether adjustments to the dose are needed to safely achieve FBG targets of 80-120 mg/dL (4.4-6.6 mmol/L) and will continue throughout the study (See Section 6.1).

4.4. End of Study Definition

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

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 the following criteria apply:

Age

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

Type of Participant and Disease Characteristics

2. Have a diagnosis of T2D according to the WHO criteria currently treated with basal insulin
3. Are receiving ≥10 units of basal insulin per day and ≤110 units/day at screening
4. Have HbA1c value 6.5%-10% inclusive, as determined by central laboratory at screening
5. Have been treated with a stable regimen in the opinion of the investigator of one of the following insulin regimens (includes biosimilars) used according to local product label with or without non-insulin diabetes therapy for at least 90 days prior to screening:
   - once-daily U100 or U200 insulin degludec
   - once-daily U100 or U300 insulin glargine
   - once or twice-daily U100 insulin detemir (Levemir [Novo Nordisk A/S., Bagsvaerd, Denmark]), or
   - once or twice-daily human insulin NPH.

   Acceptable non-insulin diabetes therapies may include 0 to up to 3 of the following:

   - dipeptidyl peptidase (DPP-4) IV inhibitors
   - SGLT2 inhibitors
   - metformin
   - alpha-glucosidase inhibitors, or
   - GLP-1 receptor agonists.

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

Weight

6. Have a body mass index less than or equal to 45 kg/m^2, at screening

Participant Protocol Compliance

7. Have a usual wake/sleep pattern such that midnight to 0600 hours will reliably reflect a usual sleeping period
8. In the investigator's opinion, are well-motivated, capable, and willing to
   - reliably take study-provided insulin injections as directed and other diabetes medications as required for this protocol.

    - visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the IP
    - persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the IP
- maintain an electronic study diary and use only the glucometer supplied for use in the study, including recording information on insulin doses and hypoglycemia events in the e-diary as required for this protocol
- wear the blinded continuous glucose-monitoring device supplied for use in this study at the specified times during the study and maintain proximity within 20 feet of the CGM receiver as required in the SoA and Section 8.1.5.2. Note: Participants who are already using CGM or FGM at study entry will be allowed to continue to use their personal CGM/FGM during the study when not wearing the study CGM. Participants must use the study-provided glucometer for all FBG values and any other BG values reported during the study
- not wear a personal CGM/FGM during the study blinded CGM assessments
- not initiate the use of personal CGM/FGM if not already routinely using CGM/FGM at study entry.

Sex and Contraceptive/Barrier Requirements

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

9. Male participants: No male contraception required except in compliance with specific local government study requirements. See the requirements in Section 10.4, Appendix 4.
10. Female participants: See the requirements in Section 10.4, Appendix 4.

Informed Consent

11. Capable of giving signed informed consent as described in Section 10.1, Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

5.2. Exclusion Criteria

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

Medical Conditions

12. Have had a significant weight gain or loss in the past 3 months in the investigator's opinion (for example, ≥5%)
13. 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, drug-induced or chemical-induced diabetes)
14. Are currently receiving or have received any time in the past 6 months, any of the following insulin therapies (outside of pregnancy) prior to screening, except for short-term treatment of acute conditions, and up to a maximum of 4 continuous weeks:
    - prandial insulin

- insulin mixtures
- inhaled insulin
- U-500 insulin, or
- continuous subcutaneous insulin infusion therapy

Note: Insulin use of any type or of any duration during a previous pregnancy is not considered an exclusion criterion.

15. Have received any of the following nonallowed diabetes medications within 90 days prior to screening: glinides, sulfonylureas, pramlintide, or thiazolidinediones
16. Have a history of greater than 1 episode of ketoacidosis or hyperosmolar state/coma requiring hospitalization in the 6 months prior to screening

Prior/Concomitant Therapy

17. Are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding replacement therapy for adrenal insufficiency; topical, intraocular, intranasal, or inhaled preparations or intra-articular injection) or have received such therapy for >14 days within the month preceding screening

Prior/Concurrent Clinical Study Experience

18. Are currently enrolled in any other clinical study involving an IP or any other type of medical research, judged not to be scientifically or medically compatible with this study
19. Have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to Visit 1 (Week -3)
20. 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
21. 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
22. Are Eli Lilly and Company employees or are employees of any third party involved in the study who require exclusion of their employees.

Diagnostic Assessments

23. Cardiovascular: have had New York Heart Association Class IV heart failure or any of the following CV conditions in the past 3 months prior to screening:
    - acute myocardial infarction,
    - cerebrovascular accident (stroke), or
    - coronary bypass surgery.
24. Gastrointestinal: have undergone gastric bypass (bariatric) surgery, restrictive bariatric surgery (for example, Lap-Band®), or sleeve gastrectomy within 1 year prior to screening
25. Hepatic: have acute or chronic hepatitis, cirrhosis, or obvious clinical signs or symptoms of any other liver disease, except NAFLD (that is, study participants with NAFLD are eligible for participation), and/or

- have elevated liver enzyme measurements, as determined by the central laboratory at screening and as indicated below:
  - total bilirubin >2x the ULN (except for participants with Gilbert's syndrome)
  - ALT/serum glutamic pyruvic transaminase >3x ULN
  - AST/serum glutamic oxaloacetic transaminase >3x ULN, or
  - ALP >2.5x ULN

26. Renal: have a history of renal transplantation, are currently receiving renal dialysis, or have an eGFR <20 mL/min/1.73 m^2, calculated by the CKD-EPI equation, as determined by the central laboratory at screening
27. Have active or untreated malignancy, have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years, or are at increased risk for developing cancer or a recurrence of cancer in the opinion of the investigator
28. Have known hypersensitivity or allergy to any of the study medications or their excipients
29. Have any other serious disease or condition (for example, known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, would pose a significant risk to the study participant, preclude the study participant from following and completing the protocol
30. Have evidence of a current or recent, within 6 months' time frame, history of any substance use disorder(s) of any severity as defined by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) in the opinion of the investigator, except disorders of nicotine or caffeine use
31. Hematologic: have had a blood transfusion or severe blood loss within 90 days prior to Visit 1 (Week -3) or have known hemoglobinopathy, hemolytic anemia or sickle cell anemia, or any other traits of hemoglobin abnormalities known to interfere with the measurement of HbA1c in the opinion of the investigator
32. Women of childbearing potential (for example, not surgically sterilized and between menarche and 1-year postmenopausal) who
    - are pregnant or intend to become pregnant during the study
    - are lactating/breastfeeding (including the use of a breast pump)
    - are unwilling to remain abstinent or use birth control, and
    - test positive for pregnancy at the time of screening (Visit 1 [Week -3] or any time before randomization).

    Note: a urine pregnancy test is conducted at Visit 3 (Week 0), and randomization will not be allowed with a positive result.

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), qualified site staff 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. Study participants should continue their usual

exercise habits and generally follow a healthy meal plan throughout the course of the study. Diabetes self-management counseling may be reviewed throughout the study, as needed.

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

Study participants should be instructed not to donate blood or blood products during the study or for 4 weeks following the study.

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 for this study. All entry criteria must be met within the specified intervals in the SoA.

6. Study Intervention(s) and Concomitant Therapy

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

Investigators and other study team members 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/national standards of care for diabetes, the investigators should follow current published standards of care from the American Diabetes Association (ADA 2021).

Site Responsibilities Related to Study Drugs

The investigator or their designee is responsible for the following:

- explaining the correct use and storage of the study drug to the participant and verifying those instructions are followed properly
- using the dosing algorithm to assess and titrate the doses weekly for the first 12 weeks and at least monthly throughout the remainder of the study
- maintaining accurate records of IP dispensing, and
- collecting of all unused study medication at the end of the study, returning it to Lilly, or designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3209590	Insulin Degludec
Type	Drug	Drug
Dosage Formulation	Solution	Solution
Unit Dose Strength(s)	500 units/mL	100 units/mL
Dosage Levels	Individualized dosing	Individualized dosing
Frequency of Administration	Once weekly	Once daily
Routes of Administration	Subcutaneous	Subcutaneous
Use	Experimental	Active comparator
IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor

Abbreviation: IMP = Investigational Medicinal Product.

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

1. Provided for use in this study are the prefilled pen injectors, for the delivery and administration of either LY3209590 or insulin degludec.
2. Instructions for device use and storage requirements are provided in the "Instructions for Use."
3. All Product Complaints, including malfunction, use error, and inadequate labeling, shall be documented and reported by the investigator throughout the study (see Section 8.3) and appropriately managed by the sponsor.

6.1.2. LY3209590 and Insulin Degludec Dosing

Frequency of Dosing with LY3209590 and Insulin Degludec

LY3209590 will be administered once weekly at approximately the same time and day each week using an insulin-prefilled pen (with 5-unit increments). 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 an interval of less than 3 days remains before the next scheduled dose, the missed dose should be skipped and the next dose should be administered 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, as long as the last dose has been administered at least 3 days earlier.

Insulin degludec (U100) will be administered daily at approximately the same time each day using commercially available insulin-prefilled pens (with 1-unit increments).

Maximum Units of Dosing with LY3209590 and Insulin Degludec

For LY3209590, the maximum number of units per injection in the LY3209590-prefilled pen is 400 units. Doses greater than 400-units a week (approximately 57-units per day of basal insulin [57 × 7 days = 399]) will require more than 1 injection. The maximum one-time loading dose for this study is 1600-units, and the maximum weekly dose is 1400-units. The maximum doses are supported by the current product safety assessment.

For insulin degludec, the maximum number of units per injection of insulin degludec (U100) is 80 units. For participants who require >80-units per day, more than 1 injection will be required to administer the full daily dose of insulin degludec.

Anatomical Location of Injections

For both treatments, participants will be instructed to 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.

6.1.3. General Insulin Dose Considerations for Both Treatment Groups

Transition to Study Insulins

The participants' initial and weekly dose of LY3209590 or daily dose of insulin degludec will be determined based on the participant's usual daily basal insulin dose prior to randomization. The starting doses take into consideration the prestudy basal insulin's label with regards to the ability

to do unit-to-unit conversions across insulin types/regimens. For participants whose prestudy basal insulin regimens are typically adjusted to the more conventional once-daily (U-100) basal insulin regimens (for example, twice-daily NPH or once-daily U-300 glargine), the total daily dose is reduced by 20% before multiplying by 7 to obtain the weekly dose equivalent.

The dosing and titration algorithms to be used will be based on the participant's treatment assignment to either LY3209590 or insulin degludec as described in Sections 6.1.4 and 6.1.5 respectively. Participants will be instructed to not take their prestudy basal insulin on the day of randomization since they will be dosed at the site with the allocated study insulin.

Insulin Dose Titration and Dose Maintenance

In this treat-to-target study, both treatment groups will undergo titration to achieve and maintain an FBG target within the range of 80-120 mg/dL (4.4-6.6 mmol/L). Active titration will occur in both treatment groups between Visits 3 to 15 (Weeks 0 to 12) which will be designated as the Titration Period with the goal to achieve insulin dose stabilization by Visit 15 (Week 12) with a minimum of monthly adjustments as necessary during the Maintenance Period from Visit 15 to 37 (Weeks 12 to 78).

Using the e-diary-linked study-provided glucometer, participants in both treatment groups will perform daily self-monitored FBGs. A minimum of 3 FBG readings on separate days each week must be obtained so that investigators can review the data to make dose adjustments using the titration algorithms for once-weekly or once-daily insulins (Sections 6.1.4 and 6.1.5). The median FBG to use in determining the dose adjustments starting at Visit 5 (Week 2) is obtained from the 3 most recent FBGs in the previous week. The median is the middle value when the 3 values are placed in ascending or descending order. For example, if a participant's FBGs for the past 3 consecutive measurements were 180, 202, and 190, the median is 190.

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

When considering any dose adjustments (in either treatment group), the investigator will review whether the participant experienced any documented episodes of hypoglycemia. 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 criteria for hypoglycemia dose reduction are met, the prior week's basal dose is decreased according to the treatment as indicated in the Hypoglycemia Dose Reduction Criteria for LY3209590 or the Hypoglycemia Dose Reduction Criteria for Insulin Degludec tables below. Investigators are expected to follow the dosing algorithms for the protocol; however, modifications of the basal insulin dose may be influenced by other clinical circumstances or safety considerations known to the investigator. If the investigator prescribes a dose other than the algorithm recommended dose, the investigator is responsible for documenting the clinical rationale for the prescribed dose in the Study Works web portal.

6.1.4. LY3209590 Dose Initiation and Modification

In this section, dosing instructions for LY3209590 are provided for

- dose initiation at Visit 3 (Week 0)

- administration of the weekly dose at Visit 4 (Week 1), and
- dose titration beginning at Visit 5 (Week 2) and continuing throughout the treatment period.

Note: The first dose is administered by site personnel; subsequent doses are self-administered.

Visit 3 – (Week 0): Randomization Visit

Determine the median FBG from the week prior to randomization (Visit 3 [Week 0])

Follow instructions in the LY3209590 Loading Dose Calculation table below for participants with FBG >120 mg/dL (6.6 mmol/L)

Follow instructions in the LY3209590 Starting Weekly Dose Calculation table below for participants with FBG ≤120 mg/dL (6.6 mmol/L)

Note: If a participant is on NPH twice-daily or U300 glargine, the prestudy basal insulin dose should be reduced by 20% when determining Usual Daily Dose of the prestudy basal insulin before calculating the Starting Weekly Dose.

LY3209590 Loading Dose Calculation –Participants with FBG >120 mg/dL (6.6 mmol/L)

Step	Action	Example Participant A (FBG >120 mg/dL [6.6 mmol/L])
1.	Determine usual prior daily basal dose from lead-in period	30 units/day
2.	Calculate **Starting Weekly Dose** (Usual Daily Dose multiplied by 7 and round to nearest 10)	210 units/Week
3.	Multiply **Starting Weekly Dose** by 3 to determine the Loading Dose[a]	630 units Loading Dose

[a] The Loading Dose should not exceed a dose of 1600 units.

If the calculated Loading Dose is >1600 units, the maximum loading dose of 1600 units is given as the one-time dose at Visit 3 (Week 0).

LY3209590 Starting Weekly Dose Calculation – Participants with FBG ≤120 mg/dL (6.6 mmol/L)

Step	Action	Example Participant B (FBG ≤120 mg/dL [6.6 mmol/L])
1.	Review usual prior daily basal dose from lead-in period	30 units/day
2.	Calculate **Starting Weekly Dose** ➢ (Usual Daily Dose multiplied by 7 and round to nearest 10)	210 units/Week

The maximum weekly dose should not exceed 1400 units. If the calculated weekly dose is greater than 1400 units, prescribe only 1400 units.

Visit 4 (Week 1): Starting Weekly Dose

If the participant experienced hypoglycemia in the previous week and met any of the criteria for a dose reduction listed in the Hypoglycemia Dose Reduction for LY3209590 table below,

subtract 40 units from the **Starting Weekly Dose** to obtain the dose for administration at Visit 4 (Week 1).

If the Hypoglycemia Dose Reduction criteria are not met, administer the **Starting Weekly Dose**.

CAUTION: DO NOT REPEAT ADMINISTRATION OF THE LOADING DOSE

Hypoglycemia Dose Reduction for LY3209590

Hypoglycemia Dose Reduction Criteria Based on BG Values	Unit Dose Decrease
≥3 episodes ≤70 mg/dL (3.9 mmol/L)	40 units
≥1 nocturnal episode ≤70 mg/dL (3.9 mmol/L)	
≥1 episode <54 mg/dL (3.0 mmol/L)	
Any confirmed severe hypoglycemia	

The following steps illustrate an example calculation for Visit 4 (Week 1) of Starting Weekly Dose.

Step	Action	Example Participant B
1.	Review Starting Weekly Dose from Visit 3 (Week 0) calculations	210 units/day
2.	Determine if any of Hypoglycemia Dose Reduction criteria are met in prior week: If yes, subtract 40 units from Starting Weekly Dose If not, administer Starting Weekly Dose	a. If a Hypoglycemia Dose Reduction criterion is met, ➢ Week 1 Dose = 210 - 40 = 170 units/week b. If no Hypoglycemia Dose Reduction criterion was met, the Week 1 Dose=210 units/week

Visit 5 (Week 2): Titration to Week 77

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 participant experienced hypoglycemia in the previous week and met criterion for a dose reduction as described in the Hypoglycemia Dose Reduction for LY3209590 table above, subtract 40 units from the previous weekly dose.

If no BG ≤70 mg/dL (3.9 mmol/L) was reported, use the median FBG from the previous week to obtain the dose adjustment from the titration algorithm in the LY3209590 Dose Adjustment Based on Median FBG table below. If participant's median FBG from the week prior to randomization is ≤120 mg/dL (6.6 mmol/L) or prestudy basal insulin dose <20 units/day as described below, use dose adjustments that correspond to that column. If the median FBG is within the target range from 80 to 120 mg/dL (4.4 to 6.6 mmol/L) inclusive, no change would be made to the dose from the previous week.

LY3209590 Dose Adjustment Based on Median FBG

Median FBG		LY3209590 Dose Adjustment Units (U)	
mg/dL	mmol/L	When Median FBG ≤120 mg/dL (6.6 mmol/L) or Prestudy Basal Insulin Dose <20 U	When Median FBG >120 mg/dL (6.6 mmol/L) Units
<80	<4.4	(–) 20 U	(–) 20 U
80–120	4.4–6.6	No change to dose	No change to dose
121–140	6.7–7.7	(+) 10 U	(+) 20 U
>140	>7.7	(+) 20 U	(+) 40 U

(–) = decrease dose; (+) = increase dose

6.1.5. Insulin degludec Dose Initiation and Modification

In this section, dosing instructions for insulin degludec are provided for

- dose initiation at Visit 3 (Week 0), and
- administration of the daily dose at Visit 4 (Week 1) and subsequent dosing/dose adjustments throughout the treatment period.

Note: The first dose is administered by site personnel; subsequent doses are self-administered.

Visit 3 – (Week 0): Randomization Visit Insulin Degludec Dose Determination from Equivalent of Prestudy Insulin Dose

Follow instructions in the Equivalent Dose of Insulin Degludec table below, to calculate the equivalent dose of insulin degludec to be administered by the participant once daily.

Note: If a participant is on NPH twice-daily or U300 glargine, the prestudy basal insulin dose should be reduced by 20% when determining the once-daily dose of insulin degludec to initiate in the study.

Equivalent Dose of Insulin Degludec

Step	Action	Example Participant C Prestudy insulin: glargine, U100 20 units once-daily	Example Participant D Prestudy insulin: NPH, 10 units twice-daily
1.	Determine usual prior daily basal dose from lead-in period	20 units/day	10 units × 2 = 20 units/day
2.	Determine daily dose of insulin degludec	20 units/day	20 units – [20 × 0.2] units = 20 units – 4 units = 16 units/day

Visit 4 (Week 1) to Visit 37 (Week 78)

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 participant experienced hypoglycemia in the previous week that met dose reduction criterion, decrease the daily dose as described in the Hypoglycemia Dose Reduction Criteria for Insulin Degludec table below.

Hypoglycemia Dose Reduction Criteria for Insulin Degludec

Hypoglycemia Dose Reduction Criteria Based on BG Values	Unit Dose Decrease
≥3 episodes of ≤70 mg/dL (≤3.9 mmol/L)	2–6 units [a]
≥1 nocturnal episode ≤70 mg/dL (3.9 mmol/L)	
≥1 episode <54 mg/dL (3.0 mmol/L)	
Any confirmed severe hypoglycemia	

[a] Dose reductions of 2 or 4 units may occur every 3 days to achieve a gradual weekly reduction of 6 units as clinically indicated.

If hypoglycemia dose reduction criteria are not met, use the median FBG from the previous week to obtain the dose adjustment from the titration algorithm in the Insulin Degludec Dose Adjustment table below. If the median FBG is within the target range from 80 to 120 mg/dL (4.4 to 6.6 mmol/L), no change would be made to the dose from the previous week.

Insulin Degludec Dose Adjustment

Median FBG		Insulin Degludec Dose Adjustment
mg/dL	mmol/L	units
<80	<4.4	(-) 3 units (decrease)
80-120	4.4-6.6	No change
121-140	6.7-7.7	(+) 3 units (increase)
>140	>7.7	(+) 6 units (increase)

6.1.6. Management of Hypoglycemia

At Visit 2 (Week -2), participants who have not screen failed will be trained by authorized site personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia and how to document episodes in the e-diary.

This section provides guidance on management of episodes of hypoglycemic events. For effective implementation of measures described here, it is important that participants, and their caregivers, if applicable, be well-educated about the signs and symptoms of hypoglycemia (for example, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders) and its treatment. Participants should be instructed how to treat all levels of hypoglycemia and that if they experience an event of severe hypoglycemia, they should notify the site as soon as possible after the event has been successfully treated (see Section 8.3.3).

The allowable non-insulin antihyperglycemic medications are not insulin secretagogues; therefore, clinically relevant increases in the risk of hypoglycemia due to these medications are not expected. To date, effects of LY3209590 on hypoglycemia are not different as compared to other basal insulins, so the management of hypoglycemia is similar for the study participants in both treatment groups.

Study participants will be instructed to use standard precautions prior to and during exercise.

Study participants will be instructed to check their BG, when they experience signs and symptoms suggestive of hypoglycemia, and to administer appropriate treatment for when BG

≤70 mg/dL (3.9 mmol/L). They will be instructed to recheck BG levels 15 minutes following treatment of hypoglycemia and repeat treatment and BG recheck after another 15 minutes until the BG level has returned to the target range of 80-120 mg/dL (4.4-6.6 mmol/L) (CDC 2021). Instructions will be provided for clinical management of participants who experience frequent or repeated hypoglycemia. As necessary, additional instruction/education may be provided to participants by investigative staff, including increased BG monitoring, treatment adjustments, or other approaches (for example, behavioral interventions and lifestyle modification) to mitigate hypoglycemia frequency or severity.

Investigators should prescribe glucagon to participants, and family members, housemates, or support care providers should be educated about glucagon administration.

In cases where a participant experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the participant has been fully compliant with the assigned therapeutic regimen and ensure that there is no evidence of other possible causes of hypoglycemia, for example, omission of meal, inadequate meal, and unexpected increase in exercise.

Participants experiencing severe hypoglycemia at any time should be evaluated by the investigator to determine if criteria are met for adjustment of the basal insulin based on the dosing algorithm (Section 6.1) first and then if needed, consider adjusting current concomitant antihyperglycemic medications. If discontinuation of IP is required for hypoglycemia that is refractory to decreasing the dose of non-insulin anti-hyperglycemic medications or other interventions or there are other safety concerns, the investigator should notify the sponsor and complete an AE form, indicating discontinuation of IP related to hypoglycemia. The investigator and the Lilly research scientist or physician will determine alternative treatment (if applicable) and whether continued participation in study and safety follow-up while not on IP is appropriate.

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.

In-use storage conditions must 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. Study participants will be provided with cartons containing the required number of pens at clinic visits as shown in the SoA (Section 1.3).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Investigators and participants will be unblinded to the assigned treatment groups. Assignment to treatment groups will be determined by an IWRS. Participants will be randomly assigned to 1 of the 2 treatment groups in 2:1 ratio (LY3209590:insulin degludec) at Visit 3 (Week 0). Stratification will be by country, HbA1c stratum at Visit 1 (Week -3) (<8.0%, ≥8.0%), and the type of basal insulin regimen at randomization (a. typical once-daily basal insulin; b. U-300 or NPH BID regimens which need reduction in total daily dose (TDD)/conversion to equivalent dose for typical once-daily U-100 basal insulin regimen).

All study IP will be assigned by IWRS. Site personnel will confirm that they have located and are dispensing the correct IP by entering a confirmation number found on the IP label into the IWRS.

The Lilly study team members who are closely involved in data interpretation and analysis planning will remain blinded throughout the course of the trial; 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.

Interim analyses will be conducted under the auspices of an external DMC. Only the external statisticians from the SAC will have access to the unblinded data that are presented to the DMC. The SAC and members of the DMC will abide by the principles and responsibilities described in the DMC charter, which include all unblinded information confidential until the planned unblinding of the trial.

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

The investigator or trained designee will assess the treatment (LY3209590 or insulin degludec) compliance at each contact (visit or phone contact) based on review of the participant glycemic control, e-diary completion, and adherence to prescribed dose and study procedures.

Study participants considered to be poorly compliant with their medications and/or study procedures (for example, missed visits or specific diagnostic tests) will be retrained as needed by designated site personnel.

6.5. Dose Modification

Dosing will be individualized based on FBG and the sponsor provided algorithm for both study drugs (LY3209590 or insulin degludec) as mentioned in Sections 6.1.4 and 6.1.5. In particular, the dose will be reduced as specified if hypoglycemia criteria are met (See Section 6.1).

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

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

6.7. Treatment of Overdose

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

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

- contact the Lilly-designated medical monitor (for example, CRP/CRS) immediately.
- evaluate the participant to determine, in consultation with the Lilly-designated medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention no longer has a clinical effect, and
- if the participant is assigned to LY3209590, a plasma sample for PK analysis may be obtained.

6.8. Concomitant Therapy

Study participants will be permitted to use concomitant medications that they require during the study, except excluded medications described in Section 5.2 (Exclusion Criteria) and the table below.

Investigative site staff will inform study participants that they must consult with the investigator or a designated site staff member when prescribed any new medications that may substantially affect glycemic values during the study, except when initiated for treatment of medical emergencies. Any additional medication initiated during the study (including OTC drugs, such as aspirin) must be documented in the CRF with the name of the drug and date(s) of administration. In addition, for permitted concomitant non-insulin antihyperglycemic medications, the dosage will also be documented and collected.

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

This table provides a summary of criteria for use of concomitant medications during the study.

Criteria for Use of Concomitant Medications

Drug Class	Use during Screening/ Lead-In	Conditions for Use after Randomization			
		During Treatment Period	Acute Therapy	Rescue Therapy	During Safety Follow-Up Period
Drugs with approved weight loss indication[a]	Y	Y	N	N/A	N
Systemic glucocorticoid therapy[b]	N	N	Y[c]	N/A	N
Antihyperglycemia Medications					
GLP-1 RAs	Y[d]	Y[d]	N/A	Y	Y
DPP-4 inhibitors	Y[d]	Y[d]	N/A	Y	Y
SGLT2 inhibitors	Y[d]	Y[d]	N/A	Y	Y
Non-study basal insulins	Y[d]	(allowed only if study basal insulin is discontinued)	(allowed only if study basal insulin is temporarily discontinued)	See note	Y
Insulin mixtures	N	N	(allowed only if study basal insulin is discontinued)	See note	Y
Prandial insulin	N	N	Y	Y	Y
Meglitinides	N	N	N	N	Y
Alpha-glucosidase inhibitors	Y[d]	Y[d]	N/A	Y	Y
Sulfonylureas	N	N	N/A	N	Y
Thiazolidinediones	N	N	N/A	N	Y
Metformin[e]	Y[d]	Y[d]	N/A	Y[f]	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] Participants should not initiate, or change the dose of, any weight loss medication for any reason after screening. Continued use is allowed during study lead-in and treatment period if on stable therapy 90 days prior to screening. These include, but not limited to, liraglutide 3.0 mg, orlistat, sibutramine, mazindol, phentermine, lorcaserin, phentermine/topiramate combination, naltrexone/bupropion, semaglutide injection 2.4 mg, or similar other body weight loss medications, including OTC medications, for example, orlistat 60 mg capsules.

[b] Does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

[c] Acute therapy = treatment for up to 14 days.

[d] Continued use is allowed during study lead-in and treatment period if on stable therapy 90 days prior to screening.

[e] Switching metformin manufacturers 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.

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

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.

6.8.1. Rescue Therapy for Management of Participants with Severe / Persistent Hyperglycemia during the Treatment Period

Participants in this clinical trial will be treated with basal insulin (LY3209590 or insulin degludec) that will be titrated to achieve FBG levels at 80-120 mg/dL (4.4- 6.6 mmol/L). They will also be instructed to regularly perform SMBG (predominantly FBG but investigator may instruct the participant to check BG at other timepoints to better inform dose adjustments and manage other aspects of clinical care). An additional antihyperglycemic medication should be considered if a participant develops severe, persistent hyperglycemia after randomization, based on meeting one of the following criteria and in the absence of intercurrent cause of the hyperglycemia (investigators should first confirm that the participant is fully compliant with the assigned therapeutic regimen and that they do not have an acute condition causing severe hyperglycemia):

- average of FBG over 2-week period >270 mg/dL (15 mmol/L) from Visit 11 (Week 8) to Visit 15 (Week 12)
- average of FBG over 2-week period >240 mg/dL (13 mmol/L) from Visit 15 (Week 12) to Visit 22 (Week 26), and
- average of FBG over 2-week period >200 mg/dL (11 mmol/L) from Visit 22 (Week 26) to Visit 37 (Week 78).

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.

Rescue therapy for consideration will commence with dose optimization of the participant's concomitant antihyperglycemic medications and/or addition of allowed concomitant antihyperglycemic medications if applicable so the participant is on up to 3 antihyperglycemic medications at effective doses before considering insulin rescue therapy. If severe, persistent hyperglycemia is not improving and there is participant compliance with the assigned therapeutic regimen and optimization of other/concomitant glucose-lowering agents, the addition of prandial insulin may be considered.

At Visit 22 (Week 26) or after, addition of prandial insulin may also be considered for rescue therapy without changing the participant's concomitant glucose-lowering medications if it is apparent that overbasalization is a problem. Situations that may suggest potential overbasalization include persistent elevated FBG due to elevated post-dinner BG, or elevated BGs at other times of the day (for example, following or in-between meals) while FBG is relatively well controlled or accompanied by hypoglycemia that is unexplained by activity, diet, or other factors.

Participants who receive rescue therapy for hyperglycemia management should also continue administering IP for the remaining period in the trial.

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.

6.8.2. Concomitant Antihyperglycemia Medication

Where appropriate, allowable non-insulin antihyperglycemic medication therapy may be obtained locally by the Lilly affiliate in the participating country from local commercial supplies and distributed to sites. It is acceptable for study participants to continue obtaining their non-insulin antihyperglycemic medications by the previous prescribing process. In the United States and Puerto Rico, a prescription card will be available for study participants to obtain their non-insulin antihyperglycemic medications with a prescription.

Dose adjustments of allowable non-insulin antihyperglycemic medications are permitted after randomization (during the treatment period) under the following circumstances and should be documented:

- 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 eGFR
- in the case of increased hypoglycemia risk during the treatment period (as described in Section 8.3.3)
- a dose increases as part of rescue therapy, and
- for safety reasons at the discretion of the investigator.

6.8.3. Medications that Promote Weight Loss

Prescription or OTC medications that promote weight loss cannot be initiated after screening. If started after screening, these medications should be stopped immediately.

6.8.4. Systemic Glucocorticoids

Chronic systemic glucocorticoid therapy is allowed for no more than 14 consecutive days during the first 26 weeks, and during the periods from 26 to 52- weeks and 52 to 78- weeks.

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.

6.8.5. Treatment after the End of the Study

6.8.5.1. Treatment after Study Completion

Study interventions will not be made available to study participants after Visit 37 (Week 78) or after the participant's early discontinuation from study treatment.

At the last treatment visit (Visit 37 [Week 78] or ET visit), the investigator will 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: Study participants will receive the last injection of LY3209590 at Week 77 of the study and can begin the transition to the non-study insulin after Visit 37 (Week 78). At Visit 37 (Week 78), 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 during the safety follow-up period based on FBG and according to the modified Riddle algorithm or investigator judgement in accordance with any country-specific label. 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: Study participants assigned to the insulin degludec treatment arm will transition to a non-study basal insulin after Visit 37 (Week 78). The investigator will prescribe the non-study insulin and titrate the dose based on their 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.

6.8.5.2. Emergency Situations and Special Circumstances

In emergency situations or special circumstances (for example, elective surgery, acute illness, and interrupted access to medicines), it may be necessary for study participants to change their dose of non-insulin antihyperglycemic medications and/or be treated with a non-study insulin. This will be allowed for up to 3 consecutive weeks for degludec or 3 consecutive doses for LY3209590 prior to Visit 22 (Week 26). After Week 26, dose changes to non-insulin antihyperglycemic medications or temporary treatment with a non-study insulin is allowed but must be documented by the investigator.

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 Section 10.1, Appendix 1.

7.1. Discontinuation of Study Intervention

Permanent Discontinuation of Study Intervention

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

A participant will be permanently discontinued from study intervention in the following situations:

- if the participant decides to stop study intervention
- if the participant becomes pregnant
- if participant has any significant study intervention-related hypersensitivity reaction
- if a participant is diagnosed with an active or untreated malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- if the participant has not taken insulin degludec for more than 21 consecutive days or has missed more than 3 consecutive doses of LY3209590 during the period from randomization to Visit 22 (Week 26) unless the investigator has instructed the participant to temporarily stop treatment
    - if the investigator determines that the participant is persistently noncompliant after the 26-week treatment period
- if the investigator or sponsor decides that the study participant should be withdrawn from IP. If the decision is made because of a severe AE, an SAE, or a clinically significant laboratory value, the appropriate measures are to be collected and Lilly or its designee should be alerted

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 Lilly-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 Lilly-designated medical monitor.

7.1.1. Liver Chemistry Stopping Criteria

The study drug should be interrupted or discontinued if one or more of these conditions occur:

Elevation from baseline	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 drug interruption/ 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 drug interruption/ 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%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009, and other consensus guidelines, with minor modifications	

Abbreviations: ALP = alkaline phosphatase; ALT= alanine aminotransaminase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; INR = International normalized ratio; TBL = Total bilirubin level; ULN = Upper Limit of Normal

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

7.1.2. Temporary Interruption of Study Treatment

The investigator may interrupt study treatment, due to an AE, clinically significant laboratory value, hospital visits, travel, or shortage of study treatment supply. Refer to Section 6.8.5.2 for allowable intervals for temporary study treatment interruptions.

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.

Participant should resume the dose prescribed before the temporary dosing interruption at the discretion of the investigator. Participant noncompliance should not be recorded as interruption of study intervention on the eCRF.

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

Participants who have a temporary interruption of the study intervention will continue participating in the trial and continue study visits through the safety follow-up according to the protocol.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent, and
- if a study participant is diagnosed with any type of diabetes mellitus other than T2D.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Section 10.2, Appendix 2 lists the laboratory tests that will be performed for this study.

- 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

8.1.1. Primary Efficacy Measure

The primary efficacy measure is HbA1c change from baseline to Visit 22 (Week 26).

8.1.2. Key Secondary Efficacy Measures

The following Secondary efficacy measures will be collected as shown in the SoA (Section 1.3):

- HbA1c
- Number of nocturnal hypoglycemia episodes
- Time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM

8.1.3. Other Secondary Measures

- Fasting glucose measured by SMBG
- CGM measurements:
  - Time in glucose range
  - Glucose variability
  - Time in hyperglycemia or hypoglycemia.
- Number of level 2 and 3 hypoglycemia episodes
- Body weight
- Insulin dose
- TRIM-D
- DTSQ

8.1.4. Other Efficacy Measures

The following efficacy measures will be collected as shown in the SoA (Section 1.3):

- Fasting serum glucose by central lab

- Number of level 2 or level 3 hypoglycemia episodes
- Antibody against LY3209590
- SIM-Q
- Responses to “Basal Insulin Experience: Likelihood of incorporating into routine”
- Responses to “Basal Insulin Experience: Preference”

8.1.5. Additional Information on Efficacy and Health Outcomes Measures

8.1.5.1. Self-Monitoring of Blood Glucose

Self-Monitoring of Blood Glucose (SMBG)

At Visit 2, participants who are enrolled in the study will receive a 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. Participants must use only the study-provided glucometer until the participant completes the 5-week safety follow-up period. 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. (Section 8.3.3).

Fasting Blood Glucose (FBG) Measurement

Study participants will be instructed 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.

SMBG for Hypoglycemia or Hyperglycemia

Participants should perform SMBG with the study-provided BG meter whenever hypoglycemia is experienced or suspected (with or without symptoms), when there is perceived, increased risk related to changes in dietary intake, physical activity, or inadvertent or atypical insulin dosing.

The participant’s FBG and events of hypoglycemia will be used to determine the insulin dose and titration based on the dosing and titration algorithm (Section 6.1).

Participants may perform SMBG more frequently to check for instances of hyperglycemia, or as directed by the investigator. Investigators may also instruct participants to collect SMBG, at time points other than at fasting, to evaluate glycemic control.

8.1.5.2. CGM Monitoring

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

Training and Initiation

Site personnel will dispense CGM supplies and initiate blinded CGM sessions at the times specified in the SoA. Participants will be trained on the CGM system before use and will be required to replace the sensor at designated intervals per the investigator instruction. A CGM

Participant User Guide that provides an overview of device components and study specific instructions is available for at-home use.

Participants are not allowed to connect the transmitter of the Dexcom G6 system to a personal smartphone, smartphone application, or other system and to use a personal CGM or FGM during the sessions when they are wearing the study-provided blinded CGM.

CGM Data Compliance

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

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

8.1.5.3. e-diary – Study Procedures

At Visit 2 (Week -2), participants who are enrolled in the study will receive an e-diary and be trained on use of the e-diary for documenting data related to study intervention dose administration, and events of hypoglycemia including related signs and symptoms. Data from the participant's study-provided glucometer will wirelessly transmit all blood glucose measurements to the e-diary. Participants should complete e-diary entries each week. If a participant is not compliant with diary completion, site personnel will re-educate the participant on study requirements for continued study participation.

8.1.5.4. Insulin Dose Entry

Participants will be instructed to enter the date of their daily or weekly insulin dose and dose amount in the dosing record. The participant will return the e-diary to the site at Visit 802 or at the ET visit if the participant will not complete the safety follow-up period.

8.1.5.5. Investigator Portal

Participant e-diary information including insulin dosing data, SMBG values, and events of hypoglycemia will be available for review through a web-based portal that can be accessed by designated investigative site personnel at any time. The site personnel can remotely view the completed e-diary data at any time during the study including between visits and print reports of diary data.

8.1.5.6. Patient-Reported Outcomes Assessments

The self-administered questionnaires will be translated into the native language of the region and administered at the site during the designated visits in the SoA (Section 1.3) At these visits, the questionnaires should be completed before the participant has discussed their medical condition

or progress in the study with the investigator and/or site staff, if the participant is not adversely affected by their fasting condition.

Preferred administration order of these questionnaires throughout the trial are

1. TRIM-D
2. DTSQ (status) (baseline only)
3. DTSQ (change) (after randomization)
4. EQ-5D-5L
5. SIM-Q
6. Basal Insulin Experience: Preference, and
7. Basal Insulin Experience: Likelihood of incorporating into routine.

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

The TRIM-D is a self-administered instrument, which assesses the impact of diabetes treatment on participants' functioning and well-being across available diabetes treatments (Brod et al. 2009). The TRIM-D consists of 28 items each assessed on a 5-point scale, where higher scores indicate a better health state, with a recall period of "over the past 2 weeks." In addition to an overall score, the TRIM-D items assess 5 domains of impact:

- Treatment Burden (6 items)
- Daily Life (5 items)
- Diabetes Management (5 items)
- Compliance (4 items), and
- Psychological Health (8 items).

8.1.5.6.2. Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs)

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

The DTSQs consists of 8 items that assess treatment satisfaction as well as concerns about hyperglycemia and hypoglycemia over the past few weeks, prior to the visit. Each item is rated on a 7-point Likert scale. Items 1 and 4-8 are rated from 0 (very dissatisfied) to 6 (very satisfied) and can be summed up to produce a treatment satisfaction score. Items 2 and 3 evaluate the perceived frequency of hyperglycemia and hypoglycemia and are rated from 0 (none of the time) to 6 (most of the time).

8.1.5.6.3. Diabetes Treatment Satisfaction Questionnaire – Change (DTSQc)

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

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

- the higher the score, the greater the improvement in treatment satisfaction

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

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

8.1.5.6.4. EQ-5D-5L

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

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

The 5L version, scores each dimension at 5 levels:

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

In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). The second part of the questionnaire consists of EQ Visual Analog Scale which records the respondent's self-rated health status. The participant rates his/her perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health). In conjunction with the health state data, it provides a composite picture of the respondent's health status.

8.1.5.6.5. Simplicity Questionnaire (SIM-Q) Single Medication status version

The Simplicity of Diabetes Treatment Questionnaire (SIM-Q) single medication status version is a brief 10-item measure developed to assess the simplicity and complexity of treatment for T2D. This measure asks participants to think about a specific medication (prior basal insulin or current study medication) when completing each item on a 5-point scale ranging from 'Very complex' to 'Very simple'. In Study BDCU, 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?"

8.1.5.6.6. Basal Insulin Experience: Likelihood of incorporating into routine

This is a Lilly-developed, participant-completed question to understand the participant's likelihood of incorporating their study insulin into their diabetes management routine. The question is rated on a 5-point scale with responses ranging from "very unlikely" to "very likely."

8.1.5.6.7. Basal Insulin Experience: Preference

This is a Lilly-developed, participant-completed question to understand the participant's preference for their pre-study or current study treatment. The question is rated on a 5-point scale with responses ranging from "strongly prefer the study insulin" to "strongly prefer my previous insulin." The question also includes a "not applicable" option for participants that stayed on the same insulin in the treatment phase.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs and symptoms related to T2D as well as related illnesses.
- Additionally, investigators should inspect injection sites during the physical examination.

8.2.2. Vital Signs

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

- Sitting BP and pulse rate will be measured.
- Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required (see SoA, Section 1.3).
- The participant should be required to sit quietly for 5 minutes before vital sign measurements are taken. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of BP measurements. The arm used for the BP measurement should be supported at heart level. BP should be measured consistently using the same arm throughout the study.
- For each parameter (pulse rate, systolic BP, and diastolic BP), 3 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart, and each measurement of sitting pulse rate and BP will be recorded in the eCRF.

8.2.3. Electrocardiograms

- Local 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3).
- Study participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs will be performed prior to collection of any blood samples.
- ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon as possible after the time of ECG collection, and ideally while the study participant is still present, to determine whether the study participant meets entry criteria at the relevant visit(s) and for immediate study participant management should any clinically relevant findings be identified.
- ECGs may be performed at additional visits based on investigator's discretion for safety assessment.
- If there is a clinically significant finding identified by the investigator, the investigator or qualified designee will determine if the participant should remain in study and if any changes should be made to participant care. The review of the electrocardiogram (ECG) printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Tests

- See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 5 weeks after the last dose of study intervention, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly- designated medical monitor (CRP/CRS).
    - If such values do not return to normal/baseline within a 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, Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and the 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 Safety Monitoring

Please see Section 10.5, Appendix 5 for details on Hepatic Safety Monitoring.

8.2.6. Pregnancy Monitoring

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 5-weeks (~35 days) days after the last dose.

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

The definitions of the following events can be found in Section 10.3, Appendix 3:

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

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

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 the study (see Section 7).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESI as defined in 8.3, respectively, 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 PCs, 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, Appendix 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 ICF	The last safety follow-up visit	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event (SAE)					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	The last safety follow-up visit OR participation in study has ended	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days after the last dose	Within 24 hours of learning of the pregnancy (see Section 8.3.2)	Pregnancy form	Pregnancy paper form
Product Complaints (PCs)					
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 (after participant's study participation has ended and the investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; eCRF= electronic case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. 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 stillbirth (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, he or she may learn of an SAE through spontaneous reporting.

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

8.3.3. Hypoglycemia

The following classifications of hypoglycemia are used to characterize hypoglycemic events:

Level 1 hypoglycemia:

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 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L): Level 2 hypoglycemia is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia: A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, a participant with altered mental status, and could not assist in their own care, or was semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance. **If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE**. In addition, the investigator will be asked to determine whether the episode was preceded by repeated or prolonged episodes of hypoglycemia.

Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep (between midnight and 6 AM).

8.3.4. Systemic Hypersensitivity Reactions

Many drugs, including oral agents and 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 generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Section 10.2, Appendix 2, "Laboratory Assessments for Hypersensitivity Events". Laboratory results are provided to the sponsor via the central laboratory.

8.3.5. Injection site reactions

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

If an ISR (Injection-Site Reaction) is reported by a participant or site staff, the ISR CRF will be used to capture additional information about this reaction (for example, injection-site pain, degree and area of erythema, induration, pruritis and edema). If an injection-site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the eCRF.

8.3.6. Adjudicated events: Cerebrocardiovascular Events

Potential cerebrocardiovascular events will be identified by the investigative site or by a medical review conducted by the sponsor or designee.

A blinded external Clinical Event Committee will adjudicate the events in a consistent and unbiased manner. Events include

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

8.4. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), blood samples will be collected for all participants. Only samples from participants assigned to treatment with LY3209590 will be analyzed for drug concentration. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Bioanalytical

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

8.5. Pharmacodynamics

Pharmacodynamic parameters will be evaluated as described in Sections 3 and 9.3.6.1.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of study participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Serum and plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 1.3) where local regulations allow.

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 and/or research methods, or in validating diagnostic tools or assay(s) related to T2D.

8.8. Immunogenicity Assessments

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

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

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 or medical resource utilization and health economics parameters are not evaluated in this study

9. Statistical Considerations

The first version of the SAP will be finalized prior to first participant visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

Primary Hypothesis

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control as measured by change from baseline to Week 26 (Visit 22) in HbA1c in participants with T2D currently on basal insulin. The null hypothesis (H_0) to be tested is the difference in the change from baseline to Week 26 (Visit 22) in HbA1c (LY3209590 – insulin degludec) is greater than the noninferiority margin (NIM). The NIMs of 0.4% and 0.3% will both be tested to meet different regulatory requirements. The 2-side 95% confidence interval (CI) will be used for testing the noninferiority.

Secondary Hypotheses

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

- change from baseline in HbA1c at Week 26 (Visit 22)
  H_0: the difference (LY3209590 – insulin degludec) ≥0.0
- the event rate of nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment period up to Week 78 (Visit 37)
  H_0: the relative event rate (LY3209590 vs. insulin degludec) ≥1
- time in glucose range between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) inclusive measured by CGM collected during the CGM session prior to Week 26 (Visit 22)

  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 9.1.1.1).

9.1.1.1. 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

The following populations are defined for purpose of analysis:

Analysis Populations/Data Sets	Description
Entered Population	All participants who sign the informed consent form.
Randomized Population	All randomized participants. Participants will be analyzed according to the treatment they were assigned.
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.
EAS1	The data will include • mITT population excluding participants discontinuing the study treatment due to inadvertent enrollment, and • all measurements regardless of the use of study treatment or the initiation of rescue medication.
EAS2	The data will include • mITT population excluding participants discontinuing the study treatment due to inadvertent enrollment, and • measurements up to the discontinuation of study treatment or the initiation of rescue medication.
SS	The data will include • mITT population, and • all measurements regardless of the use of study treatment or the initiation of rescue medication.

Abbreviations: EAS = efficacy analysis set; mITT = modified intent-to-treat; SS = safety analysis set.

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 (for treatment regimen estimand) or EAS2 (for efficacy estimand) and the safety analyses will be conducted on SS. All tests of treatment effects using statistical models will be conducted at a 2-sided alpha level of 0.05 and 2-sided 95% CI will be provided. Unless otherwise specified, other secondary and tertiary efficacy measures will be analyzed using EAS2 with the data up to the discontinuation of study treatment (defined by the date of last study dose + 10 days) or the initiation of rescue medication whichever is earlier.

9.3.2. Primary Endpoint/Estimand Analysis

The primary objective is to compare the HbA1c change from baseline to Week 26 between LY3209590 and insulin degludec and will be based on either of the 2 estimands: ***treatment regimen estimand*** for the US FDA submission and ***efficacy estimand*** for registrations in other countries.

The ***treatment regimen estimand*** will be estimated using the HbA1c data at baseline and Week 26 (Visit 22) for the EAS1, regardless of the use of study treatment or rescue medications. The missing measures at the primary endpoint will be imputed using multiple imputation by the retrieve dropout approach. The retrieved dropout participants are those who discontinue IP prior to Week 26 (Visit 22) but have non-missing measures at Week 26 (Visit 22). If there are only a limited number of retrieved participants that leads to a failure in performing the multiple imputation analysis, such as the model cannot converge, or the number of retrieved dropout participants is small, the missing HbA1c at Week 26 (Visit 22) will be imputed by return-to-baseline multiple imputations. After the imputation, the observed and imputed data will be analyzed by the analysis of covariance (ANCOVA). The model will include treatment, strata (country, and the type of basal insulin at randomization), and baseline value of the dependent variable. The statistical inference will be based on the multiple imputation framework by Rubin (1987).

The ***efficacy estimand*** is the treatment differences in the change in HbA1c from baseline to Week 26 (Visit 22) if all participants would adhere to the treatment without intercurrent events. The EAS2 with data up to the discontinuation of study treatment or the initiation of rescue medication, whichever is earlier, and the HbA1c collected at all planned postbaseline visits will be used in the analysis. There may be missing values due to the early discontinuation of study treatment or use of rescue medication. The mixed-model repeated measures (MMRM) model will be used, and the missing values will be handled in the MMRM analysis under the assumption of missing at random. The MMRM model will include treatment, strata (country, and the type of basal insulin 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.

The 2-sided 95% CI of the least-squares (LS) mean for individual treatment groups, treatment LS mean difference (LY3209590 – insulin degludec) in the HbA1c change from baseline to Week 26 (Visit 22) will be estimated. For both estimands, LY3209590 will be declared noninferior to

insulin degludec if the upper limit of the 2-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).

9.3.3. Secondary Endpoints Analysis

9.3.3.1. Multiplicity Adjusted Endpoints

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

1) change from baseline in HbA1c at Week 26 (Visit 22)
2) the event rate of nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment period up to Week 78 (Visit 37), and
3) 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 (Visit 22).

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

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

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%], and the type of basal insulin at randomization), and baseline of the dependent variable will be used. The MMRM model will include treatment, strata (country, baseline HbA1c stratum [<8.0%, ≥8.0%], and the type of basal insulin 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 IP or reported to worsen in severity from baseline will be considered TEAEs. The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity.

TEAEs will be summarized in tables using the Medical MedDRA preferred term (PT), sorted by decreasing frequency within the LY3209590 treatment group for all TEAEs, TEAEs by maximum severity and common TEAEs (defined as ≥1% before rounding for LY3209590-treated participants). TEAEs will also be summarized by PT sorted by decreasing frequency within System Organ Class (SOC). For events that are specific to one sex, the denominator and computation of the percentage will include only participants from the given sex.

The number and percentage of participants who reported a serious AE (SAE) will be summarized by treatment group using MedDRA PT. A listing of all SAEs will also be provided.

The AEs leading to study treatment discontinuation will be summarized by treatment group using MedDRA PT. A listing of AEs leading to study treatment discontinuation will also be provided.

The participant-reported hypoglycemia: Level 1 (defined by glucose value ≥54 to <70 mg/dL [≥3.0 to <3.9 mmol/L]), Level 2 (defined by glucose <54 mg/dL [3.0 mmol/L]), Level 3 (severe hypoglycemia) and the composite of Level 2 and Level 3, will be analyzed using data from e-diary. The analysis periods of 0-6, 0-12, 0-26, 0-52, 0-78, 12-26, 26-52, 26-78 weeks of treatment will be considered. Episodes for the 24-hour period, the non-nocturnal period (defined by 6 AM to midnight), and nocturnal period (defined by midnight to 6 AM) will be used to define all documented hypoglycemia, non-nocturnal hypoglycemia, and nocturnal hypoglycemia respectively. The incidence and rate of hypoglycemia will be summarized by treatment and analysis period for different types of hypoglycemia.

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

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

9.3.6. Other Analyses

9.3.6.1. Pharmacokinetic and Pharmacodynamic Analyses

LY3209590 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. The relationships between LY3209590 dose and/or concentration and efficacy, and safety as well as biomarker endpoints may be characterized. In addition, if population PK and PK/PD models can be established, the impact of additional participant factors, such as age, weight, gender, and renal function on PK and/or PD

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

9.3.6.2. Evaluation of Immunogenicity

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

The number and percentage of participants who are treatment-emergent ADA positive (TEADA+) will be summarized by treatment group. A participant who is evaluable for TEADA is TEADA+ if either of the following holds:

- treatment induced ADA: the participant has baseline status of ADA Not Present and at least 1 postbaseline status of ADA Present with titer ≥2-fold (1 dilution) of the minimum required dilution (1:20)
- treatment boosted ADA: the participant has baseline status of ADA Present and at least 1 postbaseline status of ADA Present with the titer being ≥2 dilutions (4-fold) of the baseline titer. That is, the participant has baseline status of ADA Present, with titer 1:B, and at least 1 postbaseline status of ADA Present, with titer 1:P and P/B≥4.

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

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

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. 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 939 participants will be randomly assigned to LY3209590 and insulin degludec in a 2:1 ratio. With the assumption of 15% dropout at Week 26, approximately 532 and 266 participants will complete 26 weeks of treatment on LY3209590 and insulin degludec, respectively.

The primary objective of this study is to test the hypothesis that LY3209590 is noninferior to insulin degludec on glycemic control as measured by change from baseline to Week 26 (Visit 22) in HbA1c in participants with T2D currently on basal insulin.

Assuming a noninferiority margin (NIM) of 0.4%, no true difference between treatment groups, and a SD of 1.1%, 798 completers (532 on LY3209590 and 266 on insulin degludec) will provide greater than 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). 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 26.

The 798 completers will provide 95% statistical power to demonstrate the superiority (LY3209590 vs. insulin degludec) of change in HbA1c from baseline to 26 weeks (assuming a SD of 1.1% and true mean difference is -0.3%) using the alpha of 0.05.

The 798 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 26 between LY3209590 and insulin degludec (assuming a SD of 18% and true mean difference is 5%) at alpha = 0.05.

The 798 participants will provide at least 80% statistical power to show the superiority of the event rate of clinically significant nocturnal hypoglycemia (<54 mg/dL [3.0 mmol/L] or severe) during treatment phase up to Week 78 (assuming event rate of 0.67 [SD = 2.6] and 1.1 [SD = 2.6] events per participant per year for LY3209590 and insulin degludec, respectively) using a negative binomial distribution at alpha = 0.05.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
    - applicable ICH GCP Guidelines, and
    - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
    - 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.
- Investigator sites are compensated for participation in the study as detailed in the CTA.

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that 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 Cerebrocardiovascular Events

A blinded Clinical Event Committee, external to Lilly, will adjudicate cerebrocardiovascular events.

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.

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

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.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK. 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, 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

- 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.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the period outlined in the 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.

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

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant or investigator site personnel, into an instrument (for example, handheld smart phone, tablet, or web portal). 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 collected via the sponsor-provided data capture system(s) will be stored at a third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). 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 PC 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 eCRF and that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

For study termination:

- discontinuation of further study intervention development.

For site termination:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and
- 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 for the studied indication.

Sample Type	Custodian	Retention Period After Last Participant Visit[a]
Biomarkers	Sponsor or designee	15 years
Pharmacokinetics	Sponsor or designee	1 year
Immunogenicity	Sponsor or designee	15 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by local or Lilly-designated laboratory.
- Local laboratory results are only required in the event that the Lilly-designated 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.
- In circumstances where the sponsor approves local laboratory testing in lieu of Lilly-designated 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	
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	
Albumin	
Creatinine	
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.
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. Fasting per SoA
HbA1c	
C-Peptide	
Glucose	
Exploratory Biomarker 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.

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c.

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

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

Timing	Sample Type	Laboratory Test[a]
Collect from 30 min to 4 hr after the start of the event. ● 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 only if not already collected on the same day as the event. ● Note: If collecting, collect up to 12 hr after the start of the event.	Serum	LY3209590 ADAs
	Serum/plasma	LY3209590 concentration

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

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

Information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.

10.3.1. Definition of AE

AE Definition
• Drug 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. • Device definition: 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 medication errors under Section 10.8.

- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy 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. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product Complaint

- A PC 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 PCs:
  - deficiencies in labeling information, and
  - use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC 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/PC 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/PC 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 PC information is reported on the Product Complaint Form.
  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC 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 PCs.
- 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 AE 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 AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is

assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) 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 Lilly-designated medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in site training materials.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the Lilly-designated medical monitor or the SAE coordinator.
- 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 materials.

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 related BDCU study documents and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

Females are considered a WOCBP if they have had at least 1 cycle of menses. Any amount of spotting should be considered menarche.

Women in the following categories are not considered WOCBP

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, or tubal ligation.

Postmenopausal State

The postmenopausal state should be defined as:

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

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

10.4.2. Females

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Must…	Must Not…

agree to either remain abstinent, or
stay in a same sex relationship without sexual relationships with males
	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method.

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Topic	Condition
Pregnancy testing	Negative serum result at screening followed by a negative serum result at randomization.
Contraception	Agree to use 1 highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception. These forms of contraception must be used for the duration of the study.

Examples of different forms of contraception:

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
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide
	Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, 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 • lactational amenorrhea

Please also refer to Sections 5.1 and 5.2.

10.4.3. Males

No male contraception required except in compliance with specific local government study requirements. See Section 5.1.

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

Close hepatic monitoring

Laboratory tests (Section 10.2, Appendix 2), including alanine aminotransaminase, aspartate aminotransferase, alkaline phosphatase, total bilirubin level, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

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

Abbreviations: ALP = alkaline phosphatase; ALT= alanine aminotransaminase; AST = aspartate aminotransferase; TBL = Total bilirubin level; ULN = Upper Limit of Normal

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor (CRP/CRS). At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

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

Comprehensive hepatic evaluation

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

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

ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT= alanine aminotransaminase; AST = aspartate aminotransferase; TBL = Total bilirubin level; ULN = Upper Limit of Normal

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

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

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and 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:

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

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

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

Hepatic Evaluation Testing

See above 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	

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

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

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

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

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

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

Refer to Section 10.3, Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

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

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with 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, if written approval is provided by the sponsor. Assessments will be completed according to the SoA.

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 PCs 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. However, central 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, as per the SoA.
- All labs will be reviewed by the investigators. Lilly Medical should be informed of any labs that meet criteria for temporary or permanent study intervention discontinuation.
- 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.
- Safety labs should be obtained as specified in the SoA.
- The local laboratory must be qualified in accordance with applicable local regulations.

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,
- 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/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 screening/lead-in visits to randomization visit: the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 30 days from first screening/lead-in visit.
    - 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 screening/lead-in visits to 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 screening visit to ensure participant eligibility by 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.

Primary endpoint visit (Visit 22; Week 26) should be completed as 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 (that is, ±7 days), additional study drug 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, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

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

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
Blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment, but the participant is not, or vice versa, or when the sponsor is aware of the treatment, but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BG	blood glucose
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 to 10 mmol/L) and 70 to 140 mg/dL (3.9 to 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.
CIOMS	Council for International Organizations of Medical Sciences
BGM	blood glucose meter
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CI	confidence interval
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration equation
CRF	case report forms
CRP	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CTA	Clinical Trial Agreement
CT	Computed tomography
CV	cardiovascular
DMC	Data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
Device deficiencies	equivalent to product complaint
EAS	efficacy analysis set
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
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.
FBG	fasting blood glucose
FGM	flash glucose monitoring
FSH	follicle-stimulating hormone
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
IB	investigator’s brochure

ICF	informed consent form
ICH	International Council for Harmonization
IFU	instructions for use
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 his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	Investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB/IEC	Institutional Review Boards/Independent Ethics Committees
ITT	Intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.

misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
NAFLD	nonalcoholic fatty liver disease
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.
NPH	Neutral Protamine Hagedorn
OTC	over the counter
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
PPS	per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QTc	corrected QT interval
SAC	statistical analysis center
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
SMBG	self-monitoring of blood glucose
SS	safety analysis set
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus

TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.9. Appendix 9: Protocol Amendment History

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

Amendment [a]: (28-JAN-2022)

Overall Rationale for the Amendment

The overall rationale for the changes implemented in the protocol amendment is to update the titration algorithm for insulin degludec so that it will more closely match the total weekly dose adjustments used in the LY3209590 titration algorithm and to include requirement that medication errors will be reported as adverse events.

Section # and Name	Description of Change	Brief Rationale
Title Page	Deleted descriptive acronym text	For consistency
Table of Contents	List of tables removed and table numbers were removed throughout the protocol	For consistency with protocol template
Section 1.1. Synopsis	Key secondary objective modified deleting "by CGM collected"	For clarity and consistency
Section 1.2. Schema	Moved one telephone visit from treatment period to the Safety Follow-Up period	For consistency with SoA
	Edited visit numbers (renumbered) and added additional visit in the Safety Follow-Up period	
Section 1.3. Schedule of Activities	Text added directing participants to Section 10.7 for exceptional circumstances	For clarity
	Added "Lead/In" to Section 1.3.1 header and updated subheading to include Visit numbers 38, 801 and 802	For consistency
	Deletion of "history of CV disease"	For consistency
	Added "X" at 16 weeks for weight	This procedure was previously inadvertently omitted
	Added "X" at 8 and 16 weeks for vital signs	These procedures were previously inadvertently omitted
	Added additional telehealth visit to the Safety Follow-Up period at Week 80; this	Telehealth visit to allow

Section # and Name	Description of Change	Brief Rationale
	visit is numbered 801 and the Week 83 visit is now numbered 802. Updated the visit numbers throughout the protocol. Updated header rows for both of the SoA tables. A "T" and "F" were added to indicate telehealth and fasting visits.	continued titration of non-study insulin as participants transition off study drug
	Added interval tolerance for Weeks 50 and 76 (Visits 29 and 36, respectively)	For consistency and clarity
	Deleted "Fasting" from "Fasting Glucose"	For consistency
	Added text "participant" to "Site administers study intervention and trains participant"	For clarity
	Added text "and storage" to "Assess study and compliance"	For clarity
	Deleted patient and added "participant" to "Patient returns unused study drug"	Correction
	Addition of "X" for "Concomitant medications" "Adverse events (AEs)" "Hypoglycemia events" "Diary compliance check" "IWRS"	To add activities that should occur in the 801 visit
	Added Activity for Diary Compliance Check at Visit 801	For consistency
	Diary Return comment was revised. "added the last study visit"	For clarity
	Added "X" at 52 weeks for EQ-5D-5L	To indicate that EQ-5D-5L should be administered at 52 weeks
	Added note to SIM-Q stating "Administered only if ET occurs before Visit 26"	For clarity
	Urine pregnancy collection added for ET and 802 visits. Comment was updated	To verify WOCBP participants pregnancy status at study discontinuation or completion

Section # and Name	Description of Change	Brief Rationale
	Deletion of "X" from "Insulin dose assessment /adjustment/documentation"	The activity is not necessary at the 801 visit
	Moved activity "Study participant may resume nonstudy insulin as clinically indicated" up within the table	To align with other similar activities
	Added an activity "Nonstudy insulin dose assessment/adjustment/documentation" with "X" at Visits 37, ET, 801 and 802	For clarity
	Removed the 801 visit for insulin dose assessment/adjustment/documentation	Not necessary
	Note bullet point 6: text revised	For clarity
	Note bullet point 8: text revised regarding PK sampling	
Section 2.3.1. Protocol Risk Mitigation Factors	Text added	To allow investigator to use clinical judgement to adjust the dose and not use the algorithm if clinically indicated
Section 3. Objectives, Endpoints, and Estimands	Key secondary modified adding "during the" and deleting "by …collected"	For consistency and clarity
	Other secondary modified adding text "measured"	
	PK/PD objective added to Tertiary Objectives the endpoints added are as follows: • LY3209590 PK and concentration-response relationships to key safety and efficacy measures • Potential intrinsic and extrinsic factors	To specify PK/PD objectives
	Tertiary patient-reported outcomes modified to add text to include ED-5D-5L scale	To indicate tertiary objective for EQ-5D-5L outcome

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1. Design Outline	Visit 2: text added "and record the insulin doses in the e-diary."	To clarify that participants will record their insulin doses in the e-diary throughout the study
	Visit 3: text added "Participants will continue to record their insulin doses in the e-diary throughout the study."	
	Visit 4: text added "and document the dose administered in the e-diary before leaving the site."	For clarity that participants will record their insulin doses in the e-diary throughout the study
	Visit 5 (Week 2) - Visit 37 (Week 78): Visit 38 was changed to Visit 37	To accurately reflect the visit numbers in the SoA
	Study Period III: Safety Follow-up Period: text added "Non-insulin antihyperglycemic medications will be continued. Investigators will prescribe and document the prescribed insulin dose during the safety follow-up period."	For clarity regarding Visit 801
	Text added "Study participants must measure their FBG levels each day when possible or at a minimum 3 times per week."	For clarity regarding Visit 802
Section 4.2. Scientific Rationale for Study Design	Text edited regarding stable insulin dose Added " and other published algorithms" and the associated references	For clarity
Section 4.3. Justification for Dose	Justification for the LY3209590 single loading dose: text revised to state "Following a once-weekly subcutaneous administration of LY3209590, the time to reach steady-state PK without a loading dose is estimated to be between 8 and 10 weeks based on the long half-life of LY3209590.	To clarify difference in time to steady state with and without a loading dose

Section # and Name	Description of Change	Brief Rationale
	With a loading dose, the estimated time to reach steady state is within 2-3 weeks."	
Section 4.4. End of Study Definition	Text revised	For consistency
Section 5.1. Inclusion Criteria	Inclusion criteria modified to add "insulin regimens (includes biosimilars)"	For clarity
Section 6.1. Study Intervention(s) Administered	Added text "This table lists the interventions used in this clinical study."	For clarity
	In table: edited Use text to indicate "Experimental" and " Active comparator"	
	Packaging and Labeling text moved from Section 6.7 and revised	For consistency
Section 6.1.1. Medical Devices	Medical devices text moved to Section 6.1.1	For consistency with clinical protocol template
Section 6.1.2 LY3209590 and Insulin Degludec Dosing	Added Section titled "LY3209590 and Insulin Degludec Dosing"	For clarity
	Text added to indicate the anatomical locations 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 protocol

Section # and Name	Description of Change	Brief Rationale
Section 6.1.3. General Insulin Dose Considerations for Both Treatment Groups	Deleted last sentence	Duplicate
	Text added regarding hypoglycemia dose reduction criteria	For clarity
Section 6.1.3 General Insulin Dose Insulin Dose Titration and Dose Maintenance	Minor text revisions	For clarity
	Text added "Investigators are expected to follow the dosing algorithms for the protocol; however, modifications of the basal insulin dose may be influenced by other clinical circumstances or safety considerations know to the investigator. If the investigator prescribes a dose other than the algorithm recommended dose, the investigator is responsible for documenting the clinical rationale for the prescribed dose in the Study Works web portal."	For clarity
Section 6.1.4. LY3209590 Dose Initiation and Modification	Text and two tables (Tables 7 and 8) were deleted and a single table was created combining the dose adjustment information	For clarity
Section 6.1.5. Insulin Degludec Dose Initiation and Modification	Hypoglycemia dose reduction criteria for insulin degludec unit dose decrease revised to 2-6 units. Footnote a was also added.	To align with FDA recommendation for insulin degludec dose reduction criteria to match the LY3209590 weekly unit dose reduction more closely
	Units of insulin degludec in the Insulin degludec Dose Adjustment table were revised.	To align with FDA recommendation for cumulative daily insulin units for week used in degludec

Section # and Name	Description of Change	Brief Rationale
		titration algorithm to more closely match the LY3209590 weekly unit titration algorithm
Section 6.1.6. Management of Hypoglycemia	Revised text regarding prescription of glucagon to participants	For clarity
Section 6.2 Preparation, Handling, Storage, and Accountability	Text was updated information from "instructions for use" to "pharmacy manual" Also removed statement around insulated bags	Corrected text
Section 6.7 Treatment of Overdose	Added medical monitor to include "lilly designated"	For clarity

Section # and Name	Description of Change	Brief Rationale
Section 6.8. Concomitant Therapy	Deleted text “In addition, certain permitted medications (for example, treatments for blood pressure or dyslipidemia) may be continued.”	For clarity
	Added text “that may substantially affect glycemic values”	For clarification that participants do not have to consult with the investigator before any new medication is prescribed
	Added the word “non-insulin” to the last sentence	For clarity
	Added “This table” to This table provides a summary of criteria for use of concomitant medications during the study.	Inadvertently deleted
	Criteria for Use of Concomitant Medications table revised: the rescue therapy column not applicable for non-study basal insulins and insulin mixtures	For consistency
Section 6.8.5.1. Treatment after Study Completion	Added text “and continue to monitor their FBG and complete the e-diary.” to the sentence Participants will continue their concomitant non-insulin antihyperglycemic medications at the discretion of the investigator	To add monitoring information
	Study Participants treated with LY3209590: revised text	For clarity
	Study Participants treated with insulin degludec: revised text Deleted: If their pre-study basal insulin was insulin degludec, they can continue with the same dose used of the study. If they transition to another basal insulin (for	

Section # and Name	Description of Change	Brief Rationale
	example, insulin glargine), study participants should inject a daily dose and titrate Added text The investigator will prescribe the non-study insulin and titrate the dose based on their 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.	
Section 6.8.5.2. Emergency Situations and Special Circumstances	Text added “consecutive” was also added in front of “weeks”; “glucose-lowering” was changed to “antihyperglycemic” “After Week 26, dose changes to non-insulin antihyperglycemic medications or temporary treatment with a non-study insulin is allowed but must be documented by the investigator.”	For clarity

Section # and Name	Description of Change	Brief Rationale
Section 7.1. Discontinuation of Study Intervention	Permanent Discontinuation of Study Intervention: edited text—deleted "In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant may receive another glucose-lowering intervention and will continue participation in the study for continued monitoring. Both efficacy (including HbA1c) and safety data will continue to be collected per the SoA." Updated to template text	To align with template required text and for consistency
	Sub-bullet added "if the investigator determines that the participant is persistently noncompliant after the 26-week treatment period"	For clarity
	Bullet deleted: "if a study participant is inadvertently enrolled and it is determined that continued treatment with IP would not be medically appropriate"	For consistency
	Sub-bullets deleted • Discontinuation due to a hepatic event or liver test abnormality • Participants who are discontinued from IP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.	Information is duplicate of Section 7.1.1
	Added Hypersensitivity reactions standardized text	To align with protocol template

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1 Liver Chemistry Stopping Criteria	Section title was added along with the following text “The study drug should be interrupted or discontinued if one or more of these conditions occur:” “Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified.”	To align with protocol template
Section 7.1.2. QTc Stopping Criteria	Deleted the section	There is no specific QTc stopping criteria due to no known or suspected safety-related risk with insulins or LY3209590
Section 7.2. Participant Discontinuation/Withdrawal from the Study	Edited discontinuation and withdrawal text	To align with template required text
Section 7.3. Lost to Follow-Up	Deleted text regarding collection of vital status information	To align with template required text
Section 8.2.3. Electrocardiograms	Text added “If there is a clinically significant finding identified by the investigator, the investigator or qualified designee will determine if the participant should remain in study and if any changes should be made to participant care. The review of the electrocardiogram (ECG) printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.”	Responsibility of investigator to determine participation in study if clinically significant findings on ECG
Section 8.3.1 Timing and Mechanism for Colleting Events	Throughout the table added the word “last” to safety follow-up visit	For clarity
Section 8.3.2 Pregnancy	Text added “This applies only to male participants who receive study intervention.”	To align with protocol template required text

Section # and Name	Description of Change	Brief Rationale
Section 8.3.3. Adverse Events of Special Interest	Deleted the section	Section is not applicable
Section 8.3.4 Systemic Hypersensitivity Reactions	Updated first paragraph language to standardized template text	For consistency
Section 8.3.5 Injection Site Reactions	Added Section header	For consistency and clarity
Section 8.4. Pharmacokinetics	Text revised regarding sample collection	For consistency
Section 8.8. Immunogenicity Assessments	Section edited to describe instructions for handling blood samples	For clarity and consistency
Section 9.1. Statistical Hypotheses	Section edited	For clarity and consistency
Section 9.3.2. Primary Endpoint/Estimand Analysis	Deleted the text for superiority of HbA1c	The superiority of HbA1c belongs to key secondary objectives and similar text is in Section 9.3.3 Secondary Endpoints Analysis
Section 9.3.3. Secondary Endpoints Analysis	Section edited	To clarify the treatment regimen estimand on the time in glucose range measured by CGM to address FDA feedback
Section 9.3.3.1 Multiplicity Adjustment Endpoints	Updated text deleting Visit 1[Week 3] and adding “randomization”	Correction
Section 9.3.6.1. Pharmacokinetic and pharmacodynamic analyses	Section added	To characterize the PK/PD analyses
Section 10.1.5. Committees Structure	Section added	Section was inadvertently

Section # and Name	Description of Change	Brief Rationale
		deleted in previous version
Section 10.1.7 Data Quality Assurance	Deleted text "that is laboratory tests' Under Data Capture System added "or web portal;"	For clarity
Section 10.1.12 Sample Retention	The following note was deleted "**Note:** The sponsor has a right to retain a portion of submitted biopsy tissue. Archival blocks will be returned to the study site. Slides and tissue samples collected on study will not be returned."	The note was not applicable since biopsy tissues are not collected in this study.
Section 10.2 Clinical Laboratory tests	Added comment to glucose under the Urinalysis section "Fasting or random (Refer to SoA)	For clarity
	Added comment to Additional Testing "Fasting per SoA"	For clarity
Section 10.2.1. Laboratory Samples to be Obtained at the Time of A Systemic Hypersensitivity Event	Updated section heading, text, and table	To align with updated standardized protocol text
Section 10.3.1. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting	Events Meeting the AE Definition: edited text regarding medication error Footnotes were updated to refer to the correct ones in the table	To align with template required text
Section 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	Added Section and Section numbers were updated	Section was inadvertently deleted in previous protocol version
Section 10.7 Provisions for Changes in Study Conduct During Exceptional Circumstances	Screening period guidance updated to 24 days instead of 14 days	For consistency

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized

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