Protocol I8H-MC-BDCP(d)

A Phase 2, Randomized, Parallel, Open-Label Comparator-Controlled Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants with Type 1 Diabetes Mellitus Previously Treated with Multiple Daily Injection Therapy.

NCT04450407

Approval Date: 28-Oct-2020

Title Page

Confidential Information

Protocol Title: A Phase 2, Randomized, Parallel, Open-Label Comparator-Controlled Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants with Type 1 Diabetes Mellitus Previously Treated with Multiple Daily Injection Therapy

Protocol Number: I8H-MC-BDCP

Amendment Number: d

Compound: LY3209590

Study Phase: Phase 2

Short Title: A Study of LY3209590 in Participants with Type 1 Diabetes Mellitus

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 129390

EudraCT: 2019-003589-41

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

Lilly Medical Name and Contact Information will be provided separately.

Approval Date: 28-Oct-2020 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	11-Dec-2019
Amendment (a)	08-Apr-2020
Amendment (b)	12-Jun-2020
Amendment (c)	14-Aug-2020

Amendment [d]

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The amendment provides information to reflect termination of the investigational medical device study arm evaluating the individualized accruing data algorithm (Algorithm 2) investigational device in the Phase 2 Study 18H-MC-BDCP (BDCP). Study BDCP will continue to evaluate dosing regimens of investigational medicinal product LY3209590, a long-acting insulin receptor agonist that is being developed as a basal insulin administered once-weekly for treatment of type 1 diabetes mellitus (T1DM). Study BDCP is evaluating T1DM participants previously treated with multiple daily injections (MDI) therapy in paper algorithm (Algorithm 1). Insulin degludec is an unblinded active comparator in this study.

Lilly is terminating the Algorithm 2 study arm due to the extent of data entry errors generated by patients and the impact these errors have on dosing recommendations from the investigational device Algorithm 2. These errors (missing, unchecked, or uncorrected by site verification) provide less than complete data set inputs that are submitted by the investigator into the Algorithm 2 dosing calculation. The limited data set inputs have revealed shortcomings in the dosing calculation confounding factors for the limited number of Algorithm 2 dosing recommendations observed from a limited number of sites and participants during the early enrollment phase. In some cases, had the investigator not applied clinical judgement to override the recommended dose, a serious adverse consequence on patient health and/or safety associated with the device may have resulted.

The extent of the investigator Algorithm 2 recommended dose overrides experienced to date have confounded evaluation of Algorithm 2's effectiveness. Lilly recognized that the planned expansion to include all sites participating in the United States would increase both the number of participants exposed to the investigational device Algorithm 2 and the number of investigators providing oversite of the Algorithm 2 dosing recommendations. This amendment reflects the preventive action to terminate the Algorithm 2 investigational device trial arm of Study BDCP due to challenges associated with the ability to evaluate the effectiveness of Algorithm 2, to prevent potential patient safety issues and avoid a delay in the study.

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Removal of language related to Algorithm 2	Alignment of protocol for removal of Algorithm 2
Section 1.1. Synopsis Section 6.1. Study Intervention(s) Administered Section 9.2. Sample Size Determination Section 10.10. Appendix 10: Changes to Study Procedures due to the COVID-19 Pandemic or Natural Disasters	Change in number of participants, randomization ratio, and distribution by country	Based on the removal of Algorithm 2, the participant number was updated and randomization variation by country is no longer applicable.
Section 1.3. Schedule of Activities	Addition of language for footnote d	Clarification that a triplicate ECG for insulin degludec is only required one time.
	Addition of language for footnote e	Clarification of the collection of 2 PK samples is for LY3209590.
	Removal of CGM data download at Visit 16	Removed CGM data download at Study Visit 16 as this is a phone visit and download is not possible.
Section 6.1. Study Interventions(s) Administered	Addition of language for participants transitioning from Algorithm 2	Clarification for participants in Algorithm 2 to proceed with study procedures for those treated with LY3209590.
Section 8.4. Treatment of Overdose	Addition of procedural language	Clarification added to contact the sponsor in case of an accidental overdose.
Section 9.3. Populations for Analysis Section 9.4.1. General Considerations Section 9.4.2.2. Patient Characteristics Section 9.4.6.3. Hypoglycemia Episodes	Change in language related removal of Algorithm 2	Update of statistical analysis after removal of Algorithm 2
Section 10.3.3. Definition of an Unanticipated Adverse Device Effect (UADE)	Removal of section related to Algorithm 2	Clarification that UADE will not be applicable after removal of Algorithm 2
Section 10.8. Appendix 8: Dosing Guidance for LY3209590 and Insulin Degludec	Updated title of appendix	Clarification that dosing guidance is available for LY3209590 and Insulin Degludec
Section 10.10. Appendix 10: Change to Study Procedures due to the COVID-19 Pandemic or Natural Disasters	Addition of language for Remote Visits	Clarification that sites must receive sponsor approval prior to implementing site mobile visits and visits by a sponsor organized home nursing service provider to replace on-site visits.
Throughout the document	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2, Randomized, Parallel, Open-Label Comparator-Controlled Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants with Type 1 Diabetes Mellitus Previously Treated with Multiple Daily Injection Therapy

Short Title: A Study of LY3209590 in Participants with Type 1 Diabetes Mellitus

Rationale:

LY3209590 is a long-acting insulin receptor agonist being developed for the treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). This Phase 2 study of LY3209590 will evaluate the effects of LY3209590 on glycemic control compared with insulin degludec in T1DM participants previously treated with multiple daily injections (MDI) therapy.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the efficacy of LY3209590 compared with insulin degludec in study participants with T1DM	• HbA1c change from baseline to Week 26
Secondary	
Efficacy • To investigate the efficacy of LY3209590 compared with insulin degludec in study participants with T1DM	• HbA1c change from baseline to Week 12 • Fasting glucose change from baseline to Weeks 12 and 26 • Insulin dose change for bolus insulin from baseline to Weeks 12 and 26
Safety • To investigate the safety of LY3209590 compared with insulin degludec in study participants with T1DM	• Incidence and rate of hypoglycemia events during the treatment period • Incidence of treatment-emergent serious AEs
Pharmacokinetics • To characterize the PK of LY3209590 in study participants with T1DM	• LY3209590 population-based parameters, such as AUC within dosing interval at Weeks 12 and 26

Abbreviations: AE = adverse event; AUC = area under the curve; HbA1c = hemoglobin A1c; PK = pharmacokinetics; T1DM = type 1 diabetes mellitus.

Overall Design

Study I8H-MC-BDCP is a multicenter, randomized, open-label, parallel, comparator-controlled Phase 2 study with 3 study periods. The study is designed to evaluate the efficacy and safety of LY3209590 compared with insulin degludec in patients with T1DM treated with MDI without interruption for at least 3 months.

Disclosure Statement: This is a parallel, unblinded, treatment study with 2 arms.

Number of Participants:

Approximately 238 participants will be randomly assigned to study intervention such that approximately 190 evaluable participants complete the study.

Intervention Groups and Duration:

Participants will be randomized in a 1:1 ratio to receive the interventions listed below:

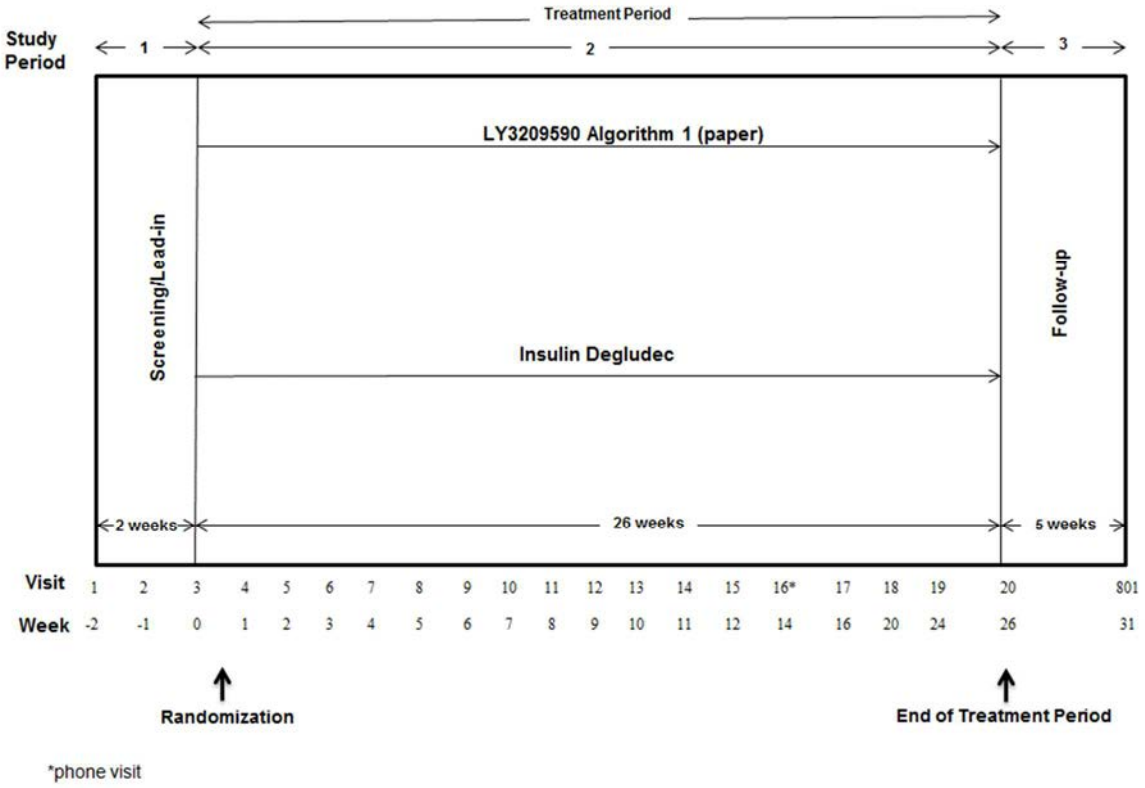
- LY3209590 subcutaneously weekly, dosed per Algorithm 1
- Insulin degludec subcutaneously daily, dosed per a modified Riddle algorithm

The maximum total duration of study participation for each participant is up to 33 weeks, across the following study periods:

- Study Period 1: screening and lead-in period, approximately 2 weeks
- Study Period 2: treatment period, 26 weeks
- Study Period 3: safety follow-up period, 5 weeks

Data Monitoring Committee: No

1.2. Schema



*phone visit

1.3. Schedule of Activities (SoA)

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
Weeks	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	20	24	26		ED1 +5	31		
Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Informed consent	X																								
Inclusion and exclusion criteria	X																								
Randomization			X																						

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
Weeks	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	20	24	26		ED1 +5	31		
Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Clinical Assessments																									
Height	X																								
Body weight	X	X	X			X			X						X		X			X	X	X	X	X	See Section 8.2.7.
Blood pressure and pulse rate	X	X	X			X			X						X		X			X	X	X	X	X	See Section 8.2.2.
Demo-graphy	X																								
Medical history (includes substance usage and family history of premature CV disease)	X																								Substances: drugs, alcohol, tobacco, and caffeine
Pre-existing conditions	X	X	X																						

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
Weeks	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	20	24	26		ED1 +5	31		
Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Concomitant medication review	X	X	X			X			X						X		X			X	X	X	X	X	X	
Full physical examination	X																			X	X	X	X	X	X	
12-lead ECG	X		X[d]			X[d]			X[d]						X[d]		X[d]			X	X	X	X	X	X	
AE/SAE/ PC review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
Weeks	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	20	24	26		ED1 +5	31		
Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Laboratory Assessments																									
Pharmaco-kinetic samples (LY3209590)			X[e]	X	X	X			X						X		X		X	X	X	X	X	X	Collected for participants randomized to LY3209590. See Section 8.5.
Serum pregnancy test (WCBP only)	X																								See Section 5.1.
Urine pregnancy test (WCBP only)			X																			X	X	X	Additional pregnancy testing may be performed if required by local regulations.

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
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Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
FSH	X																								Collect for women whose menopausal status needs to be determined. If menopausal status is known, this test does not need to be collected.
Urinalysis	X																			X	X	X	X	X	
eGFR	X																			X	X			X	
Chemistry panel	X	X	X						X						X		X		X	X	X	X	X	X	
Hepatitis B	X																								
HbA1c	X		X						X						X		X			X	X			X	
Hematology	X		X						X						X		X			X	X	X	X	X	
HDL, LDL		X	X												X					X	X	X	X	X	

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
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Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Free fatty acid		X	X			X			X						X		X		X	X	X	X	X	X	
Immuno genicity			X			X			X						X					X	X	X	X	X	See Section 8.9.
C-peptide	X																								If the C-peptide was assessed in a non-fasting state at V1 and was >0.30 nmol/L, the evaluation can be repeated at V2 in a fasting state
Pharmaco-genetic sample			X																						
Nonpharma cogenetic Stored Samples (plasma/ serum)		X	X						X						X		X			X	X	X	X	X	

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
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Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Ancillary Supplies/ Diaries/ Investigational Product																									
Study participant training/ education		X																							Includes diabetes counseling, hypoglycemia Section 8.3.7.1), diary completion, and CGM sensor replacement
Dispense supplies		X	X			X			X						X		X			X	X				Participant diaries will be visit specific. All of the diaries will be electronic.
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
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Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Remind participants to document 6-point glucose profiles in the week prior to next indicated visit		X						X						X					X	X	X				See next line for indicated visits. See Section 4.1.1 for additional details.
Review 6-point SMBG profiles			X						X						X					X	X	X	X			
Review diary data and make dose individualiz-ation assessment			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X							Assessment performed per participant assigned group (Algorithm 1 or insulin degludec)
Dispense IP			X	X	X	X	X	X	X	X	X	X	X	X	X			X								

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
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Visit window, days	±7	±3		±2	±2	±3	±2	±2	±3	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
Study personnel administer IP at site			X	X	X	X	X	X	X	X	X														
Train participants in IP administra-tion												X	X	X	X		X								IP can be self-administered by study participants Weeks 13-25. Information on self-injection can be reviewed as necessary throughout the study.
Study participant CGM[f] training		X																							

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
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Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
CGM sensor insertion at site		X																							
Distribute CGM sensor if necessary		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X				Patients will replace CGM sensor every 10 days at home and will be trained for this procedure at Visit 2. At each visit patient will be supplied with the necessary sensors for the respective interval
CGM data download			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		

Procedure	Study Period 1 Screening and Lead-in		Study Period 2 Treatment Period																		Early Discontinuation		Study Period 3 Follow-up	ET	Notes
eCRF Visit Number	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16[b]	17	18	19	20[c]	ED1	ED2[c]	801[c]		
Weeks	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	16	20	24	26		ED1 +5	31		
Visit window, days	± 7	± 3		± 2	± 2	± 3	± 2	± 2	± 3	± 2	± 2	± 2	± 2	± 2	±3	±3	±3	± 3	±3	±3	±3	±3	±3		
Fasting		X	X			X			X						X		X		X	X	X	X	X	X	Minimum 8 hours
LY3209590 and insulin degludec accounta-bility (collect used and unused IP)																		X		X	X			X	

Abbreviations: AE = adverse event; BG = blood glucose; CGM = Continuous Glucose Monitoring; CV = cardiovascular; ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; ET = early termination; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; HIV = human immunodeficiency virus; IP = investigational product; IWRS = interactive web response system; LDL = low density lipoprotein; LY = LY3209590; PC = product complaint; PK = pharmacokinetics; SAE = serious adverse event; SMBG = self-monitoring blood glucose; WCBP = women of childbearing potential.

[a] All measures to be performed at Visit 3 should be done prior to injection of the participant's assigned investigational product (IP) to ensure that appropriate baseline measurements are obtained.

[b] Visit 16 is a Phone visit.

[c] Visits 20 and ED1 are performed approximately 1 week after the last dose of LY and 1 day after the last dose of degludec. Visit 801 is performed for participants who complete Visit 20. ED1 and ED2 are performed for participants who discontinue study drug but remain in the study.

[d] A triplicate, central ECG will be performed in a fasting state at Visits 3, 6, 9, 15, and 17, prior to each PK sample. Patients randomized to insulin degludec treatment will undergo ECG in a fasting state without PK sampling. Only one triplicate ECG is needed for insulin degludec treated patients.

[e] Collect 2 PK samples of LY3209590: 1 predose and one approximately 2 hours postdose or as late as possible just prior to departure from the site. ECG will be performed in triplicate prior to the time of each PK sampling at this visit. Note: PK samples are not intended to be collected for participants in the insulin degludec treatment group.

[f] Patients will be fitted with Dexcom G6® for CGM monitoring.

Note: Additional visits to ensure correct dosing, titration, and study drug administration can occur anytime during the study if deemed necessary by the investigator and are explicitly allowed and part of the protocol.

2. Introduction

2.1. Study Rationale

LY3209590 is a long-acting insulin receptor agonist being developed for the treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). This Phase 2 study of LY3209590 will evaluate the effects of LY3209590 on glycemic control compared with insulin degludec in T1DM patients previously treated with multiple daily injection (MDI) therapy.

2.2. Background

LY3209590 was designed as a novel, once-weekly, long-acting insulin receptor agonist that is intended for the treatment of hyperglycemia in study participants with T1DM and T2DM. In real life, only about 30% of patients with T1DM in the United Kingdom (UK) reach the target HbA1c of <7.5% (58 mmol/mol) (NDA 2017), and a once-weekly insulin receptor agonist could help to increase this number. The potential downside of such a long-acting insulin receptor agonist could theoretically be a higher risk for hypoglycemic events or a longer duration of such events. In contrast to this theoretical risk the long-acting insulin degludec has shown a reduced potential to induce hypoglycemia as compared to insulin glargine while its half-life is twice as long as that of insulin glargine (Heise et al. 2012). The current Phase 2 study will therefore evaluate the safety and efficacy of LY3209590 compared to insulin degludec while very closely monitoring glycemic profiles.

Phase 1 studies evaluating the pharmacokinetics (PK) and pharmacodynamics (PD) effect of LY3209590 in healthy volunteers and patients with T2DM have been completed. Data from CCI , which was the single-ascending dose (SAD) study, demonstrated clear evidence of glucose lowering in study participants with T2DM following single doses of LY3209590 ranging from CCI mg. The PK of LY3209590 following single doses demonstrated prolonged time-action profile to support once-weekly administration. LY3209590 reached maximum concentration approximately 4 days after dosing, followed by a mean elimination CCI in study participants with T2DM. With a long elimination half-life, following a weekly fixed-dose regimen, PK steady-state was predicted to be reached in CCI with approximately CCI higher concentration due to accumulation than after single dose. Therefore, based on PK modeling a loading dose strategy CCI times the weekly dose would achieve steady-state exposure after 1 dose. Based on data in study BDCB, the multiple-ascending dose (MAD) study, PK following a single loading dose (CCI the initial weekly dose) during the first week was demonstrated to be comparable to concentration profile at Week 6 (at CCI dose delivered once weekly), supporting the loading dose strategy. No clinically significant persistence in hypoglycemia was observed in the study. Besides the known risk of hypoglycemia, no relevant safety signals have been observed in the Phase 1 studies.

The toxicity profile of LY3209590 has been characterized in 6-week and 6-month repeat-dose toxicology studies in rats and dogs, and reproductive toxicology studies in rats and rabbits. These studies demonstrated a familiar spectrum of effects typically associated with changes secondary to hypoglycemia and/or hyperinsulinemia resulting from repeat dosing of exogenous

insulin in normoglycemic test systems. All findings were considered to be target-related with no evidence of off-target effects in any of the parameters assessed.

Additional information about LY3209590 can be found in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

The data from the SAD study and the MAD study (studies BDCA and BDCB, respectively), as well as the ongoing Phase 2 BDCM study have shown that LY3209590 was well tolerated and the adverse drug reactions are in line with those reported for long-acting insulins.

Potential risks associated with LY3209590, derived from the known risks of long-acting insulins are hypoglycemia, hypersensitivity reactions (localized allergy and/or systemic allergy), undesirable effects at the injection site (injection-site reactions and lipodystrophy), and peripheral edema. Besides the expected risk of hypoglycemia, serious presentations of the listed side effects have not been observed in study participants or healthy volunteers exposed to LY3209590 for up to 12 weeks.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with LY3209590 are justified by the anticipated benefits that may be offered to participants with T1DM.

More information about the known and expected benefits, risks, Serious Adverse Events (SAEs), and reasonably anticipated adverse events (AEs) of LY3209590 may be found in the IB.

The Algorithm 1 (paper) was developed to initiate and guide LY3209590 dose adjustment for this study to safely and efficiently achieve glycemic goals.

2.3.1. Protocol Risk Mitigation Features

Methods to minimize potential risks are relevant for participants assigned to LY3209590 Algorithm 1 and insulin degludec treatment groups. These include:

- Thorough training on the protocol design elements and inclusion/exclusion criteria; use of an electronic diary (eDiary), a web-interface, and reporting system along with availability of associated instruction manuals and reference documents.
- Careful data validation: After patient-reported data has been entered and synced remotely to the central web server, the investigator is able to view the data through the web portal and generate summary reports. An important feature of the study requires careful review of the reported information with the patient and verification of its accuracy at each study visit.
- Email notification to investigator any time the patient reports a potential severe episode of hypoglycemia (requiring assistance due to neurological impairment) in the eDiary.
- Specific criteria for fasting or persistent hyperglycemia are described protocol Section 6.1.2.3.
- Use of CGM with appropriate low/high glucose alarms throughout the study.

Importantly, in both treatment groups, the final dosing decisions remain subject to clinical judgement of the investigator. Decisions to override an algorithm recommended dose are documented in the electronic case report form (eCRF) for Algorithm 1 and insulin degludec.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the efficacy of LY3209590 compared with insulin degludec in study participants with T1DM	• HbA1c change from baseline to Week 26
Secondary	
Efficacy • To investigate the efficacy of LY3209590 compared with insulin degludec in study participants with T1DM	• HbA1c change from baseline to Week 12 • Fasting glucose change from baseline to Weeks 12 and 26 • Insulin dose change for bolus insulin from baseline to Weeks 12 and 26
Safety • To investigate the safety of LY3209590 compared with insulin degludec in study participants with T1DM	• Incidence and rate of hypoglycemia events during the treatment period • Incidence of treatment-emergent serious AEs
Pharmacokinetics • To characterize the PK of LY3209590 in study participants with T1DM	• LY3209590 population-based parameters, such as AUC within dosing interval at Weeks 12 and 26
Tertiary/Exploratory	
• To establish the equivalent dose of LY3209590 relative to insulin degludec	• Insulin dose at baseline and Week 26
• To investigate the safety and tolerability of LY3209590 compared with insulin degludec in study participants with T1DM	• Treatment-emergent AEs • Incidence and rate of hypoglycemia events during the post-treatment follow-up period • Discontinuation of IP due to AEs • Clinical laboratory results • Systematic assessment of injection site reactions • Insulin dose for prandial as well as basal insulin during treatment period and follow-up period • Incidence and rate of hypoglycemia during treatment and follow-up period

Objectives	Endpoints
	• Incidence and rate of daytime hypoglycemia • Liver aminotransferase change from baseline to Weeks 12 and 26 • Triglyceride and FFA change from baseline to Weeks 12 and 26 • Body weight change from baseline to Weeks 12 and 26
• To explore quality of glycemic control compared with insulin degludec using CGM	• Glucose time in target range, time in hyperglycemia, time in hypoglycemia • Duration of hypoglycemic events
• To establish the relationships between dose/exposure and key safety and efficacy measures for LY3209590	• LY3209590 exposure-response relationships for key efficacy and safety measures (e.g., glycemic control, hypoglycemia and safety labs).
• To characterize the effects of LY3209590 on exploratory PD biomarkers • To explore the development of LY3209590 ADAs • To explore the compliance with the dosing regimen	• Lipids (cholesterol, LDL, HDL, triglycerides) • 6-point SMBG glucose profiles • Biomarkers of lipolysis (FFA) • The frequency of antibody formation to LY3209590 and relationship to safety and efficacy markers will be determined • Incidence and percentage of missed doses of LY3209590 and insulin degludec.

Abbreviations: ADA = antidrug antibodies; AE = adverse events; AUC = area under the curve; CGM = continued glucose monitoring; FFA = free fatty acids; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; IP = investigational product; LDL = low density lipoprotein; PD = pharmacodynamics; SMBG = self-monitoring blood glucose; T1DM = type 1 diabetes mellitus.

4. Study Design

4.1. Overall Design

Study I8H-MC-BDCP (BDCP) is a multicenter, randomized, open-label, parallel, comparator-controlled Phase 2 study with 3 study periods. The study is designed to evaluate the efficacy and safety of LY3209590 compared with insulin degludec in patients with T1DM treated with MDI for at least 3 months prior to screening.

The study will consist of 3 periods:

- Study Period 1: screening and lead-in period, approximately 2 weeks
- Study Period 2: treatment period, 26 weeks
- Study Period 3: safety follow-up period, 5 weeks

The study schema is presented in Section 1.2.

Study governance considerations are described in detail in Section 10.1.

4.1.1. Study Visits

Study Period 1: Screening and Lead-in

The purpose of procedures at screening is to establish eligibility for inclusion in the study (see Sections 5.1 and 5.2. During this period (upon signing the informed consent form [ICF]), study participants will be trained on disease monitoring and disease management procedures, study diaries, and study procedures.

Electronic participant diaries and participant paper note sheets will be dispensed at Visit 2 and as specified in the Schedule of Activities (Section 1.3) for future visits. Collection of baseline self-monitoring blood glucose (SMBG) profiles via continuous glucose monitoring (CGM) will start at Visit 2. Participants will continue on their same regimen of basal and short acting insulin during the lead-in period up to randomization.

A participant will be considered ineligible and will be discontinued from a trial before randomization if they:

- initiate agents that are prohibited (Section 6.5), or
- initiate insulin pump treatment (Section 5.2)

For all study participants meeting study entry criteria, the Dexcom G6® CGM device will be inserted and activated at (Visit 2). The CGM sensor, transmitter and receiver will be distributed to the participant as needed per the Schedule of Activities (Section 1.3).

SMBG:

Participants will record two 6-point glucose profiles (using the CGM device) at non-consecutive days between Visit 2 and Visit 3. The profile should include readings before and 2 hours after each major meal of the day (breakfast, lunch, and dinner).

Continuous Glucose Monitoring (CGM)

A standard system, Dexcom G6, will be used according to manufacturer's directions for CGM in an unblinded mode. The study participants will wear this device beginning at Visit 2, as shown

in the Schedule of Activities (Section 1.3). In addition, all study participants will be allowed to use their personal blood glucose (BG) meters for additional BG testing, or for taking SMBG measurements during the outpatient period. Therapeutic decisions will be based on the CGM readings. Blood glucose meters must not be used to calibrate the CGM device. CGM calibration must be done using the code provided with each sensor. Participants must use the study-specific CGM receiver and are not allowed to connect the transmitter of the CGM system to a personal smartphone to ensure data availability for download from the receiver at the respective visits as described in the Schedule of Activities (Section 1.3).

At Visit 2, study participants who fulfill eligibility criteria will be trained on the use of the CGM device, CGM sensor replacement, interpretation of CGM-based BG values and alarms, and the requirements for CGM. For the first CGM session, study participants meeting all study-entry criteria will have the CGM sensor inserted as part of the Visit 2 activities.

Study Period 2: Treatment Period

Randomization

Participants who continue to be eligible for the study will be randomized to 1 of the 2 treatment groups. All measures, including a urine pregnancy test, to be performed at Visit 3 (see Schedule of Activities, Section 1.3) should be done prior to injection of the participant's assigned investigational product (IP) to ensure that appropriate baseline measurements are obtained. The participant will begin IP if the urine pregnancy test is negative. If the result of the serum pregnancy test is positive, the participant will be discontinued from the study (see Section 7.2)

Study personnel will inject the first dose of IP at the study site. The PK sample and electrocardiograms (ECGs) at randomization must be collected as described in the Schedule of Activities (Section 1.3).

Treatment

Following randomization at Visit 3, participants will participate in a 26-week treatment period.

For patients randomized to the LY3209590 arm the following guidance for IP administration is applicable:

- During Weeks 0 to 8, site personnel will administer IP at the site. Participants will receive education and training on how to self-administer IP (for details, see the Schedule of Activities). The training should include information on reconstitution of IP, appropriate injection site locations, injection technique, and the signs and symptoms of local adverse reactions, should those occur.
- During Weeks 9 to 12, IP will be reconstituted and administered at the site by the participant, under supervision of trained site personnel to assure that the participant is capable of self-administration.
- During Weeks 13 to 25, outside of titration visits IP can be self-administered by the participant at home unless local regulations require administration at the site, or optionally can be administered once weekly by site personnel.
- Information on self-injection can be reviewed as necessary throughout the study. Additional visits to ensure correct dosing, titration, and study drug administration can occur anytime during the study if deemed necessary by the investigator.

LY3209590 will be administered as follows:

- Algorithm 1 (paper algorithm): dose adjustment guidance provided; study participant will receive an individualized LY3209590 loading dose on Day 1 with weekly adjustments based on fasting glucose (FG) and hypoglycemia data for the first 12 weeks, then every 4 weeks.

For patients randomized to LY3209590 Algorithm 1, documented guidance for dose adjustment is provided (Section 10.8).

For patients randomized to the insulin degludec arm the following guidance for administration is applicable.

Insulin degludec will be self-administered daily by participants after a training and first administration under site personnel supervision on Day 1 according to a modified Riddle algorithm (Section 10.8).

General considerations

Study procedures will be performed as listed in the Schedule of Activities (Section 1.3).

To allow timely sampling for PK assessments, visits for collection of the samples will be scheduled within the required time windows provided in the Schedule of Activities (Section 1.3).

Participants will continue to use concomitant short-acting insulin throughout the treatment period. Discontinuation or changes to regimen are not permitted, except in situations where dose adjustment is required for medical reasons or when allowed per study protocol (see Section 6.5).

Study participants will be instructed to document fasting glucose (FG) each day in their electronic diary (eDiary) by using the values displayed on their CGM device after wakening. In addition, two 6-point SMBG profiles (prior to and 2 hours after the morning, midday, and evening meals) should be done on nonconsecutive days in the week prior to the required visits noted in the Schedule of Activities (Section 1.3).

Participants who develop severe, persistent hyperglycemia based on prespecified thresholds (see Section 6.1.2.3) will receive an unscheduled intensification of their insulin treatment based on clinical judgment of the investigator with a parallel information of Lilly Medical by email. Participants who need unscheduled intensification of their insulin treatment will continue on IP in the trial until they complete all study visits.

Study Period 3: End-of-Treatment and Safety Follow-up, Visits 20, 801, Early Discontinuation 1 and 2 (ED1 and ED2)

All randomized participants should have a comprehensive efficacy and safety evaluation approximately 1 week after the last dose of LY3209590 and 1 day after the last dose of insulin degludec, and a safety follow-up visit approximately 6 weeks after the last dose of LY3209590 and 5 weeks after the last dose of insulin degludec. During the safety follow-up study period, participants will continue CGM and will be switched back to their previously used basal insulin therapy if appropriate (see Section 6.7.1). Participants will also be required to return any remaining used or unused IP at Visit 20 and the eDiary at Visit 801 to the investigative site.

Participants who *complete the treatment period* will have a comprehensive End-of-Treatment efficacy and safety assessment (Week 26; Visit 20) approximately 1 week after the last dose of

LY3209590 and 1 day after last dose of insulin degludec and a safety follow-up assessment (Visit 801) approximately 6 weeks after the last dose of LY3209590 and 5 weeks after the last dose of insulin degludec.

Participants who *discontinue IP prior to completion* of the treatment period for any reason should follow the visit schedule off study drug and also have a comprehensive End-of-Treatment efficacy and safety assessment (ED 1) approximately 1 week after the last dose of LY3209590 and 1 day after the last dose of insulin degludec or as soon as reasonably possible thereafter, and should have a safety follow-up assessment (ED 2) approximately 6 weeks after the last dose of LY3209590 and 5 weeks after the last dose of insulin degludec. Study activities at Visits ED 1 and ED 2 are identical to Week 26 (Visit 20) and Visit 801, respectively. This close follow-up is necessary since LY3209590 has a CCI and the switch to an alternative, commercially available insulin must be closely monitored to prevent hypoglycemia due to an accumulation of insulin action.

Participants who discontinue IP prior to the completion of the treatment period will be encouraged to remain in the study and to complete any scheduled study procedures that occur until Visit 20. Participants remaining in the study will receive an appropriate glucose-lowering regimen.

Participants who *discontinue IP for any reason and are unwilling to return for a safety follow-up* visit, will be asked to perform an early termination (ET) visit as their final study visit. At this visit, participants will perform procedures listed in the Schedule of Activities (Section 1.3).

4.2. Scientific Rationale for Study Design

This study will evaluate LY3209590 in patients with T1DM, compared with an active control.

The study will last 26 weeks to have an adequate duration of exposure necessary to assess efficacy and safety of LY3209590.

Insulin degludec is an unblinded active comparator in this study and will be used to compare the effects of LY3209590 on glycemic control, hypoglycemia, and weight gain with a daily basal insulin.

4.3. Justification for Dose

CCI a single loading dose, followed by weekly dose adjustments is recommended for LY3209590 dosing regimen. The loading dose is determined based on the patient's previously used basal insulin dose, baseline fasting glucose, and available LY3209590 data to inform the CCI loading dose strategy. Dose adjustments are based on prior fasting glucose and hypoglycemia events. Alterations to the doses recommended by these dose adjustment algorithms are also under discretion of the investigator and will take hypoglycemia and other study participant safety concerns into account. In case of a deviation from the algorithm-recommended dose, a medical rationale for this deviation must be documented by the principal investigator.

The starting dose for insulin degludec is the same dose as the basal insulin that the study participant used prior to entering the study. The study participant will start a titration phase based on FG and the presence of hypoglycemia or other safety concerns. Dose adjustments will be performed according to a modified Riddle algorithm, which is widely used in clinical trials and clinical practice (Section 10.8).

As it may be desirable to achieve therapeutic goal of LY3209590 in less than 12 weeks with low risk of hyperglycemia, an initiation dose strategy may be appropriate where the first dose sufficient to achieve an efficacious exposure is given initially, followed by individually optimized weekly dose adjustments to achieve target response. Table for Algorithm 1 shows the loading doses, as well as those to be used when adjusting the dose during the dose-individualization visits. See Section 10.8 for description of the dose adjustment algorithms.

Guidance is provided for dosing suggestions for investigators based on FG and hypoglycemia of the study participant (Section 10.8).

Safety of study participants will be closely monitored during the early stages of dose titration to determine whether adjustments to the conversion and dose adjustment algorithm is needed. As additional data emerges, guidance from the sponsor on these dosing algorithms may be modified (Section 10.8).

4.4. End of Study Definition

End of the trial is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 1.3) for the last patient.

5. Study Population

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

5.1. Inclusion Criteria

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

Type of Study Participant and Disease Characteristics

[1] Have a diagnosis of T1DM for at least 1 year. A diagnosis of T1DM is based on medical history with a fasting C-peptide ≤0.30 nmol/L at screening or before randomization.

[2] Have been using MDIs without interruption for at least 3 months prior to screening.

Study Participant Characteristics

[3a] No male contraception required except in compliance with specific local government study requirements.

[3b] Female participants:

1) Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
2) Otherwise, women of child-bearing potential participating must agree to use 1 highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception for the entirety of the study.
    a) Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

b) Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) will be used. The participant may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

3) Women not of childbearing potential may participate and include those who are:
   a) infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
   b) post-menopausal – defined as either
      i) A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone (FSH) >40 mIU/mL; or
      ii) A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
      iii) A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[4] Are at least 18 years of age, at the time of signing the informed consent.

[5] Have HbA1c values of 5.6% to 9.5% inclusive, as determined by the central laboratory at screening.

[6] Have been treated with a stable regimen of once- or twice-daily insulin glargine (U-100 or U-300), insulin detemir, or insulin degludec (U-100 or U-200) for 3 months prior to screening.

[7] Are currently treated with the same SC rapid-acting analog insulin (insulin lispro U-100 or U-200, insulin aspart, FiAsp, or insulin glulisine) in MDI for at least the last 30 days prior to screening.

[8] Have a body mass index (BMI) $\leq$35 kg/m^2, with no significant weight gain or loss in the past 3 months ($\geq$5%).

[9] In the investigator's opinion, are well-motivated, capable, and willing to:

- learn how to self-inject treatment;
- maintain study diaries, as required for this protocol;

- wear study-provided CGM (Dexcom G6) during the complete study duration without interruption and use this device for therapeutic decision-making;
- must have a normal wake/sleep pattern such that midnight to 0600 hours will reliably reflect a usual sleeping period.

[10] In the investigator's opinion, are proficient in:

- counting carbohydrates
- adjusting meal- and correction boluses based on glucose readings with a stable insulin/carbohydrate ratio as well as correction factors
- adjusting insulin and dietary therapy during special situations (e.g., exercise, stress, intermittent diseases)

[11] Are willing and able to follow the visit schedule during the complete duration of the trial.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

[13] Have had more than 1 emergency room visit or hospitalization due to poor glucose control (hyperglycemia or diabetic ketoacidosis [DKA]) within 6 months prior to screening.

[14] Have had any episodes of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) and/or hypoglycemia unawareness within the 6 months prior to screening.

[15] Have significant lipohypertrophy, lipoatrophy, scars, or h/o abscess in areas of injection.

[16] Have vision or hearing loss that impairs recognition of CGM screens, alerts and alarms.

[17] Cardiovascular (CV): have had any of the follow CV conditions: acute myocardial infarction, New York Heart Association Class III or IV heart failure (Section 10.6), or cerebrovascular accident (stroke)

[18] Gastrointestinal: have gastroparesis or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (e.g., Lap-Band®) prior to screening

[19] Hepatic: have acute or chronic hepatitis, or obvious clinical signs or symptoms of any other liver disease except non-alcoholic fatty liver disease (NAFLD) (i.e., patients 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 level (TBL) >2x the upper limit of normal (ULN), or
- Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) >2.5x ULN, or
- Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) >2.5x ULN

[20] Renal:

- Have history of renal transplantation
- Are currently receiving renal dialysis
- Have serum creatinine >2.0 mg/dL (177 µmol/L) at screening, or
- Have an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2

[21] Have experienced significant weight loss or gain (>5%) in body weight in the 3 months prior to screening.

[22] Have active or untreated malignancy, or 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.

[23] Have known hypersensitivity or allergy to any of the study medications or their excipients.

[24] Have any other serious disease or condition (e.g., known drug or alcohol abuse/regular consumption or psychiatric disorder) that, in the opinion of the investigator, would pose a significant risk to the patient, preclude the patient from following and completing the protocol, or interfere with the interpretation of safety, efficacy, or PD data.
Alcohol abuse/regular consumption is defined as an average daily intake of >3 units for males or >2 units for females within 6 months prior to the study. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

[25] Have had a blood transfusion or severe blood loss within 3 months prior to screening or have any hematologic condition that may interfere with HbA1c measurement (e.g., hemoglobinopathy, hemolytic anemia, sickle-cell disease).

[26] Have fasting triglycerides >400 mg/dL or non-fasting triglycerides >600 mg/dL.

[27] Women of childbearing potential who

i) are pregnant or intend to become pregnant

ii) are lactating/breastfeeding (including the use of a breast pump)

iii) are unwilling to remain abstinent or use birth control as described in Appendix 4

iv) test positive for pregnancy at the time of screening (Visit 1). Note: a urine pregnancy test is conducted at Visit 3.

Prior/Concomitant Therapy

[28] Are taking drugs that may significantly affect glycemic control (e.g., niacin [allowed if <1.0 g/day], bile acid sequestrants).

[29] Are receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (including intravenous, intramuscular, SC, and oral) or intra-articular (but excluding topical, intraocular, intranasal, and inhaled preparations), or have received such therapy within 4 weeks immediately prior to screening with the exception of replacement therapy for adrenal insufficiency.

[30] Are currently taking or have taken within the 3 months preceding screening, prescription or over-the-counter medications to promote weight loss. Patients who participate must agree not to initiate a diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment.

[31] Are taking total daily dose of insulin >100 Units at the time of screening.

[32] Are receiving any oral or injectable medication intended for the treatment of diabetes mellitus other than rapid-acting and basal analog insulin in MDI in the 90 days prior to screening.

[33] Are using or have used blood pressure-lowering medication at a dose that has not been stable for 1 month prior to screening.

Prior/Concurrent Clinical Trial Experience

[34] 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.

[35] Have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[36] Have previously completed or withdrawn from this study or any other study investigating LY3209590.

Other Exclusions

[37] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[38] Are Lilly employees.

5.3. Lifestyle Considerations

Per the Schedule of Activities (Section 1.3), qualified medical 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.

Prescription or over the counter (OTC) medications that promote weight loss are exclusionary if used within 3 months prior to screening (study entry), or between screening and randomization. These medications are also not allowed at any time during the treatment period. If started after randomization, these medications should be immediately withdrawn.

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

5.3.1. Meals and Dietary Restrictions

Patients should continue their usual exercise habits and generally follow a healthy meal plan (with consistent meal size and time of day) throughout the course of the study. Dietary counseling may be reviewed throughout the study, as needed.

In addition, patients should not receive 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.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are 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) may be rescreened once. The interval between screening and rescreening should be at least 4 weeks. A new ICF must be signed at the time of rescreening and the study participant will be assigned a new identification number. A single repeat testing of suspected erroneous/spurious central laboratory results is allowed without rescreening the study participant.

6. Study Intervention

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

6.1. Study Intervention(s) Administered

LY3209590 will be provided in a 20 mg vial of lyophilized powder. Upon reconstitution per the pharmacy instructions provided by the sponsor, LY3209590 will be administered once weekly as SC injections. Each patient will receive 1 injection each week, as described in the "Treatment Regimens" table below. SC injections of LY3209590 will be administered rotating between left and right abdominal regions, and upper and lower quadrants. Refer to Study Period 2 in Section 4.1.1 for details on how IP will be administered.

Patients will receive treatment with LY3209590 by an algorithm described in Section 10.8.

The LY3209590 Algorithm 1 is a paper-based algorithm that uses similar principals to the established Riddle algorithm.

Insulin degludec will use the established Riddle algorithm and is a paper-based algorithm.

Approximately one-half of the subjects will be randomized in each of the 2 remaining treatment arms.

Insulin degludec will be provided as 100 units/mL in a prefilled pen. It will be administered once daily at approximately the same time of day, rotating between left and right abdominal regions, and upper and lower quadrants.

See Section 6.7.1 for transitioning to treatment after study completion.

Treatment Regimens

Regimen	Dose Randomization through Week 26
LY Dose Algorithm 1 (paper)	LY injection
Insulin degludec	insulin degludec injection (open-label)

Abbreviations: LY = LY3209590.

The investigator or his/her designee is responsible for the following:

- explaining the correct use and reconstitution of the investigational agent(s) to the patient
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

Clinical study materials will be labeled according to the country's regulatory requirements.

6.1.1. Selection and Timing of Doses

For patients randomly assigned to LY3209590, a loading dose will be determined using Table 1 in Algorithm 1 (see Section 10.8). The weekly dose adjustment thereafter will be based on guidance provided in Section 10.8. The doses will be administered at approximately the same time and day each week. The actual date, time and dose of each dose administrations (LY3209590 and insulin degludec) will be recorded in the participant's diary (and participant's medical record when administered at the site).

If a patient misses a scheduled dose of LY3209590, it should be administered a soon as possible, but no later than 3 days after the scheduled administration. If more than 3 days have elapsed since the scheduled administration, the dose should be skipped and the next injection will occur at the next scheduled day and time.

Insulin degludec should be administered at the same time each day adjusted per the modified Riddle algorithm (Section 10.8).

Patients who miss a dose of insulin degludec should inject their daily dose during waking hours upon discovering the missed dose. Instruct patients to ensure that at least 8 hours have elapsed between consecutive insulin degludec injections (Tresiba® USPI).

For details on the titration algorithms to be used, refer to Section 10.8.

6.1.2. Special Treatment Considerations

6.1.2.1. Standards of Medical Care

Investigators and other study team members are expected to treat patients 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 standards of care for diabetes, the investigators should follow current published standards of care from the American Diabetes Association (2016) and the European Association for Study of Diabetes (Inzucchi et al. 2015) during their patients' participation in this study. Standards of prevention of persistent hyperglycemia and ketone monitoring must be followed during the course of the study to prevent DKA.

Patients will continue their short acting insulin treatment throughout the duration of the study. Investigators are responsible to adapt mealtime and correction bolus dosing according to

standards of medical care. When titrating basal insulin a reduction of the mealtime insulin is necessary in most cases and should be considered by investigators to prevent hypoglycemia.

This section provides guidance on management of episodes of hypoglycemic events and events of severe, persistent hyperglycemia. For effective implementation of measures described here, it is important that patients, and their caregivers, if applicable, be well-educated about the signs and symptoms of hyperglycemia (e.g., severe thirst, dry mouth, frequent micturition, or dry skin) and hypoglycemia (e.g., intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders). Patients should be instructed to contact the investigative site in the event of severe, persistent hyperglycemia or severe hypoglycemia between study visits.

6.1.2.2. Management of Increased Hypoglycemia Risk

To date, effects of LY3209590 on hypoglycemia in patients with T2DM are not different as compared to other basal insulins. An objective of the study is to assess the risk of hypoglycemia in T1DM patients receiving LY3209590 as compared to insulin degludec.

In this study, increased risk of hypoglycemia is defined as having a single episode of severe hypoglycemia or having more than 1 episode of documented hypoglycemia with BG <54 mg/dL within a 1-week period at any time during the treatment period. Documented hypoglycemia is defined as any time a participant reports a SMBG ≤70 mg/dL (<3.9 mmol/L) or any investigator confirmed case of severe hypoglycemia.

In cases where a patient experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the patient has been fully compliant with the assigned therapeutic regimen and also that there is no evidence of other possible causes of hypoglycemia (e.g., omission of meal, inadequate meal or correction bolus, unexpected increase in exercise).

Patients fulfilling the definition of increased risk of hypoglycemia should first correct their bolus dosing, then decrease their dose of IP per the respective dosing algorithm, followed by discontinuation of IP, if needed.

6.1.2.3. Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period

Transient hyperglycemia may be observed during the first 1 to 2 weeks of treatment with LY3209590 and additional correction doses of rapid acting insulin may be used to manage hyperglycemia during this transition period.

An additional therapeutic intervention should be considered in patients who develop severe, persistent hyperglycemia after randomization based on the following criteria (FDA 2008):

a) average fasting glucose (FG) >270 mg/dL (>15.0 mmol/L) over any 2-week period or longer during the first 6 weeks postrandomization; or
b) average FG >240 mg/dL (>13.3 mmol/L) over any 2-week period or longer from Week 6 to Week 12 postrandomization; or
c) average FG >200 mg/dL (>11.1 mmol/L) over any 2-week period or longer after Week 12.

Investigators should first confirm that the patient does not have an acute condition causing severe hyperglycemia, and after the first 12 weeks of the study, that the patient is fully compliant with the assigned therapeutic regimen. The investigator will decide, in consultation with the patient, on an appropriate intensification of insulin therapy after considering relevant clinical criteria. Patients who receive a new intervention for hyperglycemia management should also continue administering IP for the remaining period in the trial.

6.1.3. Medical Devices

The sponsor will provide syringes for subcutaneous injection.

6.2. Preparation/Handling/Storage/Accountability

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

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

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions will be provided by the sponsor.

The study site must store all study intervention in a locked and secure environment.

Investigators should consult the study drug information provided in the Pharmacy Instructions or label for the specific administration information (including warnings).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; thus, it will be unblinded. However, the specific intervention to be taken by a participant will be assigned using an Interactive Web Response System (IWRS). The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment in the appropriate data capture tool. Potential bias will be reduced by the following steps: central randomization, stratification, blinded adjudication for CV endpoints.

Patients who meet all criteria for enrollment will be randomized to treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. The IWRS will be used to assign IP to each patient. Site personnel will confirm that they have located the correct IP by entering a confirmation number found on the IP label into the IWRS.

To achieve between-group comparability for site factor, the randomization will be stratified by baseline HbA1c (<8.5%, ≥8.5%), and country. The randomization scheme will be performed using IWRS, which will ensure balance between treatment groups.

6.4. Study Intervention Compliance

The assessment of treatment compliance with IP (LY3209590 or insulin degludec) will be determined by the following:

- Information about the once weekly IP injections administered at home by the patient will be entered into the patient diary by the patient and reviewed by the site personnel at each study visit; this information will be collected in the electronic study diary;
- IP accountability will be checked according to the Schedule of Activities (Section 1.3). Study participants will be instructed to return all dispensed vials, any *unused* pens, and/or all empty cartons at the next visit to the study site for the purpose of performing drug accountability.

Other aspects of compliance will also be assessed at each visit, including the patient's adherence to the visit schedule, compliance with the concomitant short acting insulin requirements and other medication guidances (Section 6.5), completion of study diaries, results of SMBG through CGM, and any other parameters the investigator considers necessary. Patients considered to be poorly compliant with their medications and/or study procedures (e.g., missed visits or specific diagnostic tests) will receive additional training and instructions, as required.

When participants are dosed at the site, they will receive IP directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the diary.

When participants administer study treatment at home, compliance with study treatment will be assessed at each visit. Compliance will be assessed by direct questioning, reviewing eCOA documentation, counting returned pens, etc. during the site visits.

A record of the number of the pens and study medications dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates, and
- Dosage information including dose and frequency for concomitant therapy of special interest.

Lilly Medical should be contacted if there are any questions regarding concomitant or prior therapy.

Participants will be permitted to use concomitant medications that they require during the study, except prohibited medications described in Section 5.2 and Sections 6.5.1 and 6.5.2 below. In addition, certain permitted medications (e.g., treatments for blood pressure or dyslipidemia) described in Sections 6.5.3 and 6.5.4 should be continued, but not changed, during the study.

Participants will continue to use concomitant short-acting insulin throughout the treatment period. Discontinuation or changes to regimen are not permitted, except in situations where dose adjustment is required for medical reasons or when allowed per study protocol.

Investigative site staff will inform patients that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study, except when initiated for treatment of medical emergencies.

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

6.5.1. Medications that Promote Weight Loss

Prescription or OTC medications that promote weight loss are exclusionary if used within the 3 months prior to screening, or any time after screening (see Section 6.5). If started after screening, these medications should be stopped immediately. In addition, patients should not receive 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 (see Section 5.3).

6.5.2. Systemic Glucocorticoids

Chronic systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) is exclusionary if used >14 consecutive days during the 1-month period before screening or between screening and randomization at Visit 3.

Patients treated with these medications after randomization will be excluded from the efficacy evaluable population for analyses if they receive:

- >14 days consecutive days of therapy, or
- More than 1 course of therapy during the study.

6.5.3. Antihypertensive Medications

If used, anti-hypertensive therapy should be kept stable throughout the trial to allow assessments of the effect of randomized therapies on blood pressure.

6.5.4. Dyslipidemia Medication

If used, dyslipidemia therapy should be kept stable throughout the trial to allow assessments of the effect of randomized therapies on lipid endpoints.

6.6. Dose Modification

Dosing of basal insulin will be individualized based on FG. See Section 10.8 for details of dose modification.

6.7. Intervention after the End of the Study

After the end of the treatment period patients should continue to monitor their FG levels. The treating physician should then make the decision based on local clinical practice, if and what additional antihyperglycemic treatment needs to be administered.

Investigational product will not be made available to patients after conclusion of the study. After IP is discontinued, an appropriate diabetes treatment regimen will be initiated by the investigator.

6.7.1. Treatment after Study Completion

The last study treatment administration for patients treated with LY3209590 will be at Week 25 and for patients treated with insulin degludec the evening before the last study visit at Week 26. The washout of LY3209590 may take up to 10 weeks to complete. Any appropriate basal insulin treatment must therefore be instituted slowly and under regular supervision of BG profiles after discontinuation of LY3209590. Since CCI [redacted] Therefore, a slow up-titration of another basal insulin is necessary to prevent hypoglycemia due to overlapping insulin action. For example, no insulin would be required until the study participant's FG increases to >100 mg/dL, and then daily basal insulin would be initiated and adjusted based on FG.

Study participants assigned to the insulin degludec treatment group will switch to the basal insulin used before entering the study. If insulin degludec was the pre-study basal insulin, they can continue with the same dose used until Visit 20 of the study. If they switch to another basal insulin (e.g., insulin glargine), study participants should inject a daily dose, which is 20% lower than the last dose of insulin degludec used before Visit 20 and titrate under supervision of the investigator using the country-specific label for their pre-study basal insulin.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Study drug may be permanently discontinued or temporarily withheld during the study.

Participants who permanently discontinue study drug early will undergo ET procedures, which include

- an ET visit or,
- post-treatment follow-up visits (ED 1, ED 2).

The investigator will complete any AE reporting and necessary follow-up.

7.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product include, but are not limited to:

- **Participant decision**
  - the patient or the patient's designee, for example, parents or legal guardian requests to discontinue IP.
- **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

  Discontinuation of the IP for abnormal liver tests **should be** considered by the investigator when a participant meets one of the following conditions after consultation with Lilly Medical
  - ALT or AST >8x ULN
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio (INR) >1.5
  - 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
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

In addition, participants will be discontinued from the IP in the following circumstances:

- If a patient is inadvertently enrolled and it is determined that continued treatment with IP would not be medically appropriate (see Section 7.2.1)

- if a patient is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
- if the investigator or sponsor decides that the patient should be withdrawn from IP; if the investigator decides to permanently discontinue IP because of an SAE or a clinically significant laboratory value, Lilly or its designee should be alerted immediately
- if the investigator, after consultation with Lilly Medical, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from IP.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Patients who stop the IP permanently may receive another glucose-lowering intervention, if appropriate, and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements.

7.1.2. Temporary Discontinuation

In certain situations after randomization, the investigator may need to temporarily discontinue (interrupt) IP (e.g., due to an AE or a clinically significant laboratory value). The maximum time allowed for a temporary interruption of IP is 14 days. If IP interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 8.3 of this protocol. Investigators should inform the sponsor that IP has been temporarily interrupted. Every effort should be made by the investigator to maintain patients on IP and to restart IP after any temporary interruption, as soon as it is safe to do so. The data related to temporary interruption of IP and use of non-study insulin will be documented in source documents and entered in the eCRF.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant will be discontinued (withdrawn) from the study in the following circumstances:

- if he or she is diagnosed with any type of diabetes mellitus other than T1DM
- at any time at his/her own request
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the participant should be discontinued from the study

  - if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- participant decision:
  - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Activities (Section 1.3). See Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor clinical research physician (CRP) agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. Safety follow up is as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.3. Lost to Follow up

A study 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.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8. Study Assessments and Procedures

Study procedures and the study visits at which they are performed, including tolerance limits for the study visits, are listed in the Schedule of Activities (Section 1.3). Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

Efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with T1DM.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

The primary efficacy measure is HbA1c change from baseline to Week 26.

8.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments for this study are:

- HbA1c change from baseline to Week 12
- FG change from baseline to Weeks 12 and 26
- Bolus insulin dose change from baseline to Weeks 12 and 26

8.2. Safety Assessments

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

The following safety assessments will be evaluated as secondary objectives:

- Incidence and rate of hypoglycemia
- Incidence of treatment-emergent SAEs
- Clinical laboratory assessments with specific focus on liver aminotransferase changes

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the CV, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious 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 Schedule of Activities (Section 1.3).

Sitting blood pressure (BP) and pulse rate will be measured using automated electronic sphygmomanometer according to the Schedule of Activities (Section 1.3). 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 Schedule of Activities, 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. Blood pressure 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

For each patient, triplicate 12-lead digital ECGs and single safety ECGs will be collected according to the Schedule of Activities (Section 1.3). Patients 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 patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management should any clinically relevant findings be identified.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (e.g., demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless an overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

8.2.4. Self-monitoring of Blood Glucose (SMBG)

At Visit 2, patients will receive the Dexcom G6 CGM device and training on its use, sensor placement, interpretation of CGM values and alarms, and the requirements for CGM. SMBG will be performed through this CGM device. In the receiver of the CGM device 2 alarm settings are mandatory: an hypoglycemia alarm at 70mg/dl and a hypoglycemia alarm at 55mg/dl. Glucose readings should be obtained for monitoring patient safety (hypoglycemia) and may be checked as frequently as necessary. Patients should record 6-point glucose profiles in the eDiary provided, prior to the visits indicated by the Schedule of Activities (Section 1.3). Patients with missing eDiary glucose entries should be retrained on the importance of glucose reporting in the eDiary.

Patients will be instructed to record a prebreakfast (fasting) reading every morning and to record all results in the eDiary. Patients will also review BG using the CGM device as needed to evaluate symptoms of hypoglycemia.

Patients will be instructed to record 6-point glucose profiles over a 24-hour period on 2 nonconsecutive days during the 7-day period prior to visits indicated in the Schedule of

Activities (Section 1.3) using their CGM sensor. The 6-point profile consists of pre-meal and 2-hour postprandial glucose readings for the morning, midday, and evening meals in 1 day. Pre-meal measurements should be taken before the patient begins eating the meal. Patients should record their glucose measurements in their eDiaries and bring the diary to the investigative site at each study visit.

Participants are permitted to use a personal glucose meter for additional monitoring if deemed necessary or by personal choice. This data, however, should not be used for dosing decisions within the study as long as the CGM system is functional. In case of technical issues or during the calibration period of the CGM system a personal BG meter can be used for therapeutic decision making.

8.2.5. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those, which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 6 weeks after the last dose of study intervention (i.e., within the follow up period) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly medical.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.6. Safety Monitoring

The principal investigator will monitor safety and laboratory data throughout the study and should discuss safety concerns with the sponsor immediately upon occurrence or awareness of the concern to determine whether the participant should continue or discontinue study drug.

8.2.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Section 10.5) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or

worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study Lilly Medical. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- elevation of ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

8.2.7. Body Weight

Body weight will be measured at prespecified time points (see Schedule of Activities, Section 1.3). Patients will be weighed in a light hospital gown or standard clinical research site scrubs at approximately the same time in the morning after an overnight fast and after evacuation of bowel and bladder contents, if possible.

Weight will be measured once at screening (non-fasting) and recorded in the source document and eCRF. At lead-in and randomization (Visit 2 and Visit 3, respectively) and all subsequent visits indicated in the Schedule of Activities (Section 1.3), weight will be measured twice, with the patient stepping off the scale between measurements.

Both weight measurements will be recorded in the source document and the eCRF. Calibrated (within 6 months prior to study start) scales should be used. The same scale should be used for all weight measurements throughout the study and should not be moved during the conduct of the study.

8.3. Adverse Events and Serious Adverse Events

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, are 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).

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

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

The SAE reporting to sponsor begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving LY3209590, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

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

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Pregnancy (maternal or paternal exposure to IP) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Section 10.4 and to collect data on the outcome for both mother and fetus.

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 90 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Cardiovascular Events

Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. The nonfatal CV AEs to be adjudicated include: myocardial infarction; hospitalization for unstable angina; hospitalization for heart failure; coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

8.3.7. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for this program include:

a. Hypoglycemia
b. Allergic/hypersensitivity reactions

If any of these AESIs are reported, sites will be prompted to collect additional details/data.

8.3.7.1. Hypoglycemia

Patients will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (Visit 801 or ET visit). For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect in study diaries appropriate information for each episode of hypoglycemia according to the Schedule of Activities (Section 1.3).

Participants will be instructed to report hypoglycemia in the eDiary any time he/she experiences signs or symptoms of hypoglycemia with or without a SMBG ≤70 mg/dL (<3.9 mmol/L).

Severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the participant has an altered mental status and cannot assist in his/her own care, may be semiconscious or unconscious, or experience coma with or without seizures and may require parenteral therapy. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered

sufficient evidence that the event was induced by a low BG concentration (≤70 mg/dL [<3.9 mmol/L]).

If a hypoglycemic event meets the criteria of severe as confirmed by the investigator, it needs to be recorded as serious on the AE eCRF and reported to Lilly as an SAE.

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency and duration of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The patient should receive additional education, if deemed appropriate. Management of increased risk of hypoglycemia is described in Section 6.1.2.2.

8.3.7.2. Allergic/Hypersensitivity Reactions

All allergic or hypersensitivity reactions, including injection site reactions (ISR), will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Symptoms of a local ISR may include erythema, induration, pain, pruritus, 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.

Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to IP via an eCRF created for this purpose. IP should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to IP (Section 7.1.2). IP may be restarted when/if it is safe to do so, in the opinion of the investigator. If IP is permanently discontinued, see Section 7.1.1 for procedures required in this situation.

If an ISR is reported, the information will be provided to the sponsor in the eCRF. If criteria for a SAE are met, the investigator will also complete the SAE form and urgently report the SAE.

8.3.7.3. Systemic Hypersensitivity Reactions

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

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

In the case of generalized urticaria or anaphylaxis, additional samples should be collected as described in Appendix 9 (Recommended Laboratory Testing for Hypersensitivity Events). Laboratory results are provided to the sponsor via the central laboratory.

8.3.8. Product Complaints

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

a. Deficiencies in labeling information, and

b. Use errors for device or combination products due to ergonomic design elements of the product.

Sponsor collects product complaints on investigational products, medical devices, and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints are also collected on comparators and other materials supplied, as required and instructed for the study.

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

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

With each complaint related to a medical device or delivery system, the investigator will assess and indicate on the complaint form whether the product complaint could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

In the case of an accidental overdose, contact the sponsor in regards to patient management.

For patients with suspected or confirmed overdose of LY3209590, there is no specific antidote. The participant should monitor or be monitored for hypoglycemia. Treatment is supportive, depending on the participant's symptoms. The management of hypoglycemia should take into account the long duration of action of LY3209590, and if there is any concern regarding sustained glucose monitoring or nutrient access, the investigative staff should consider imposing close medical monitoring (e.g., hospitalization).

In the event of an overdose with insulin degludec, refer to the Product Label.

8.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 1.3), venous blood samples will be collected to determine the plasma concentrations of LY3209590. After Visit 3, PK samples can be taken at any time during the visit. Note: PK sample collection is not intended for participants randomized to insulin degludec treatment.

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.

All the samples will be analyzed at a laboratory designated by the sponsor and stored at a facility designated by the sponsor.

Plasma concentrations of LY3209590 will utilize a validated enzyme-linked immunosorbent assay (ELISA) method.

Bioanalytical samples collected to measure IP concentration will be retained for a maximum of 1 year following last patient visit for the study.

8.6. Pharmacodynamics

In addition to PD parameters discussed in the efficacy and safety sections, fasting free fatty acids (FFA) and triglycerides will be evaluated as PD biomarkers of lipolysis, which is a sensitive measure of peripheral insulin activity.

Samples collected to measure FFA will be identified by the patient number (coded) and retained at a facility selected by Lilly or its designee for a maximum of 2 years following last patient visit for the study at a facility selected by Lilly or its designee.

8.7. Genetics

A blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants.

See Section 10.7 for information regarding genetic research and Section 10.1.7 for details about sample retention and custody.

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient 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, ribonucleic acid, 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 T1DM, mechanisms of action of LY3209590 and/or research methods or in validating diagnostic tools or assay(s) related to T1DM.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ethic review boards impose shorter time limits, at a facility selected by Lilly. This retention period 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.

8.9. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 1.3), venous blood samples will be collected for analysis to determine antibody production against LY3209590. Antibodies may be further characterized for cross-reactive binding to insulin. In vivo laboratory indicators for glycemic control (e.g., BG, HbA1c, and/or daily insulin dose) may be utilized to detect a potential neutralizing effect of antidrug antibodies (ADAs) against LY3209590. To

interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of LY3209590. All samples for immunogenicity should be taken predose when applicable and possible.

Treatment-emergent (TE) ADAs are defined in Section 9.4.8. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken until the signal returns to baseline (i.e., no longer TE-ADA positive) or for up to 1 year after last dose.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY3209590. Any samples remaining after 15 years will be destroyed.

8.10. Health Economics

No health economic outcomes are planned.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary hypothesis is to test whether LY3209590 treatment is non-inferior to insulin degludec in HbA1c change from baseline to Week 26 in study participants who are MDI treated T1DM, using a non-inferiority margin (NIM) of 0.4%.

9.2. Sample Size Determination

Approximately 238 participants will be randomized to study treatment (LY3209590 Algorithm 1, and insulin degludec) such that approximately 119 participants will be randomized to each treatment. Assuming a 20% dropout rate, approximately 190 participants will complete the study (approximately 95 participants per treatment group).

The 190 participants who complete the treatment will provide at least 80% statistical power to demonstrate the noninferiority in the change in HbA1c from baseline to 26 weeks for LY3209590 Algorithm 1 versus insulin degludec, based on the following assumptions:

- True mean difference = 0%
- SD of 1.1%
- NIM of 0.4%
- Using 2-sided alpha level of 0.1

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered/Enrolled Population	All participants who sign the ICF
Randomized Population	All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. The participants previously randomized to Algorithm 2 will be pooled with the participants randomized to Algorithm 1 and all of these participants will be analyzed as one treatment group of LY3209590.
Efficacy Population	Participants in randomization population excluding the participants previously randomized to Algorithm 2.
Safety Population	All participants randomly assigned to study treatment and who take at least 1 dose of study treatment. The participants previously randomized to Algorithm 2 will be pooled with the participants randomized to Algorithm 1 and all of these participants will be analyzed as one treatment group of LY3209590.
Pharmacokinetic Population	All randomized participants who received at least 1 dose of LY3209590 and have at least 1 evaluable PK sample.

Abbreviations: ICF = informed consent form; PK = pharmacokinetics.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of sponsor or its designee.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, unless otherwise stated, and all confidence intervals (CIs) will be given at a 2-sided 90% level.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP 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.

9.4.1. General Considerations

Unless otherwise stated, the efficacy analyses will be conducted on efficacy analyses set (EAS) based on the Efficacy Population using the data up to the study treatment discontinuation (defined as the observed data with collection date before or at the last dose date +10 days). Sensitivity analyses for selected efficacy measures may be conducted on the Randomized Population using the data up to the study treatment discontinuation.

Unless otherwise stated, the safety analyses except for hypoglycemia will be conducted on the safety analyses set based on the Safety Population using all data collected during the study including treatment and follow-up period regardless of the treatment disposition status. The details for analyses of hypoglycemia will be documented in the SAP.

Unless otherwise specified, the baseline value used for the analyses will be the last nonmissing value obtained for each participant prior to or on the date of first study IP dose (or randomization visit date if first dose date is missing). The baseline liver enzyme lab measures will be the average of all assessments prior to and at randomization visit.

9.4.2. Treatment Group Comparability

9.4.2.1. Patient Disposition

All randomized participants who discontinue the study/treatment will be identified, and a reason for their discontinuation will be given. The reasons for study/treatment discontinuations will be listed and will be summarized by treatment. The discontinuation due to an AE will be summarized by AE and treatment. The percentage of participants discontinuing from each treatment will be compared using the Fisher's exact test.

Reasons for discontinuation prior to randomization will also be summarized.

9.4.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized by treatment group for Randomized Population and Efficacy Population. Categorical variables will be summarized by frequencies and percentages, and comparisons between treatment groups will be assessed using a Pearson Chi-Square test. Continuous variables will be summarized by mean and standard deviation, and comparisons between the treatment groups will be performed using a 1-way analysis of variance with treatment as the fixed effect.

9.4.2.3. Concomitant Therapy

Summary of concomitant therapies will be provided by treatment group for all randomized participants.

9.4.2.4. Treatment Compliance

Treatment compliance will be assessed using the EAS and summarized by treatment. The incidence of missed dose and the percentage of missed dose will be evaluated.

Adherence to the dosing algorithm will be assessed based on the number and percentage of investigator prescribed doses that did not follow the investigator-calculated algorithm dose and

the number and percentage of participant actual administration dose that did not follow the investigator prescribed dose.

9.4.3. Primary endpoint(s)

The primary objective is to compare the HbA1c change from baseline to Week 26 between LY3209590 treatment and insulin degludec. It is intended to estimate the treatment differences in the change in HbA1c from baseline to 26 weeks if participants adhered to the treatment without intercurrent events (stop of the study medication). It is a type of hypothetical estimand based on International Council for Harmonisation (ICH) E9(R1). Only data before the occurrence of the intercurrent events (stop of the study medication) will be included in the analysis and the resulting missing values will be imputed implicitly in the mixed-effect model for repeated measurements (MMRM) analysis. The MMRM model will include treatment, country, visit, and treatment by visit interaction as fixed factors and the baseline of the dependent variable as a continuous covariate.

As a sensitivity analysis, the treatment differences in HbA1c change from baseline to Week 26, only if patients could complete the treatment, will also be estimated. More details will be specified in the SAP.

9.4.4. Secondary endpoint(s)

The following secondary efficacy outcomes will be analyzed:

- HbA1c change from baseline to 12 weeks
- FG and change from baseline at 12 and 26 weeks
- Bolus insulin dose change from baseline to 12 and 26 weeks

9.4.5. Tertiary/exploratory endpoint(s)

Refer to the SAP for analyses related to tertiary/exploratory endpoints.

9.4.6. Safety Analyse(s)

Unless otherwise stated, all safety analyses will be based on the safety analysis set. Safety measures include treatment exposure, AEs, vital signs, hypoglycemic episodes, laboratory measurements, ECG and immunogenicity.

9.4.6.1. Adverse Events

AEs will be summarized as TEAEs (defined as events that are newly reported after randomization or reported to worsen in severity from baseline). The incidence of participants with at least 1 TEAE and the incidence of TEAEs by preferred term and system organ class will be presented by treatment group. The frequency and percentage of participants for each preferred team will be presented. The incidence of participants with at least 1 TEAE assessed as possibly related to the investigational drug will be summarized by treatment group, in addition to the incidence of these possibly related TEAEs by preferred term. In addition, a summary of TEAEs by severity will be presented descriptively by treatment group.

Reported and adjudicated CVs will be listed by participant, and if there are a sufficient number of cases they may be summarized by treatment group.

All SAEs will be listed by participant. If a sufficient number of SAEs are reported, incidence summaries similar to incidence of TEAEs will be included.

Discontinuations due to AE will be summarized by treatment group and preferred term.

9.4.6.2. Vital Signs

Descriptive statistics for the actual measurements and changes from baseline will be presented by treatment group and visit. Corresponding figures may be presented. Vital signs will be analyzed using a MMRM model.

9.4.6.3. Hypoglycemia Episodes

The incidence and rate per year of hypoglycemia will be presented for the periods between 0-12 weeks, 12-26 weeks, 0-26 weeks, and the follow-up period and analyzed according to the hypoglycemia definitions described in the American Diabetes Association classification system (ADA 2019). The analyses for hypoglycemia will be performed on Efficacy Population and additionally the severe (level 3) hypoglycemia analysis will also be performed for the Safety Population.

9.4.6.4. Laboratory Measures

Summary statistics will be provided for laboratory measures by treatment group and by visit. An additional listing will be presented for all laboratory measurements that are outside the normal range.

Descriptive statistics for the laboratory analyses will be presented by treatment group and visit. Laboratory analyses with categorical responses will be summarized by visit and treatment group using frequency and percentage.

The maximum/minimum post-baseline observation (as applicable for a lab) will be compared to the baseline observation by examining the proportion of participants whose test values are within and outside the reference ranges.

9.4.6.5. Electrocardiograms

ECG is mainly for participant safety monitoring. Exploratory analysis may be conducted as necessary.

9.4.6.6. Adverse Events of Special Interest

Hypoglycemia and allergic/hypersensitivity reactions are defined as AESIs (Section 8.3.7).

Descriptive statistics for the AESIs will be presented by treatment group.

9.4.7. Pharmacokinetic/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, tolerability, and safety as well as biomarker endpoints will be characterized if exploratory analyses of the PD data warrant further PK/PD analyses upon

review. Such analyses may include, but are not necessarily limited to, glucose, HbA1c, QTc, hypoglycemia, and vital signs.

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.

9.4.8. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with TE-ADA to LY3209590 may be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency of cross-reactive binding to insulin may also be tabulated in TE ADA+ subjects, when available.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3209590 may be assessed.

9.4.9. Other Analyses

Detailed analysis plan for CGM will be documented in the SAP.

9.5. Interim Analyses

9.6. Data Monitoring Committee (DMC)

No DMC is planned for this study.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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.

Under emergency circumstances, deviations from this protocol to protect the rights, safety, or well-being of participants are allowed without prior approval of Lilly and the IRB/IEC. The site shall document and report these emergent deviations to Lilly and the IRB/IEC within 5 working days after the emergency occurred.

Deviation(s) from this protocol, signed 1572, applicable regulations, and any conditions of approval imposed by an IRB/IEC or applicable regulators shall be documented (including date of and reason for deviation). Site personnel must identify and report deviations to the sponsor within 5 working days.

If appropriate, actions to secure compliance may be taken by Lilly. These actions may include removal or discontinuation of study intervention materials, removal/disposal of devices from the investigator, or termination of an investigator's participation in the study.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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 re-consented 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.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

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

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Reports

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

Data

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

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, 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.clinicalstudydatarequest.com.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., 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 (central, remote, or on-site monitoring) are provided in the contracts.

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 (e.g., 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 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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

Additionally, eCOA data (participant-focused outcome instrument) will be directly recorded by the participant, caregiver, and/or investigator site personnel, into an instrument (e.g., handheld smart phone or tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

Study Procedures

Electronic Clinical Outcomes Assessment

The use of eCOA eDiaries should also allow more complete and accurate capturing of hypoglycemic events, correction boluses and dosing, as well as more frequent and timely interactions between investigator and patients as the intensity of their individual diabetes management increases.

Physicians and designated clinical staff will have access via the eCOA portal (secured web-based site) to BG readings, hypoglycemic events, correction boluses and dosing information for each patient once transferred. It is recommended that investigators review patient data via the eCOA portal at least once weekly for clinical decision making and safety monitoring. More frequent reviews may be necessary for individual patient management.

An instruction manual will be provided to patients and investigative sites. Additional instruction and training will be provided to the investigative sites regarding data collection, review, retention, and archival processes. In the event of eCOA eDiary malfunction or loss, the patient will be instructed to immediately contact the investigative site for instructions regarding replacement of the equipment.

Correction Boluses

Patients will be instructed to enter all non-meal-related correction bolus doses (those not associated with a meal or combined with a meal bolus) into the eCOA diary.

Hypoglycemia

Hypoglycemic events will be entered by the patient throughout the clinical study in eCOA along with date and time of the BG level if measured and hypoglycemia treatment and outcome data.

Self-Monitoring Blood Glucose

Patients will be instructed to perform Daily Fasting BG values are expected as well as 6-point SMBG according to the Schedule of Activities (Section 1.3).

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

10.1.9. Publication Policy

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

10.1.10. Investigator Information

Principal investigators who are a diabetologist, internal medicine specialist, or primary care physician with experience in the care of type 1 diabetes patients using MDI and CGM will participate as investigators in this clinical trial.

10.1.11. Long-Term 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 becomes commercially available.

The following table lists the maximum retention period for sample types. The retention period begins after the last participant visit for the study. Any samples remaining after the specified retention period will be destroyed.

Sample Type	Custodian	Retention Period After Last Patient Visit*
Long-term storage samples	Sponsor or Designee	15 years
Biomarkers	Sponsor or Designee	15 years
PK	Sponsor or Designee	1 year
Genetics	Sponsor or Designee	15 years
PD	Sponsor or Designee	2 years
Immunogenicity	Sponsor or Designee	15 years

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

* Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Refer to Section 10.9 for recommended laboratory testing for hypersensitivity events.

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Chloride
Mean cell volume (MCV)	Bicarbonate
Mean cell hemoglobin (MCH)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Gamma glutamyltransferase (GGT)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Uric acid
	Calcium
Urinalysis	Phosphorus
Protein	Glucose
Nitrite	Total protein
Blood	Albumin
Urine leukocyte esterase	Creatine kinase (CK)
	Cholesterol
Hormones	Triglycerides
Pregnancy test serum and urine (females only)[b]	Pancreatic amylase
Follicle stimulating hormone	Lipase
Endocrine	**Lipid Panel**
C-Peptide	HDL cholesterol
	LDL cholesterol
	Hemoglobin A1c
	Free Fatty Acid
	Hepatitis B
	Hepatitis B Core Antibody
	Hepatitis B Surface Antigen
	Hepatitis B Surface Antibody
Immunogenicity[c]	**Drug concentration**[c]
Anti-LY3209590	LY3209590
Calculation	**Pharmacogenetic sample**[c]
eGFR (Calculated by CKD-EPI equation)	
	Non-pharmacogenetic samples[c]
	Serum
	EDTA Plasma

Abbreviations: CKD-EPI = chronic kidney disease epidemiology collaboration; EDTA = Ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HDL = high density lipoprotein; LDL = low density lipoprotein; RBC = red blood cells; WBC = white blood cells.

[a] All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.

[b] Urine pregnancy tests (analyzed on-site) to be performed at Visits 3 and 801/ED2, and serum pregnancy test (analyzed by central laboratory) to be performed at Visits 1 for women of childbearing potential. Additional pregnancy tests may be performed at the investigator's discretion during the study.

[c] Results will not be provided to the investigative sites.

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

10.3.1. Definition of AE

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 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.

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

AE and SAE Recording

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

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. 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.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 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 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 with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to sponsor will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Lilly Medical by telephone.

SAE Reporting to Sponsor or designee via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Lilly Medical. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • 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.

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

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

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

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as, women with:
   i. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
   ii. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
   iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

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 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 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 <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by sponsor-designated or local laboratory.

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

10.6. Appendix 6: New York Heart Association Cardiac Disease Classification

Functional Capacity

Class I

Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II

Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III

Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV

Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

1994 Revisions to Classification of Functional Capacity and Objective Assessment of Patients with Diseases of the Heart

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10.7. Appendix 7: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to study intervention or T1DM and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study intervention and/or interventions of this drug class and T1DM. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained as described in Section 10.1.11.

10.8. Appendix 8: Dosing Guidance for LY3209590 and Insulin Degludec

10.8.1. LY3209590 Algorithm 1 (paper algorithm)

In Study BDCP, a paper dosing Algorithm 1 will be used by investigators for initiating and adjusting LY3209590 to achieve the target FG ≤100 mg/dL (<5.6 mmol/L).

In situations where study participant safety is a concern, investigators may make adjustments to the dose of LY3209590 recommended by the dose-adjustment algorithm in Table 2; however, clinical rationale must be documented in the eCRF and Lilly Medical must be informed about this deviation and associated medical rationale. If the investigator has safety concerns about the algorithm, the investigator is to contact the Lilly CRP.

At the time of site visit, the investigator will assess the study participant's glycemic control for the previous week and, if necessary, inform the study participant about any needed dose adjustment. The dose will be based on the study participant's FG value obtained from the CGM system prior to the morning meal and hypoglycemia documented in the electronic diary in the previous week. Adherence to the dosing algorithm provided for this study is required from Visit 3 (randomization) up to Week 25 and will be monitored periodically by the study team.

General Algorithm Considerations:

- The treat-to-target FG in the algorithm is ≤100 mg/dL (<5.6 mmol/L). LY3209590 dose adjustments will be determined based on the median of the FG (determined from SMBG obtained from the CGM system, referred to as SMBG below) of at least 3 days (up to 7 days) obtained in the previous week leading up to the visit.
- The LY3209590 dose may not be increased if any SMBG reading was documented at ≤70 mg/dL (<3.9 mmol/L) at any time in the preceding week. Dose decreases of 0.5 mg adjustment may be permitted if multiple episodes of hypoglycemia with SMBG ≤70 mg/dL (<3.9 mmol/L) were recorded, or dose decrease of 1 mg if severe hypoglycemia (requiring assistance) occurred, or if any SMBG was documented at ≤54 mg/dL (≤3.0 mmol/L) in the preceding week.
- In dosing calculations where rounding is required, round to the nearest 0.25 mg.

The starting LY3209590 dose is determined based on both the prior basal insulin dose and baseline fasting glucose. Participants may enter the study using insulin glargine, detemir, or degludec. Consistent with product labeling these insulins may be transitioned on a unit-for-unit basis and for the purposes of this protocol are considered equivalent. Because of the long half-life of LY3209590, the change in fasting glucose response may take several weeks to reach a steady-state response; therefore, to minimize the time needed to achieve the desired target glycemic response, a loading dose strategy will be used for the first dose only. Directions are provided below to convert current basal insulin dose (in Units, U) to the dose of LY3209590 (in mg) for determination of the starting weekly dose and for dose adjustments at subsequent Visits. Examples for Visits 3-6 are provided in *italic text*.

Visit 3 (Randomization Visit):

1. Obtain the prior daily basal insulin dose of insulin glargine, detemir, or degludec assessed during the lead-in period. Calculate the "basal insulin equivalent dose" of LY3209590

(in mg) by dividing the total daily dose of basal insulin (U) by the conversion factor of 7 U/mg.

For example, if a participant uses 35 U of degludec each day, 35 U ÷ 7 U/mg = 5 mg of LY3209590.

2. The dose of LY3209590 mg is then further adjusted according to median baseline fasting glucose and the participant's current basal insulin dose (U) category as shown in Table 1.

For a participant with a median BG value of 155 mg/dL, the dose adjustment for this participant currently using a 35 U dose of degludec would be +1.5 mg.

3. The loading dose is obtained by multiplying the starting total LY3209590 weekly dose (sum of basal insulin equivalent dose and the dose adjustment from Table 1) CCI

In this example, 5 mg + 1.5 mg = LY3209590 total weekly dose of 6.5 mg CCI for a total first dose of CCI . ***This first dose, including the loading dose, is used at Visit 3 only.***

Table 1. LY3209590 Dose Adjustment (mg) Using the Median of Baseline Fasting Glucose and Prior Basal Insulin Dose (International Units, U)

Median Baseline Fasting Glucose (mg/dL)	Median Baseline Fasting Glucose[b] (mmol/L)	LY3209590 Dose Adjustment (mg)[a]		
		Basal Insulin Dose ≤15 U	Basal Insulin Dose 16 – 30 U	Basal Insulin Dose >30 U
<80	<4.4	- 0.25	- 1	- 1.5
80 - 100	4.4 – 5.5	No change	No change	No change
101 – 140	5.6 – 7.7	+ 0.25	+ 0.5	+ 0.75
141 – 180	7.8 – 10.0	+ 0.5	+ 1	+ 1.5
181 – 220	10.1 – 12.2	+ 0.75	+ 1.5	+ 2
>220	>12.2	+ 1	+2	+3

[a] This dose adjustment is added to the Basal Insulin Equivalent Dose to obtain the total weekly dose of LY3209590 in mg. The starting total weekly dose of LY3209590 is increased CCI to obtain the first loading dose of LY3209590 necessary to reduce the time to achieve target glycemic response.

[b] Conversions from mg/dL to mmol/L were rounded off to prevent overlap between threshold ranges and to address that the glucose meter displays 1 significant digit after the decimal when reporting mmol/L readings.

Visit 4 (Week 1)

1. Obtain the starting total weekly dose LY3209590 mg determined at Visit 3. (This is 1/3rd the dose administered at Visit 3.)

From the Visit 3 example, the starting LY3209590 total weekly dose was 6.5 mg.

2. Use Table 2 to determine the dose adjustment needed for Visit 4 after carefully reviewing participant's fasting glucose (3-7 days prior to visit) and hypoglycemia documented since the last LY3209590 dose.

The participant reported no hypoglycemia since the last dose of LY3209590 and had a median FG of 150 mg/dL. Using the Week 1 (Visit 4) column, the LY3209590 weekly dose should be increased by 1 mg.

6.5 mg + 1 mg = 7.5 mg LY3209590 should be administered at Visit 4.

Table 2. Weekly Dose Adjustment of LY3209590 Using the Previous Week's Dose (D) using the Median Fasting Glucose and Hypoglycemic Episodes

Median Fasting glucose (mg/dL)[a]	Median Fasting glucose (mmol/L)[a,e]	Week 1 (Visit 4) (2nd dose)	Week 2 (Visit 5) (3rd dose)	Subsequent Week[c]
<80 mg/dL or have any nocturnal hypoglycemia or multiple (≥3) episodes of hypoglycemia[d]	<4.4 mmol/L or have any nocturnal hypoglycemia or multiple (≥3) episodes of hypoglycemia[d]	D^b – 1.5 mg	D^b – 1 mg	D^c – 0.5 mg
80 – 100 mg/dL	4.4 – 5.5	D^b – 1 mg	D^b – 0.5 mg	No change
101 – 140 mg/dL	5.6 – 7.7	No change	No change	D^c + 0.25 mg
141 – 180 mg/dL	7.8 – 10.0	D^b + 1 mg	D^b + 0.5 mg	D^c + 0.25 mg
>180 mg/dL	>10.0	D^b + 2 mg	D^b + 1 mg	D^c + 0.5 mg

[a] Based on median fasting glucose from at least 3 fasting glucose readings from previous week.

[b] D for Week 1 (Visit 4) is CCI of the dose administered at (Week 0, Visit 3). D for Week 2 (Visit 5) is the dose administered at Week 1 (Visit 4).

[c] D for Subsequent Visits is the dose administered one week prior to the current visit.

[d] The LY3209590 dose may not be increased if any SMBG reading was documented at ≤70 mg/dL (<3.9 mmol/L) at any time in the preceding week. If multiple episodes of hypoglycemia with SMBG ≤70 mg/dL (<3.9 mmol/L) were recorded, follow guidance for dose reduction according to the applicable Visit number. Dose decreases of 1 mg should be made when severe hypoglycemia (requiring assistance) occurred, or if any SMBG was documented at ≤54 mg/dL (≤3.0 mmol/L) in the preceding week.

[e] Conversions from mg/dL to mmol/L were rounded off to prevent overlap between threshold ranges and to address that the glucose meter displays 1 significant digit after the decimal when reporting mmol/L readings.

Visit 5 (Week 2)

1. Confirm the dose of LY3209590 mg administered at Visit 4.

   From the Visit 4 example, the LY3209590 weekly dose was 7.5 mg.

2. Use Table 2 to determine the dose adjustment needed for Visit 5 after carefully reviewing participant's fasting glucose (3-7 days prior to visit) and hypoglycemia documented since the last LY3209590 dose.

The participant reported no hypoglycemia since the last dose of LY3209590 and had a median FG of 153 mg/dL. Using the Week 2 (Visit 5) column, the LY3209590 weekly dose should be increased by 0.5 mg.

7.5 mg + 0.5 mg = 8.0 mg LY3209590 should be administered at Visit 5.

Visit 6 (Week 3)

1. Confirm the dose of LY3209590 administered at Visit 5 (Week 2).

   From the Visit 5 example, the LY3209590 weekly dose was 8.0 mg.

2. Use Table 2 to determine the dose adjustment needed for Visit 6 after carefully reviewing participant's fasting glucose (3-7 days prior to visit) and hypoglycemia documented since the last LY3209590 dose.

   The participant reported one episode of nocturnal hypoglycemia since the last dose of LY3209590 and had a median FG of 133 mg/dL. Using the Subsequent Week column in Table 2, and because of the case of nocturnal hypoglycemia, LY3209590 dose should be reduced by 0.5 mg.

   8.0 – 0.5 = 7.5 mg of LY3209590 should be administered at Visit 6.

Subsequent visits are managed using the same approach as for Visit 6 (Week 3), always confirming the LY3209590 dose administered at the prior visit, the median fasting glucose during the week prior to the visits, and hypoglycemia status since the last dose of study drug.

10.8.2. Insulin Degludec

A dosing algorithm (adapted from Riddle et al. 2003) will be used by investigators for initiating and adjusting insulin degludec to target an FG ≤100 mg/dL (<5.6 mmol/L) for patients to achieve glycemic goal.

In situations where patient safety is a concern or where dose adjustments have not had the desired therapeutic effect, investigators may make increased or decreased adjustments to the dose of insulin degludec recommended by the dose-adjustment algorithm and have to document the clinical rationale for the deviation as well as inform Lilly medical per email.

At the time of site visit or telephone visit, the investigator will assess the patient's glycemic control for the previous week and, if necessary, inform the patient about any needed dose adjustment. The dose will be based on the patient's BG value. Adherence to the dosing algorithm provided for this study is mandatory from Visit 3 (randomization) up to Visit 20 (Week 26), inclusive. Dose increases may be made at weekly intervals and no sooner than 5 days following the last dose increase. In some cases, patient visits could occur sooner than 5 days apart due to the allowable visit window; however, there should be no dose increase if at least 5 days have not elapsed since the previous dose increase. In contrast, the insulin degludec dose may be reduced at any time on the judgment of the investigator. Any deviations from this guidance must be supported by clinical evidence and after consultation with Lilly Medical.

Insulin dose algorithms have been reviewed by Strange (2007). The insulin degludec dose increase algorithm is adapted from Riddle et al. 2003 and will be determined based on the definition of what is termed the "Algorithm FG." The Algorithm FG is the median of the FG (determined from SMBG) of Days 5, 6, and 7 since the last insulin dose increment. If the

interval since the last dose adjustment has been longer than 7 days, the dose increase is determined by the median of the FG of the last 3 days. If the patient only measured their FG on 2 of the last 3 days, then the lesser of those 2 FG values should be used as the Algorithm FG. If only 1 FG measurement is available for the last 3 days, then the investigator should use his/her discretion in determining whether there should be a dose adjustment based on that single FG value.

As it is desired to achieve glycemic goals in as many patients as possible, contingencies are provided to accommodate prespecified protocol visits and to increase the dose of insulin degludec in a timely manner. Therefore, if the last dose increment was 5 days previous, then the dose increment is determined by the Algorithm FG, which is the lesser of the 2 FG values from Day 4 and Day 5. If the dose increment was 6 days previous, then the Algorithm FG is the lesser of the 2 FG values from Day 5 and Day 6. In both of these cases, if only 1 of the 2 FG values is available, then the investigator should use his/her discretion in determining whether there should be a dose adjustment based on that single FG value.

The dose increase algorithm is defined as follows:

- If the Algorithm FG is 101 to 120 mg/dL (5.6 to 6.7 mmol/L), increase the dose by 2 U
- If the Algorithm FG is 121 to 140 mg/dL (6.8 to 7.8 mmol/L), increase the dose by 4 U
- If the Algorithm FG is 141 to 180 mg/dL (7.9 to 10.0 mmol/L), increase the dose by 6 U
- If the Algorithm FG is >180 mg/dL (10.0 mmol/L), increase the dose by 8 U

The treat-to-target FG is ≤100 mg/dL (<5.6 mmol/L). The insulin degludec dose will not be increased if any SMBG was documented at ≤70 mg/dL (<3.9 mmol/L) at any time in the preceding week. Dose decreases of 2 to 4 U per adjustment may be permitted if multiple episodes of hypoglycemia with SMBG ≤70 mg/dL (<3.9 mmol/L) were recorded, if severe hypoglycemia (requiring assistance) occurred, or if any SMBG was documented at ≤54 mg/dL (≤3.0 mmol/L) in the preceding week.

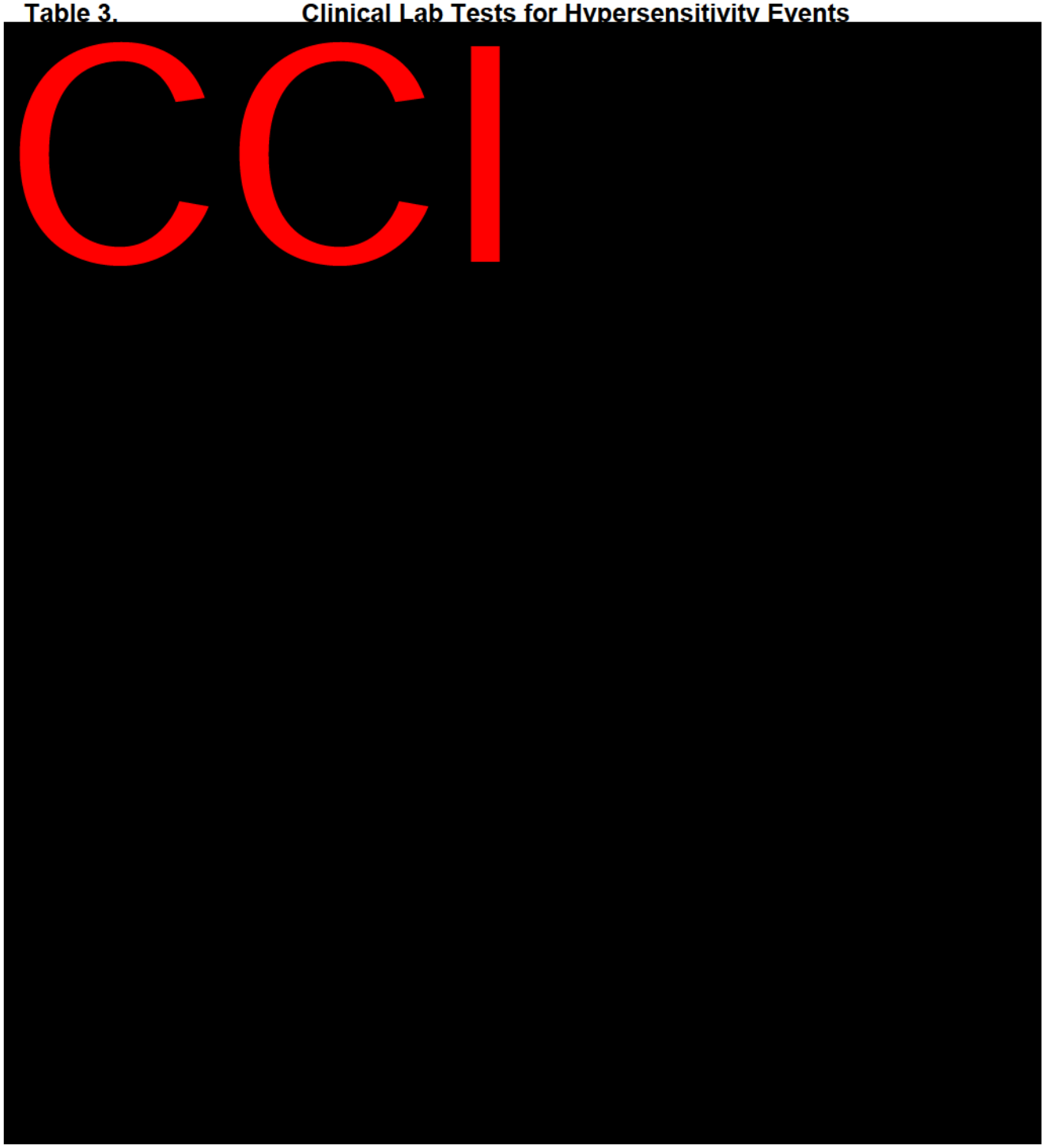
10.9. Appendix 9: Recommended Laboratory Testing for Hypersensitivity Events

Guidance for laboratory assessments for hypersensitivity events:

Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected.

- Collect sample after the participant has been stabilized, and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

Table 3. Clinical Lab Tests for Hypersensitivity Events



10.10. Appendix 10: Changes to Study Procedures due to the COVID-19 Pandemic or Natural Disasters

Remote Visits during the Study

If COVID19- or natural disaster-related travel or shelter-in place restrictions are requested by local/regional authorities or for other reasons related to the pandemic or natural disasters which make it impossible for the participant to travel to the study site for the mandatory titration visits, mitigations are required to ensure safe and timely dosing of study participants.

The study site must receive prior approval by Lilly for either site mobile visits performed by trained site personnel or visits performed by a qualified home nursing service provider organized by the sponsor, with video-conferencing ability, to replace the on-site visits.

Protocol procedures, including blood draws, data-downloads, participant (re-) education, study drug dose selection and study drug dosing may be performed at the participants' home by qualified personnel until travel or other restrictions are lifted.

The allowed visit windows can be extended based on advice from Lilly Medical in this exceptional case to allow more flexibility in performing the home visits.

Early Discontinuation Procedures:

If a participant is quarantined or contracts COVID-19 or is unable to attend the visit for other reasons during the course of the study and therefore mobile visits cannot be organized, study treatment must be discontinued early and dosing decisions for the alternative treatment are allowed to be performed by telephone.

Study supplies for blood glucose monitoring as well as alternative treatments will be provided to the participant until the end of the safety follow-up period (6 weeks after the last dose of LY3209590 or 5 weeks after the last dose of insulin degludec). If circumstances permit, efforts may be made to obtain an immunogenicity blood sample after this follow-up. After the end of the safety follow-up period, study supplies have to be returned or disposed as directed by the study team.

Participants have to continue to enter their blood glucose, hypoglycemia and insulin dose information into their electronic diaries to give the investigative site continued remote access to these data. After termination of study treatment, LY3209590/insulin degludec should be replaced by the previously used basal insulin. CCI [redacted] Therefore, a slow up-titration of another basal insulin is necessary to prevent hypoglycemia due to overlapping insulin action after the discontinuation of LY3209590. During this remote up-titration, no insulin should be dosed until the study participant's median fasting glucose over any 7-day period increases to >120 mg/dL, and then daily basal insulin would be initiated and adjusted based on fasting glucose. Study participants assigned to the insulin degludec treatment group will switch to the basal insulin used before entering the study. If insulin degludec was the pre-study basal insulin, they can continue with the same dose used until the study intervention discontinuation. If they switch to another basal insulin (e.g., insulin glargine), study participants should inject a daily dose which is 20% lower than the last dose of insulin degludec used before the study intervention discontinuation and titrate under remote supervision of the investigator using the country-

specific label for their pre-study basal insulin. In case remote visits are impossible, the participant must be hospitalized for a safe transition to an alternative antidiabetic treatment.

Replacement of Study Participants

The dropout rate will be monitored regularly during the study. If the dropout rate is over 15% prior to completion of 12 weeks of treatment, additional participants may be enrolled to ensure approximately 190 participants complete 12 weeks of treatment.

Documentation

The sites must identify and document the details of how all participants and visits were affected by the COVID-19 pandemic restrictions.

10.11. Appendix 11: Abbreviations

Term	Definition
ADA	anti-drug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
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 participants are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CGM	continuous glucose monitoring
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

CV	cardiovascular
DKA	diabetic ketoacidosis
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EAS	efficacy analyses set
ECG	electrocardiogram
ED	early discontinuation
EDC	electronic data capture system
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ET	Early termination
FFA	free fatty acids
FG	fasting glucose
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IMP	Investigational Medicinal 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.
INR	international normalized ratio

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
ISR	injection site reaction
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 (i.e., 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
MAD	multiple-ascending dose
MDI	multiple daily injections
MMRM	mixed-effect model for repeated measurements
NAFLD	non-alcoholic fatty liver disease
NIM	non-inferiority margin
NIMP	Non-investigational Medicinal Product
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
SAD	single-ascending dose
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SMBG	self-monitoring blood glucose
SOA	schedule of activities
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TE	treatment-emergent
ULN	upper limit of normal
UK	United Kingdom
US	United States
WOCBP	woman of childbearing potential

10.12. Appendix 12: Protocol Amendment History

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

Amendment [c]: 14 August 2020

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The amendment provides information to reflect and reinforce investigational medical device requirements absent in the initial study protocol for Algorithm 2. These requirements are consistent with country regulations where Algorithm 2 will be used.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 1.2. Schema Section 4.1.1. Study Visits Section 6.1. Study Interventions(s) Administered	Addition of language regarding randomization	Clarify that randomization distribution may vary based on country due to removal of randomization into LY3209590 Algorithm 2 (digital) treatment for the European Union (EU)
Section 1.3 Schedule of Activities	Addition of product complaint review in AE/SAE review	Product complaint review was added to ensure alignment with Lilly guidance
Section 2.3. Benefit/Risk Assessment	Addition of language related to LY3209590 Algorithm 1 (paper) and LY3209590 Algorithm 2 (digital)	Additions to clarify regulatory designation of LY3209590 Algorithm 1 (paper) and LY3209590 Algorithm 2 (digital)
Section 2.3.1. Protocol Risk Mitigation Features for Investigational Algorithm 2	Addition of language for protocol risk mitigation	Summarization of key risk mitigations for the protocol including investigational medical device
Section 4.1.1. Study Visits	Updated wording describing Algorithm 2	Clarification of Algorithm 2 as an investigational individualized accruing data algorithm
Section 6.1. Study Interventions(s) Administered	Addition of language describing Algorithm 1 and Algorithm 2	Clarification and description of algorithms
Section 6.1.2.3. Management of Patients with Severe, Persistent Hyperglycemia during Treatment Period	Addition of language related to transient hyperglycemia	Provide acknowledgment of the potential for transient hyperglycemia and guidance for management during transition period from prestudy basal to LY3209590
Section 6.1.3. Medical Devices	Addition of language for Algorithm 2	Algorithm 2 was added based on regulatory feedback and classification as a medical device
Section 6.2. Preparation/Handling/Storage/ Accountability	Addition of language for accountability and access	Description of labeling and appropriate access controls by authorized trained personnel to meet regulatory requirements
Section 8.3.8. Product Complaints	Addition of required section	Product complaint section added to align with Lilly template and guidance

Section # and Name	Description of Change	Brief Rationale
Section 9. Statistical Considerations	Clarifications throughout	Clarifications and corrections provided to ensure consistency with the statistical analysis plan
Section 9.2 Sample Size Determinations	Revised language related to statistical power	Language added to reflect the change in statistical power resulting from removal of Algorithm 2 from the EU
Section 10.1.1. Regulatory and Ethical Considerations	Addition of language related to emergency circumstances	Clarification of guidance during emergency circumstances requiring prior approval of Lilly for regulatory compliance
Section 10.3.3. Definition of an Unanticipated Adverse Device Effect (UADE)	Addition of section related to unanticipated adverse device effect (UADE)	Guidance on definitions and procedures for handling UADEs
Section 10.8.1. LY3209590 Algorithm 1 (paper algorithm)	Addition of language for investigators	Clarified guidance for investigators contacting Lilly Medical to be consistent with guidance provided for Algorithm 2
Section 10.8.2 LY3209590 Algorithm 2 (digital algorithm)	Addition of language related to dosing and input of data for Algorithm 2	Clarification for investigators on the use of Algorithm 2
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized

Amendment [b]: 12 June 2020

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This provides guidance if COVID-19 related local restrictions impact the participant's ability to attend their onsite study visits as originally scheduled.

Section # and Name	Description of Change	Brief Rationale
Section 10.10 Appendix 10	Added Appendix 10: Changes to Study Procedures due to the COVID-19 Pandemic or Natural Disasters	Mitigation if COVID-19 related restrictions make it impossible for the participant to travel to sites for originally scheduled visits.

Amendment [a]: 08 April 2020

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment addresses Food and Drug Administration (FDA) feedback.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Moved text from under 'Notes' for the 12-lead ECG to footnote d	To include all information relevant to the ECG assessment under one footnote
1.3. Schedule of Activities	Updated text specifying PK sample collection in participants randomized to LY3209590	To better reflect that PK samples were only collected for participants randomized to the LY3209590 group
1.3. Schedule of Activities	Added text regarding the assessment of C-peptide under 'Notes' section	To better reflect the assessment of C-peptide during screening and lead-in
1.3. Schedule of Activities	Added 'X' at Visit 3 for the procedure 'Review diary data and make dose individualization assessment'	Corrected an error: initial dose selection based on the diary entries between V2 and V3 has to be done at V3
1.3. Schedule of Activities	Updated footnotes d and e to accommodate the language in the notes section for the 12-lead ECG and to indicate that PK samples were not to be collected for participants in the insulin degludec treatment group	To streamline presentation of all relevant information under the footnotes and to better reflect that PK samples were only collected for participants randomized to the LY3209590 group
1.3. Schedule of Activities	Added footnote f to 'Study participant CGM training' to specify that the patients will be fitted with Dexcom G6® for CGM monitoring	Per regulatory feedback
3. Objectives	Deleted 'recurrence' for hypoglycemic events from the endpoints for the tertiary/exploratory objective of exploring the quality of glycemic control of LY3209590 compared with insulin degludec using CGM	Correction of an error
4.1.1. Study Visits, 5.1. Inclusion Criteria, 8.2.4. Self-monitoring of Blood Glucose (SMBG)	Included the CGM system name 'Dexcom G6'	Per regulatory feedback
4.3. Justification for Dose	Deleted 'after consultation with Lilly Medical' in the statement regarding dose alterations recommended by dose adjustments algorithms, under the discretion of investigators. Added text regarding documentation required in case of deviation from the algorithm-recommended dose	Corrected an error: prior consultation with Lilly Medical is not required for the investigator for dose alterations of LY3209590
5.1. Inclusion Criteria	Added that C-peptide needs to be assessed to be ≤0.30 nmol/L at screening or before randomization	To clarify that an additional C-peptide evaluation can also be performed, if required, at Visit 2, before randomization
5.1. Inclusion Criteria	Changed 'insulin levemir' to 'insulin detemir' in inclusion criterion 6 in the current protocol	For consistency with using the generic name

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Added the lower threshold of 5.6% to the HbA1c range for inclusion in the study	Per regulatory feedback
5.1. Inclusion Criteria	Added text to specify the dosing regimen of insulin prior to screening	Per regulatory feedback
5.2. Exclusion Criteria	Updated the exclusion criteria to explicitly exclude women of childbearing potential who are not using adequate contraception, pregnant women, women intending to become pregnant, or lactating women	Per regulatory feedback
5.2. Exclusion Criteria	Updated the exclusion criterion regarding glucocorticoid use (exclusion criterion 29 in the current protocol) to correct the duration of systemic therapy to be considered chronic to 14 days. This is consistent with Section 6.5.2	Corrected text to be consistent with Section 6.5.2
5.2. Exclusion Criteria	Updated exclusion criteria numbering due to the addition of the exclusion criteria per regulatory feedback	Update in formatting
6.1.2.1. Standards of Medical Care	Added the statement, "Standards of prevention of persistent hyperglycemia and ketone monitoring must be followed during the course of the study to prevent DKA"	Per regulatory feedback, to further clarify the steps/mitigate the risk of hyperglycemia and DKA when starting LY3209590 or transitioning to other therapies (at the end of the trial)
6.1.2.2. Management of Increased Hypoglycemia Risk	Replaced 'confirmed' with 'documented' hypoglycemia from the definition of increased risk of hypoglycemia Added the definition of documented hypoglycemia	Per regulatory feedback
6.4 Study Intervention Compliance	Updated text regarding IP accountability	To better reflect the process for IP accountability
7.1.1 Permanent Discontinuation from Study Treatment	Added text for discontinuation from following occurrence of a systemic hypersensitivity reaction	To clarify better the circumstances under which participants will be discontinued from the IP
8.3.7.1 Hypoglycemia	Deleted 'ED2' as one of the last visits	ED2 is not necessarily the last study visit if patient continues the study without IP
8.3.7.1. Hypoglycemia	Amended text regarding the reporting of hypoglycemia	To clarify how information regarding hypoglycemia is to be collected
8.3.7.1. Hypoglycemia	Deleted text describing the thresholds for analysis.	These thresholds will be used for analyses, and do not need to be included in the protocol. The thresholds for algorithms are updated in Section 10.8.1.
8.3.7.3. Systemic Hypersensitivity Reactions	Added a section on systemic hypersensitivity as adverse events of special interest	To update the protocol with systemic hypersensitivity as an adverse event of special interest

Section # and Name	Description of Change	Brief Rationale
8.4. Treatment of Overdose	Updated the text to provide guidance regarding the management of overdose with LY3209590	Per regulatory feedback
8.5. Pharmacokinetics	Updated the text to clarify that PK samples were not to be collected for participants randomized to insulin degludec	To better reflect that PK samples were only collected for participants randomized to the LY3209590 group
9.3. Populations for Analyses	Updated the description of the pharmacokinetic population to indicate that these participants have at least 1 evaluable PK sample	To clarify better the inclusion pf patients in the pharmacokinetic population
9.4.6.3. Hypoglycemia Episodes	Amended text to clarify that hypoglycemia will be analyzed according to the definitions in the American Diabetes Association classification system	To explain the analysis of hypoglycemia
10.1.6. Data Quality Assurance	Replaced 'captured' with 'entered by patient' to clarify that hypoglycemic events will be entered by patients in the eCOA	To clarify the text regarding data collection for hypoglycemic events
10.2. Appendix 2	Updated the text to clarify that the investigators must document their review of each laboratory safety report and updated the footnotes	To correct errors, add information, and improve readability
10.8.1. Appendix 8	Updated the text regarding the LY3209590 algorithm 1 (paper algorithm)	Per regulatory feedback
10.9. Appendix 9	Added an appendix to describe recommended laboratory testing for hypersensitivity events	To update the protocol with systemic hypersensitivity as an adverse event of special interest
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described

Abbreviations: ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; ED2 (visit) = Early Discontinuation 2 (visit); IP = investigational product; PK = pharmacokinetic.

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