

I8H-MC-BDCM Clinical Protocol

A Phase 2, Randomized, Open-Label Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants with Type 2 Diabetes Mellitus Previously Treated with Basal Insulin

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Safety and Efficacy of LY3209590 in Study Participants  
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Basal Insulin**

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Basal Insulin-Fc (LY3209590)

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Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 31-Aug-2018 GMT

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## 1. Synopsis

### Title of Study:

A Phase 2, Randomized, Open-Label Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants with Type 2 Diabetes Mellitus Previously Treated with Basal Insulin

### Rationale:

LY3209590 is a long-acting insulin receptor agonist being developed for the treatment of type 2 diabetes mellitus (T2DM). This Phase 2 study of LY3209590 will evaluate the effects of LY3209590 on glycemic control using 2 different dose individualization strategies compared with insulin degludec in study participants previously treated with basal insulin.

### Objective(s)/Endpoints:

Objectives	Endpoints
<p>Primary</p> <ul style="list-style-type: none"> <li>To investigate the efficacy of LY3209590 arms in study participants with T2DM</li> </ul>	<ul style="list-style-type: none"> <li>HbA1c change from baseline to Week 32</li> </ul>
<p>Secondary</p> <p><u>Efficacy:</u></p> <ul style="list-style-type: none"> <li>To investigate the efficacy of LY3209590 compared with insulin degludec in study participants with T2DM</li> </ul> <p><u>Safety:</u></p> <ul style="list-style-type: none"> <li>To investigate the safety of LY3209590 compared with insulin degludec in study participants with T2DM</li> </ul> <p><u>Pharmacokinetics:</u></p> <ul style="list-style-type: none"> <li>To characterize the PK of LY3209590 in study participants with T2DM</li> </ul>	<ul style="list-style-type: none"> <li>HbA1c change from baseline to Week 12 and 32</li> <li>Fasting glucose change from baseline to Weeks 12 and 32</li> <li>Insulin dose change from baseline to week 12 and 32</li> <li>Incidence and Rate of nocturnal and documented symptomatic hypoglycemia events during the treatment period</li> <li>Incidence of treatment-emergent serious adverse events</li> <li>Body weight change from baseline at Weeks 12 and 32</li> <li>LY3209590 population-based parameters, such as, AUC within dosing interval at Weeks 12 and 32</li> </ul>

Abbreviations: AUC = area under the curve; HbA1c = hemoglobin A1c; PK = pharmacokinetics; T2DM = type 2 diabetes mellitus

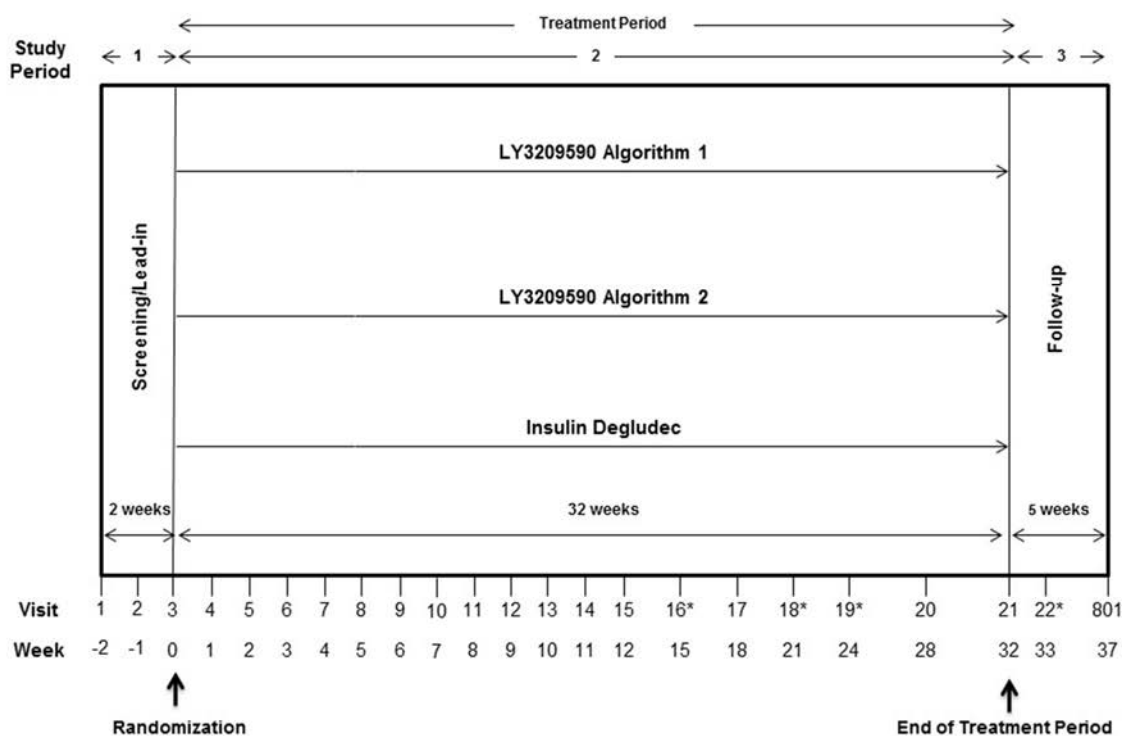
**Summary of Study Design:**

Study I8H-MC-BDCM (BDCM) is a multicenter, randomized, open-label, comparator-controlled Phase 2 study with 3 study periods: 2-week screening, 32-week treatment period, and 5-week safety follow-up period. The study is designed to evaluate the efficacy and safety of LY3209590 compared to insulin degludec in study participants with T2DM. The primary endpoint will be hemoglobin A1c (HbA1c) change from baseline to 32 weeks.

**Treatment Arms and Duration:**

Study participants will be randomized in a 1:1:1 ratio to one of two dosing algorithms of LY3209590 or insulin degludec.

Figure BDCM.1 illustrates the study design.



\*phone visits

**Figure BDCM.1. Illustration of study design for Clinical Protocol I8H-MC-BDCM.**

**Number of Study Participants:**

A total of 536 study participants with T2DM previously treated with basal insulin will be screened. Approximately 375 study participants will be randomized in a 1:1:1 ratio to

LY3209590 in one of two dosing algorithms (125 study participants in each treatment arm) or insulin degludec (125 study participants).

To ensure the safety of the screened study participants, a continuous glucose monitoring system will be used during the course of exposure to the investigational product, to alert study participants in case of expected or evident hypoglycemia.

### **Statistical Analysis:**

#### Efficacy Analysis:

The primary efficacy outcome is HbA1c change from baseline to Week 32 for the LY3209590 arms.

#### Safety Analysis:

The full analysis set (FAS), which includes all data, regardless of rescue medication use or early stop of study medication, will be used for safety analyses. Both the overall and the pairwise comparisons of each LY3209590 arm versus insulin degludec will be reported for these safety analyses.

Safety measures include liver biomarkers alanine aminotransferase (ALT), hypoglycemia, vital signs (blood pressure [BP] and pulse rate), body weight, treatment-emergent adverse events (TEAEs including serious adverse events [SAEs] and adverse events of special interest [AESI]), laboratory measures (including anti-LY3209590 antibodies), and electrocardiograms (ECGs). Summary statistics will be presented by treatment for the safety measures.

The summary statistics for continuous variables will be sample size, mean, standard deviation (SD), median, minimum, and maximum.

The summary statistics for categorical variables will be sample size, frequency, and percentage.

Exposure to each therapy during the treatment period of the study will be calculated for each study participant and summarized by treatment group.

Additional pharmacokinetics (PK)/ pharmacodynamic (PD) analyses, such as concentration-response for glucose and safety laboratory data, may be performed upon review of the data.

## 2. Schedule of Activities

**Table BDCM.1. Schedule of Activities**

Procedure	Screening and Lead-in		Treatment Period																			Follow-up				ET	Notes <sup>a</sup>	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>	803 <sup>c</sup>			
<b>eCRF Visit Number</b>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>	803 <sup>c</sup>			
<b>Weeks</b>	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	28	32	33	37					
<b>Visit window, days</b>	±7	±3		±2	±2	±3	±2	±2	±3	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3					
Informed consent	X																											
Inclusion and exclusion criteria	X																											
Randomization			X <sup>a</sup>																									
Study participants may resume pre-study insulin																						X						
<b>Clinical Assessments</b>																												
Height	X																											
Body weight <sup>a</sup>	X	X	X			X			X						X	X				X	X		X	X	X	X	X	See Section 9.1.4
Blood pressure and pulse rate <sup>a</sup>	X	X	X			X			X						X	X				X	X		X	X	X	X	X	See Section 9.4.3
Demography	X																											
Medical history (includes substance usage <sup>a</sup> and history of CV disease)	X																											Substances: (drugs, alcohol, tobacco and caffeine)

Procedure	Screening and Lead-in		Treatment Period																			Follow-up			ET	Notes <sup>a</sup>			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>			803 <sup>c</sup>		
eCRF Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>	803 <sup>c</sup>				
Weeks	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	28	32	33	37						
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						
Pre-existing conditions	X	X																											
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 <sup>d</sup>			X <sup>d</sup>			X <sup>d</sup>						X <sup>d</sup>		X <sup>d</sup>				X <sup>d</sup>		X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	For screening visit, collect a single, local ECG	
Hypoglycemia events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE/SAE review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Will include injection site inspections
<b>Laboratory Assessments</b>																													
LY3209590 PK			X <sup>e</sup>	X	X	X	X	X	X	X	X				X		X				X		X	X	X	X	X	See Section 9.5	
Fasting		X	X			X			X						X		X				X	X		X	X	X	X		
Serum pregnancy test (WCBP only) <sup>a</sup>	X																											See Section 5.1 Central lab	

Procedure	Screening and Lead-in		Treatment Period																			Follow-up			ET	Notes <sup>a</sup>					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>			803 <sup>c</sup>				
<b>eCRF Visit Number</b>	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>	803 <sup>c</sup>			
<b>Weeks</b>																															
<b>Visit window, days</b>	±7	±3		±2	±2	±3	±2	±2	±3	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3					
Urine pregnancy test (WCBP only)			X																				X		X		X	X		Local lab	
Urinalysis	X																						X		X	X	X	X			
Chemistry panel <sup>a</sup>	X	X	X						X						X		X						X	X		X	X	X	X	Visit 2: glucose, AST, ALT, GGT only	
Pancreatic Amylase	X																														
Lipase	X																														
Hepatitis B	X																														
HbA1c	X		X						X						X		X						X	X			X		X		
Hematology	X		X						X						X		X						X	X		X	X	X	X		
FSH	X																													Female study participants only	
eGFR	X														X								X			X					
HDL, LDL		X	X												X								X		X	X	X	X			
Free fatty acid, triglycerides		X	X			X			X						X		X						X		X	X	X	X		Collected in fasting state	
C-peptide			X			X			X						X								X		X	X	X	X		Collected in fasting state	
LY3209590 anti-drug antibodies <sup>a</sup>		X					X			X					X								X		X	X	X	X		See Section 9.4.7	



Procedure	Screening and Lead-in		Treatment Period																			Follow-up			ET	Notes <sup>a</sup>
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>		
eCRF Visit Number	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	28	32	33	37			
Weeks	±7	±3		±2	±2	±3	±2	±2	±3	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3				
Pharmacogenetic sample			X																							
Biomarker stored sample (plasma/serum)			X						X						X		X					X	X	X	X	
Ancillary Supplies/ Diaries/ Investigational Product																										
Study participant training/ education <sup>a</sup>		X																								Includes diabetes counseling, hypoglycemia (9.2.2.1), FPG profiles, diary completion, CGM sensor replacement
Study participant CGM Training			X																							

Procedure	Screening and Lead-in		Treatment Period																		Follow-up				ET	Notes <sup>a</sup>				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>			803 <sup>c</sup>			
eCRF Visit Number	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>	803 <sup>c</sup>		
Weeks																														
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	±3	±3					
CGM Sensor Insertion			X																											Sensor inserted and system started by study participant under site personal supervision
Distribute CGM sensor <sup>f</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X				
CGM data download				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X			
Dispense supplies and diary		X	X			X			X				X			X		X			X	X				X				
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Record diary and CGM data (including FPG <sup>g</sup> , hypoglycemia)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Review diary and CGM data (including FPG <sup>g</sup> , hypoglycemia)				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	Screening and Lead-in		Treatment Period																			Follow-up			ET	Notes <sup>a</sup>					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>			803 <sup>c</sup>				
eCRF Visit Number	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>	803 <sup>c</sup>			
Weeks																															
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	±3	±3	±3					
Record recent study drug dose/dose adjustment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense IP			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study personnel administer IP at site			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Train study participant in IP administration						X			X			X	X	X	X		X					X									
Study participant or study personnel administer at site <sup>a</sup>													X	X	X	X		X					X								Weeks 13 - 31 (except Week 18): study participants may self-administer injection at home or have injection done at site

Procedure	Screening and Lead-in		Treatment Period																		Follow-up				ET	Notes <sup>a</sup>
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 <sup>b</sup>	17	18 <sup>b</sup>	19 <sup>b</sup>	20	21	22 <sup>b</sup>	801 <sup>c</sup>	802 <sup>c</sup>		
eCRF Visit Number	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	28	32	33	37			
Weeks	±7	±3		±2	±2	±3	±2	±2	±3	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	±3	±3	±3				
Visit window, days																										
LY3209590 accountability (collect used and unused IP)																	X			X	X			X		X
Insulin degludec accountability (collect unused pens)				X	X	X	X	X	X	X	X	X	X	X	X		X			X	X			X		X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BG = blood glucose; CGM = continuous glucose monitoring; CV = cardiovascular; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; ET = early termination; FPG = fasting plasma glucose; FSH = follicle stimulating hormone; GGT = gamma-glutamyl transferase; HbA1c = glycated hemoglobin; HDL = high density lipoprotein; IP = investigational product; IWRS = interactive web-response system; LDL = low density lipoprotein; LY = LY3209590; PK = pharmacokinetics; SAE = serious adverse event; SMBG = self-monitoring of blood glucose; WCBP = women of child bearing potential.

<sup>a</sup> Indicates that a relevant note is included in the last column.

<sup>b</sup> Phone visit

<sup>c</sup> Study activities at Visits 802 and 803 are identical to Week 32 (Visit 21) and Visit 801, respectively.

<sup>d</sup> A triplicate, central ECG will be performed prior to the time of each PK sampling. These ECGs will be performed in a fasting state.

<sup>e</sup> Collect 2 PK samples: one predose and one approximately 2 hours postdose or as late as possible just prior to departure from the site.

<sup>f</sup> Study participants will replace CGM sensor according to system label at home and will be trained for this procedure at Visit 3. At each visit study participants will be supplied with the necessary sensors for the respective interval.

<sup>g</sup> Occurs the week prior to the scheduled dose adjustment check. FPG should be collected daily for **CCI** prior to dose adjustment for calculating average FPG.

## 3. Introduction

### 3.1. Study Rationale

LY3209590 is a long-acting insulin receptor agonist with a half-life enabling weekly dosing developed for the treatment of type 2 diabetes mellitus (T2DM). This Phase 2 study of LY3209590 will:

Evaluate the effects of LY3209590 on glycemic control using 2 different dose individualization strategies compared with insulin degludec in study participants previously treated with basal insulin.

### 3.2. 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 T2DM. A once weekly insulin receptor agonist has the potential to increase willingness to initiate and compliance with an insulin therapy in study participants with T2DM. In real life only about a quarter of these study participants reach the target HbA1c of 7% (Blonde L et al. 2014) 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 be a higher risk for hypoglycemic events or a longer duration of such events. The recently launched long acting insulin degludec has nevertheless 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 as compared to insulin degludec while very closely monitoring glycemic profiles using continuous glucose monitoring.

Data from the single-ascending dose (SAD) study demonstrated clear evidence of glucose lowering in study participants with T2DM at single doses ranging from CCI. The pharmacokinetics (PK) of LY3209590 following single doses demonstrated prolonged time-action profile to support once-weekly administration. LY3209590 reached maximum concentration approximately CCI after dosing, followed by a mean elimination half-life of approximately CCI in study participants with T2DM. With a long elimination half-life, following a weekly fixed-dose regimen, PK steady-state is reached in approximately CCI and results in approximately CCI concentration than after single dose. However, using a loading dose strategy that is CCI, CCI on PK modeling. PK following a single loading dose CCI during the first week was demonstrated to be comparable to concentration profile at Week CCI based on preliminary data in the multiple ascending dose (MAD) study. 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. Additional information about LY3209590 can be found in the Investigator's Brochure.

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.

### **3.3. Benefit/Risk Assessment**

The data from the SAD study and the ongoing MAD study (Studies BDCA and BDCB) 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. An additional risk based on preclinical data could be an elevation of liver aminotransferases. To date, this has not been observed in study participants or healthy volunteers exposed to LY3209590 for up to 6 weeks.

More information about the known and expected benefits, risks, Serious Adverse Events (SAE) and reasonably anticipated AEs of LY3209590 are to be found in the Investigator's Brochure.

## 4. Objectives and Endpoints

Table BDCM.2 shows the objectives and endpoints of the study.

**Table BDCM.2. Objectives and Endpoints**

Objectives	Endpoints
<b>Primary</b> <ul style="list-style-type: none"> <li>To investigate the efficacy of LY3209590 arms in study participants with T2DM</li> </ul>	<ul style="list-style-type: none"> <li>HbA1c change from baseline to Week 32</li> </ul>
<b>Secondary</b> <u>Efficacy</u> <ul style="list-style-type: none"> <li>To investigate the efficacy of LY3209590 compared with insulin degludec in study participants with T2DM.</li> </ul>	<ul style="list-style-type: none"> <li>HbA1c change from baseline to Week 12 and 32</li> <li>Fasting glucose change from baseline to Weeks 12 and 32</li> <li>Insulin dose change from baseline to week 12 and 32</li> </ul>
<u>Safety</u> <ul style="list-style-type: none"> <li>To investigate the safety of LY3209590 compared with insulin degludec in study participants with T2DM.</li> </ul>	<ul style="list-style-type: none"> <li>Incidence and rate of hypoglycemia</li> <li>Incidence and rate of nocturnal hypoglycemia</li> <li>Incidence and rate of severe hypoglycemia</li> <li>Incidence of treatment-emergent serious AEs</li> <li>Body weight change from baseline at Weeks 12 and 32</li> </ul>
<u>Pharmacokinetics</u> <ul style="list-style-type: none"> <li>To characterize the PK of LY3209590 in study participants with T2DM</li> </ul>	<ul style="list-style-type: none"> <li>LY3209590 population-based parameters, such as, AUC within dosing interval at Weeks 12 and 32</li> </ul>
<b>Exploratory</b> <ul style="list-style-type: none"> <li>To investigate the safety and tolerability of LY3209590 compared with insulin degludec in study participants with T2DM.</li> </ul>	<ul style="list-style-type: none"> <li>Treatment-emergent AEs</li> <li>Discontinuation of IP due to AEs</li> <li>Clinical laboratory results</li> <li>Systematic assessment of injection site reactions</li> <li>Insulin dose during follow up period</li> <li>Incidence and rate of hypoglycemia during treatment and follow-up period</li> <li>Incidence and rate of daytime hypoglycemia</li> <li>Liver aminotransferase change from baseline to Weeks 12 and 32</li> </ul>
<ul style="list-style-type: none"> <li>To explore quality of glycemetic control compared with insulin degludec using CGM</li> </ul>	<ul style="list-style-type: none"> <li>Glucose time in target range, time in hyperglycemia, time in hypoglycemia</li> <li>Duration and recurrence of hypoglycemic events</li> </ul>
<ul style="list-style-type: none"> <li>To establish the relationships between dose/exposure and key safety and efficacy measures for LY3209590</li> <li>To evaluate dose/exposure and key safety and efficacy measures following different dosing</li> </ul>	<ul style="list-style-type: none"> <li>LY3209590 exposure-response relationships with fasting glucose, SMBG, HbA1c, hypoglycemia, body weight, blood pressure, pulse rate, and QTc,</li> <li>Relationship of LY3209590 dose to efficacy</li> </ul>

Objectives	Endpoints
regimens	(HbA1c, fasting glucose) and safety (hypoglycemia).
<ul style="list-style-type: none"> <li>• To characterize the effects of LY3209590 on exploratory PD biomarkers</li> <li>• To explore the development of LY3209590 ADAs</li> </ul>	<ul style="list-style-type: none"> <li>• Plasma lipids (cholesterol, LDL, HDL, triglycerides)</li> <li>• Biomarkers of lipolysis (FFA)</li> <li>• The frequency of antibody formation to LY3209590 will be determined.</li> </ul>

Abbreviations: ADA = antidrug antibodies; AE = adverse events; AUC = area under the curve; CGM = continued glucose monitoring; FFA = free fatty acids; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; IP = investigational product; LDL = low density lipoprotein; PD = pharmacodynamics; PK = pharmacokinetics; QTc = corrected QT interval; SMBG = self-monitoring of blood glucose; T2DM = type 2 diabetes mellitus.



## 5. Study Design

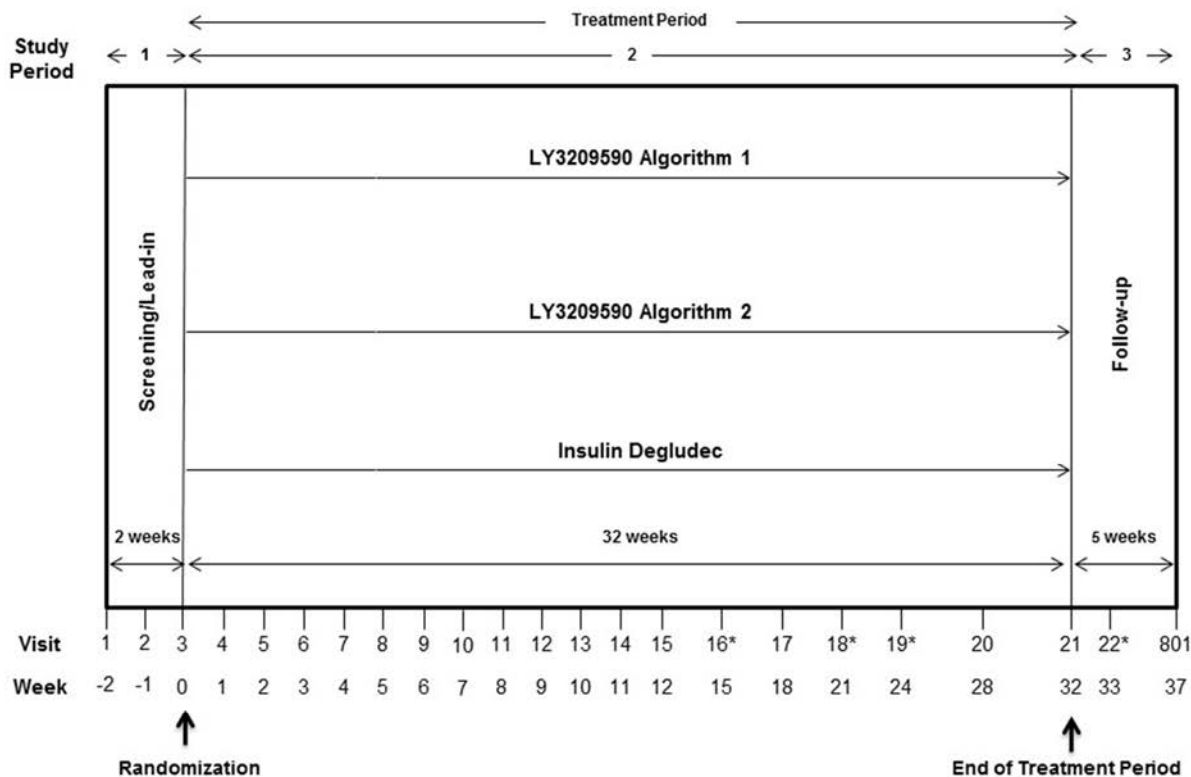
### 5.1. Overall Design

Study I8H-MC-BDCM (BDCM) is a multicenter, randomized, open-label, comparator-controlled Phase 2 study with 3 study periods. A total of 536 study participants with T2DM, previously treated with basal insulin will be screened. Approximately 375 study participants will be randomized in a 1:1:1 ratio to LY3209590 in one of two dosing algorithms ([Appendix 7](#)) or insulin degludec (modified Riddle algorithm, [Section 7.2.1.2](#)). The study is designed to evaluate the efficacy and safety of LY3209590 compared with insulin degludec.

The study will consist of 3 periods: 2-week screening, 32-week treatment period, and 5-week safety follow-up period.

Study governance considerations are described in detail in [Appendix 3](#).

[Figure BDCM.2](#) illustrates the study design.



**Figure BDCM.2. Illustration of study design for Clinical Protocol I8H-MC-BDCM.**

### **5.1.1. 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 6.1 and 6.2). During this period, study participants will be trained on disease monitoring and disease management procedures, study diaries and study procedures. Visit-specific subject diaries will be dispensed at Visit 2 and as specified in the Schedule of Activities (Section 2) for future visits.

During the lead-in period, study participants should continue the same formulation and dose of their previously used insulin therapy, as well as allowable oral antidiabetic medications (OAMs - sulfonylureas [SU] and meglitinides, dipeptidyl peptidase-4 [DPP-IV] inhibitors, sodium-glucose cotransporter 2 [SGLT-2] inhibitors, biguanides, and alpha-glucosidase inhibitors) in order to allow reliable assessment of hemoglobin A1c (HbA1c) at randomization (see Section 7.7.2).

#### **Continuing Glucose Monitoring:**

A standard system will be used for continuing glucose monitoring (CGM) in an unblinded mode. The study participants will wear this device beginning on Day 0 at randomization, as shown in the Schedule of Activities (Section 2). In addition, all study participants will be allowed to use their blood glucose meters for additional blood glucose testing or for calibration of the CGM system if deemed necessary, or for taking self-monitored plasma glucose (SMPG) measurements during the outpatient period.

At the randomization visit (Visit 3), study participants will be trained on the use of the CGM device, CGM sensor replacement, interpretation of CGM based blood glucose 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 3 activities.

#### **Study Period 2: Treatment Period**

##### **Randomization (Week 0 [Visit 3])**

Study participants who continue to be eligible for the study will be randomized to 1 of the treatment arms. All measures to be performed at Visit 3 (see Schedule of Activities, Section 2) should be done prior to injection of the study participant's assigned investigational product (IP) to ensure that appropriate baseline measurements are obtained. Urine and serum pregnancy tests will be done before IP administration. The study participant will begin IP, if the urine pregnancy test is negative. If the result of the serum pregnancy test is positive, the study participant will be discontinued from the study (see Section 8.2).

Study personnel will inject the first dose of IP at the study site. The PK samples and ECGs at randomization must be collected as described in the Schedule of Activities (Section 2).

Following randomization, study participants will participate in a 32-week treatment period. During Weeks 1 to 8, site personnel will administer IP, and study participants will receive education and training on how to self-administer IP. 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 that occur. During Weeks 9 to 12, IP will be reconstituted and administered at the site by the study participant, under supervision of trained site personnel to assure that the study participant is capable of self-administration. During Weeks 13 to 31 IP will be self-administered by the study participant at home, or optionally can be administered once weekly by site personnel. Information on self-injection can be reviewed as necessary throughout the study.

LY3209590 will be administered as one of two dose individualization algorithms ([Appendix 7](#)).

Insulin degludec will be self-administered daily by study participants after a training and first administration under site personnel supervision on Day 1 according to a modified Riddle algorithm (Section [7.2.1.2](#)).

### **General considerations**

Study procedures will be performed as listed in the Schedule of Activities (Section [2](#)).

In order 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 [2](#)).

Study participants will continue to use concomitant OAMs throughout the treatment period: discontinuation or changes to dose are not permitted, except in situations where dose adjustment or complete discontinuation is required per country-specific label or when allowed per study protocol (for further details see Section [7.7.2](#)).

Study participants will be instructed to document fasting plasma glucose (FPG) each day by using the values displayed on their CGM device after waking or using a finger-stick glucose measurement. In addition, two 6-point SMPG profiles (prior to and 2 hours after the morning, midday, and evening meals) should be documented on non-consecutive days in the week prior to the required visits noted in the Schedule of Activities using CGM-based glucose values, (Section [2](#)).

Study participants who develop severe, persistent hyperglycemia based on prespecified thresholds (see Section [7.8.2.3](#)) will receive a new glucose-lowering intervention (or rescue therapy) based on clinical judgment of the investigator (see [Table BDCM.4](#)). Study participants who need rescue therapy will continue on IP in the trial until they complete all study visits.

### **Study Period 3: End-of-Treatment and Safety Follow-Up, Visits 21, 801, 802, and 803**

All randomized study participants should have a comprehensive efficacy and safety evaluation approximately 1 week after the last dose of IP and a safety follow-up visit approximately 6 weeks after the last dose of IP. During the safety follow-up study period, study participants will continue CGM and may be treated with an appropriate glucose-lowering regimen (see [Table BDCM.4](#)) if necessary. Study participants will also be required to return any remaining study diaries and used or unused IP to the investigative site.

Study participants who *complete the treatment period* will have a comprehensive End-of-Treatment efficacy and safety assessment (Week 32; Visit 21) approximately 1 week

after the last dose of IP and a safety follow-up assessment (Visit 801) approximately 6 weeks after the last dose of IP and 5 weeks after their End-of-Treatment assessment (Visit 801). During the safety follow-up study period, study participants will continue CGM, and may be treated with an appropriate glucose-lowering regimen (see [Table BDCM.4](#)) if necessary. Study participants will also be required to return any remaining study diaries and used or unused IP to the investigative site.

Study participants who *discontinue IP prior to completion* of the study for any reason should also have a comprehensive End-of-Treatment efficacy and safety assessment (Visit 802) approximately 1 week after the last dose of IP or as soon as reasonably possible thereafter, and should have a safety follow-up assessment (Visit 803) approximately 6 weeks after the last dose of IP. Study activities at Visits 802 and 803 are identical to Week 32 (Visit 21) and Visit 801, respectively.

Study participants who discontinue IP prior to study completion will be encouraged to remain in the study and to complete any scheduled study procedures that occur after their safety follow-up (Visit 803). Study participants remaining in the study will receive an appropriate rescue glucose-lowering regimen. [Table BDCM.4](#) provides details on the use of glucose-lowering medications for rescue and for treatment of acute conditions.

Study 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, study participants will perform procedures listed in the Schedule of Activities (Section 2).

## 5.2. Number of Participants

Approximately 536 participants will be screened to achieve 375 randomized and 300 evaluable participants for an estimated total of 100 evaluable participants per treatment group.

## 5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last study participant.

## 5.4. Scientific Rationale for Study Design

This study will evaluate 2 dosing regimens of LY3209590 in study participants with T2DM who are already treated with a daily basal insulin. Study participants will take their last dose of daily basal insulin the day prior to randomization. Treatment will be initiated after randomization with either LY3209590 or insulin degludec as an active comparator. As LY3209590 has a long half-life, a weekly dosing regimen is expected to reach steady-state of PK in over **CCI** of treatment. Therefore, the withdrawal of a daily basal insulin would result in loss of glycemic control for several weeks after randomization. Therefore, a loading-dose regimen approach, by which an exposure to achieve comparable glycemic control to prior basal insulin dose can be achieved **CCI**, followed by **CCI** starting at Week 2 to maintain steady-state exposure. Subsequently, dose adjustments can be made in the initial

dose individualization phase of the study. See [Appendix 7](#) and section [7.2.1.2](#) for dosing and administration details. The 32-week treatment duration is planned as the slow dose escalation approach is necessary for LY3209590 to achieve near comparable glycemic efficacy to prior daily basal insulin.

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.

### 5.5. Justification for Dose

Following a once-weekly SC administration of LY3209590, the time to reach steady-state glucose level is estimated between 4 to 10 weeks based on the long half-life of LY3209590. Therefore, CCI weekly dose and gradual CCI dose adjustment is recommended for LY3209590 dosing regimen. CCI of LY3209590 is based on prior basal insulin dose converting the dose in units into mg of LY3209590 and is based on PK/PD modeling of limited SAD and MAD data. Dose adjustments are based on average of prior CCI 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.

The starting dose for insulin degludec is the same dose as the basal insulin that the study participant used previously before entering the study. The study participant will start a titration phase based on fasting glucose achievements under this therapy and the presence of hypoglycemia or other safety concerns. The titration will be performed each week. The dose adjustment algorithm is adapted from the well-established Riddle algorithm (Section [7.2.1.2](#)) under discretion of the investigator.

Guidance is provided for the two algorithms used in dosing LY3209590. There is also guidance for conversion of prior basal insulin dose to LY3209590 loading dose, as well as dosing suggestions for investigators based on fasting glucose and hypoglycemia of the study participant ([Appendix 7](#)).

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 algorithms are needed. As additional data emerges, guidance from the Sponsor on these dosing algorithms may be modified ([Appendix 7](#)).

## 6. Study Population

The study population will consist of study participants with T2DM previously treated with basal insulin. Eligibility of study participants will be based on the results of the following assessments performed at screening (approximately Week -2) as described in the Schedule of Activities (Section 2). The nature of any conditions present at the time of the initial screening and any pre-existing conditions will be documented in the electronic case report form (eCRF).

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

### 6.1. Inclusion Criteria

Study participants are eligible to be included in the study only if they meet all of the following criteria at screening:

#### Type of Study Participant and Disease Characteristics

- [1] Have a diagnosis of T2DM according to the WHO criteria treated with basal insulin
- [2] Are receiving  $\geq 10$  units of insulin per day or  $\leq 1.5$  units per kilo of insulin per day

#### Study Participant Characteristics

[3a] Male study participants:

Men with female partners of childbearing potential must agree to use at least one effective method of contraception ([Appendix 5](#)) for the duration of the study and for at least 15 weeks (approximately 3 half-lives plus 90 days) following the last dose of IP.

[3b] Female study participants:

Women not of child-bearing potential may participate and include those who are:

- Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or
- Postmenopausal, defined as:
  - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either:
    - a) Cessation of menses for at least 1 year, or
    - b) At least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone  $>40$  mIU/mL (local laboratory); or
  - A woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
  - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Women of childbearing potential must agree to remain abstinent (if this is their preferred and usual lifestyle), use 1 highly effective method of contraception, or a combination of 2 effective methods of contraception ([Appendix 5](#)) starting at screening and continuing for 15 weeks (approximately 3 half-lives plus 90 days) after the last dose of IP:

- Test negative for pregnancy at screening based on serum pregnancy test, followed by a negative urine pregnancy test within 24 hours prior to randomization (Visit 3)
- Not be breastfeeding

[4] Are at least 18 years of age at screening

[5] Have a baseline HbA1c value of 6.5% to 10%, inclusive, at screening

[6] Have been treated with a stable regimen of insulin glargine, insulin levemir or insulin degludec with or without OAM therapy for 3 months prior to screening and be willing to continue stable dosing throughout the study. Acceptable OAMs include up to 3 of the following:

- DPP-4 inhibitors
- SGLT-2 inhibitors
- biguanides
- alpha-glucosidase inhibitors
- sulfonylureas

Note: All OAMs must be used in accordance with the corresponding local product label at the time of screening.

[7] Have a body mass index (BMI) between 20 and 45 kg/m<sup>2</sup>, inclusive with no significant weight gain or loss in the past 3 months ( $\geq 5\%$ )

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

- learn how to self-inject treatment, as required for this protocol; visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the IP; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the IP;
- maintain a study diary, as required for this protocol;
- wear only the CGM device supplied for use in this study, without interruption, as required in the Schedule of Activities (Section 2) and Section 9.4.5;
- must have a normal wake/sleep pattern such that midnight to 0600 hours will reliably reflect a usual sleeping period.

## Informed Consent

- [9] Are able and willing to give signed informed consent

## 6.2. Exclusion Criteria

### Medical Conditions

- [10] Have a diagnosis of type 1 diabetes mellitus or latent autoimmune diabetes
- [11] Are receiving prandial insulin, insulin mixtures, or twice daily basal insulin; also if receiving <10 units of insulin per day or >1.5 units per kilo of insulin per day
- [12] Have a history of greater than 1 episode of ketoacidosis or hyperosmolar state/coma requiring hospitalization in the 6 months prior to screening
- [13] Have had any episodes of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to screening
- [14] Cardiovascular (CV): have had any of the following CV conditions: acute myocardial infarction, New York Heart Association Class III or IV heart failure ([Appendix 6](#)), or cerebrovascular accident (stroke)
- [15] Gastrointestinal: have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (e.g., Lap-Band®) prior to screening
- [16] 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., study participants with NAFLD are eligible for participation), and/or have elevated liver enzyme measurements, as determined by the central laboratory at screening and as indicated below:
- Total bilirubin >2x the upper limit of normal (ULN), or
  - ALT/serum glutamic pyruvic transaminase (SGPT) >2.5x ULN, or
  - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) > 2.5x ULN
- [17] Renal: have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m<sup>2</sup>, calculated by the Chronic Kidney Disease-Epidemiology equation, as determined by the central laboratory at screening
- [18] Have experienced significant weight loss or gain (>5%) in body weight, 3 months prior to screening (Visit 1)
- [19] 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
- [20] Have known hypersensitivity or allergy to any of the study medications or their excipients



- [21] Have any other serious disease or condition (for example, known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, would pose a significant risk to the study participant, preclude the study participant from following and completing the protocol, or interfere with the interpretation of safety, efficacy, or PD data
- [22] 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)
- [23] Have a significant history of alcoholism or drug abuse as judged by the investigator or consuming more than 24 g of alcohol per day for males or more than 12 g of alcohol per day for females
- [24] Have fasting Triglyceride levels above 400 mg/dl or non-fasting Triglycerides above 600 mg/dl at screening.

**Prior/Concomitant Therapy**

- [25] Drugs which may significantly affect glycemic control (e.g., niacin [allowed if <1.0g/day], bile acid sequestrants)
- [26] Are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, or inhaled preparations) or have received such therapy for >14 days within the month preceding screening
- [27] Are currently taking or have taken within the 3 months preceding screening, prescription or over-the-counter medications to promote weight loss. Study participants 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
- [28] 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**

- [29] 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
- [30] 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
- [31] Have previously completed or withdrawn from this study or any other study investigating LY3209590.

**Other Exclusions**

- [32] 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
- [33] Are Eli Lilly and Company (Lilly) employees or are employees of any third-party involved in the study who require exclusion of their employees

**6.3. Lifestyle Restrictions**

Per the Schedule of Activities (Section 2), 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. Study participants 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.

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 at Visit 3 (see Section 2). These medications are also not allowed at any time during the treatment period. If started after randomization, they should be immediately withdrawn. In addition, study participants 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.

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

**6.4. Screen Failures**

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 informed consent form (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.

## 7. Treatments

### 7.1. Treatments Administered

LY3209590 will be administered once weekly as subcutaneous (SC) injections. Each study participant will receive 1 injection each week, as described in [Table BCDM.3](#). SC injections of LY3209590 will be administered rotating between left and right abdominal regions and upper and lower quadrants. During the first 8 weeks, treatment will be administered by the study staff, while study participants receive education and training on how to reconstitute and self-administer LY3209590. During Weeks 9 to 12, LY3209590 will be reconstituted and administered at the site by the study participant under supervision of the site personnel to assure that the study participant is capable of self-administration. During Weeks 13 to 31, LY3209590 will be self-administered by the study participant at home, or optionally can be administered once weekly by site personnel.

Insulin degludec will be administered once daily at approximately the same time of day, rotating between left and right abdominal regions and upper and lower quadrants.

Study participants will receive treatment with LY3209590 by 1 of 2 algorithms. [Table BCDM.3](#) shows the treatment regimens. See Section [7.2.1](#) for details on dosing algorithms and Section [7.8.1](#) for transitioning to treatment after study completion.

**Table BCDM.3. Treatment Regimens**

Regimen	Dose Randomization through Week 32
LY Dose Algorithm 1	LY injection
LY Dose Algorithm 2	LY injection
Insulin degludec	Insulin degludec injection

Abbreviations: LY = LY3209590.

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

- explaining the correct use of the investigational agent(s) to the study participant
- 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

#### 7.1.1. Packaging and Labeling

LY3209590 will be provided as CCI of lyophilized powder in a vial. Reconstitution with sterile water or 0.9% sodium chloride will be required prior to dosing.

Insulin degludec will be provided as a 100 U/mL solution in a 3-mL prefilled pen.

All IP materials must be stored at the investigative sites, according to the instructions provided on the product label, in a locked and secure place. Insulin must not be frozen. Unused study treatments will remain in a locked and secured place at the investigative sites, according to instructions provided on the product label, or according to written instruction from the Sponsor, until returned to the Sponsor or destroyed.

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

## 7.2. Method of Treatment Assignment

Study participants who meet all criteria for enrollment will be randomized to open-label treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign open-label IP to each study participant. 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 country, baseline HbA1c (<8.5%, ≥8.5%), country, SU (yes/no), and baseline BMI (<30, ≥30). The randomization scheme will be performed using IWRS, which will ensure balance between treatment arms.

### 7.2.1. Selection and Timing of Doses

Study participants will be randomly assigned to a LY3209590 dose via Algorithm 1 or Algorithm 2. The doses will be administered at approximately the same time and day each week. The actual date and time of all dose administrations will be recorded in the subject's diary (or study participant's medical record when administered at the site) and in the eCRF. Insulin degludec will be administered same time each day, adjusted per modified Riddle algorithm (Section 7.2.1.2).

If a study participant misses a scheduled dose of LY3209590, it should be administered as 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. Study participants who miss a dose of insulin degludec should inject their daily dose during waking hours upon discovering the missed dose. Instruct study participants to ensure that at least 8 hours have elapsed between consecutive insulin degludec injections (Tresiba USPI).

#### 7.2.1.1. LY3209590 Algorithms

Guidance is provided for conversion of prior basal insulin dose to LY3209590 loading dose and initial weekly dose (Appendix 7). Dose adjustment is based on study participants' prior fasting glucose and hypoglycemic events (Appendix 7). Alterations to the doses recommended by these dose adjustment algorithms are allowed in situations where study participant safety is a concern or where adjustments do not show the desired therapeutic effect, after consultation with Lilly.

As additional data emerges, the guidance from the Sponsor on these dosing algorithms may be modified.

#### **7.2.1.2. Insulin Degludec**

Insulin degludec will be initiated at the same dose as the total daily basal insulin dose already administered, or in accordance with the locally approved product labeling if different.

Thereafter, a dosing algorithm adapted from Riddle et al. 2003 will be used by investigators for adjusting insulin degludec to target an FBG  $\leq 100$  mg/dL ( $< 5.6$  mmol/L) in order for study participants to achieve glycemic goals of an HbA1c value  $< 7.0\%$  and a pre-prandial capillary plasma glucose (PG) between 71 and 130 mg/dL (3.9 to 7.2 mmol/L; ADA 2011). In situations where study participant safety is a concern or where dose adjustments have not had the desired therapeutic effect, investigators may only make increased adjustments to the dose of insulin degludec recommended by the dose-adjustment algorithm after consultation with Lilly.

At the time of site visit or telephone 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 blood glucose value. Adherence to the dosing algorithm provided for this study is required from Visit 3 (randomization) up to Visit 21 (Week 32, inclusive) and will be monitored periodically by the study team. Dose increases may be made at weekly intervals and no sooner than 5 days following the last dose increase. In some cases, study participant 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 approved by Lilly.

The insulin dose increase algorithm is adapted from Riddle et al. 2003 and will be determined based on the definition of what is termed the "Algorithm FBG." The Algorithm FBG is the median of the FBG (determined from self-monitoring of blood glucose [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 FBG of the last 3 days. If the study participant only measured their FBG on 2 of the last 3 days, then the lesser of those 2 FBG values should be used as the Algorithm FBG. If only 1 FBG 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 FBG value.

As it is desired to achieve glycemic goals in as many study participants 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 prior, then the dose increment is determined by the Algorithm FBG, which is the lesser of the 2 FBG values from Day 4 and Day 5. If the dose increment was 6 days prior, then the Algorithm FBG is the lesser of the 2 FBG values from Day 5 and Day 6. In both of these cases, if only 1 of the 2 FBG values is available, then the investigator should use his/her discretion in determining whether there should be a dose adjustment based on that single FBG value.

The dose increase algorithm is defined as follows:

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

The treat-to-target FBG is  $\leq 100$  mg/dL ( $< 5.6$  mmol/L). The insulin dose will not be increased if any SMBG was documented at  $\leq 70$  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  $\leq 70$  mg/dL ( $< 3.9$  mmol/L) were recorded, if severe hypoglycemia (requiring assistance) occurred, or if any SMBG was documented at  $\leq 54$  mg/dL ( $\leq 3.0$  mmol/L) in the preceding week.

### 7.3. Blinding

This study is an open-label study. Investigators, site personnel and study participant will be aware of the treatment allocation. Due to the differences in administration of LY3209590 (once weekly) and the comparator (degludec given once daily) blinding the treatment assignment would be impossible for these titratable medications.

### 7.4. Dosage Modification

Dosing will be individualized based on FBG. See [Appendix 7](#) and section [7.2.1.2](#) for details of dose modification.

### 7.5. Preparation/Handling/Storage/Accountability

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

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

The study site must store LY3209590 and insulin degludec under refrigerated conditions (2°C to 8°C) until use. Insulin must not be frozen. In-use storage conditions must be followed according

to the storage conditions provided on the label. Study participants will be provided with cartons containing the required number of vials or pens at clinic visits as shown in the Schedule of Activities (Section 2). They will receive insulated bags with cooling gel packs for use in transporting the cartons from the site to home. Dry ice should not be used for cooling.

Unused medications will remain locked and securely stored under refrigerated conditions (2°C to 8°C) at the investigative site until returned to the Sponsor or destroyed according to written instruction from the Sponsor.

## 7.6. Treatment 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 will be entered into the study participant diary by the study participant and reviewed by the site personnel at each study visit. This information will be collected in the eCRF;
- IP accountability will be checked according to the Schedule of Activities (Section 2). 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 study participant's adherence to the visit schedule, compliance with the concomitant OAM requirements and other medication guidance (Section 7.7), completion of study diaries, results of SMBG, and any other parameters the investigator considers necessary. Study participants considered to be poorly compliant with their medications and/or study procedures (for example, missed visits or specific diagnostic tests) will receive additional training and instructions, as required.

## 7.7. Concomitant Therapy

Study participants will be permitted to use concomitant medications that they require during the study, except excluded medications described in Section 6.2 (Exclusion Criteria) and Section 7.7.1 to Section 7.7.4 below. In addition, certain permitted medications (for example, treatments for blood pressure or dyslipidemia) described in Section 7.7.5 and Section 7.7.6 may be continued, but not changed, during the course of the study.

Investigative site staff will inform study participants 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. Any additional medication initiated during the course of the study (including OTC drugs, such as aspirin) must be documented, and the name of the drug and the date(s) of administration must be recorded in the study participant's diary and on the "Concomitant Medications" section of the eCRF. In addition, for permitted concomitant glucose-lowering agents, the dosage will also be documented and collected.

Non-study medications taken by study participants 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.

Table BDCM.4 provides a summary of criteria for use of concomitant medications that may interfere with planned assessments during the study.

**Table BDCM.4. Criteria for Use of Concomitant Medications that may Interfere with Efficacy and Safety Assessments in Study BDCM**

Drug Class	Use During Screening/Lead-In	Conditions for Use After Randomization		
		Acute therapy <sup>a</sup>	Rescue therapy	During Safety Follow-up Period
Drugs with approved weight loss indication <sup>b</sup>	Excluded	N	N/A	N
Systemic glucocorticoid therapy <sup>c</sup>	Excluded except for acute therapy <sup>a</sup>	Y	N/A	N
<b>Antihyperglycemia medications</b>				
GLP-1 RAs	Excluded	N	Y	Y
DPP-4 inhibitors	Permitted	N	Y	Y
SGLT2 inhibitors	Permitted	N/A	Y	Y
Insulins and insulin mixtures	Daily basal insulins Permitted. All others Excluded except for acute therapy <sup>a</sup>	Y	Y	Y
Meglitinides	Excluded	N	N	Y
Alpha-glucosidase inhibitors	Permitted	N	Y	Y
Sulfonylureas	Permitted	N	N	Y
Thiazolidinediones	Excluded	N	N	N
Metformin <sup>d</sup>	Permitted	N	Ye	Y

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

- a Acute therapy = treatment for up to 14 days.
- b Includes Saxenda® (liraglutide 3.0 mg), Xenical® (orlistat), Meridia® (sibutramine), Sanorex® (mazindol), Adipex-P® (phentermine), Belviq® (lorcaserin), Qsymia® (phentermine/topiramate combination), Contrave® (naltrexone/bupropion) or similar other body weight loss medications including over-the-counter medications (e.g., alli® [orlistat 60 mg capsules]).
- c Does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations;
- d Switching metformin manufacturers is allowed, as long as the dosage is the same. Changing to a metformin formulation with a different action profile (i.e., from short-acting to long-acting metformin) is not permitted.
- e For rescue therapy, metformin dose may be increased if the dose is below maximum approved dose per country-specific label.

### 7.7.1. Antihyperglycemia Medications

Insulin lispro as prandial treatment or insulin degludec are the preferred choice for rescue therapy in study participants randomized to LY3209590 or insulin degludec. The only other glucose-lowering agents allowed as rescue therapy during the study are concomitant metformin,



SLGT2 inhibitors, DPP-4 inhibitors, SU and alpha-glucosidase inhibitors. In addition, insulins other than insulin degludec may be used for short-term (up to 14 days) management of medical emergencies prior to study entry and during the study. Rescue therapy with other glucose-lowering agents, may be medically indicated in certain situations after randomization (Table BDCM.4). These situations are described in Section 7.8.2.3 (severe, persistent hyperglycemia) and in Section 8.1.1 (early discontinuation of IP).

If any new glucose-lowering medication is initiated after randomization at Visit 3, other than IP, rescue therapy, or short-term use of insulin for medical emergencies, the study participant will be required to immediately discontinue the medication and the appropriate study deviation report will be generated. Any such violation of the protocol that lasts longer than 14 days will exclude the study participant from the per-protocol (PP) population for analyses.

### **7.7.2. Concomitant Antihyperglycemia Medication**

Study participants treated with metformin in this study must be on a stable dose for at least 3 months prior to screening. The prescreening dose and formulation (short-acting or long-acting) must be maintained from the time of screening through the study participant's last visit, except as required for rescue therapy (Section 7.8.2.3).

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

Dose adjustments of allowable OAM therapy are permitted after randomization (during the treatment period) under the following circumstances:

- situations that require short-term treatment interruption in line with the product labeling for each respective country;
- situations that require dose adjustment or discontinuation per country-specific label, for example, in the case of reduced eGFR;
- in the case of increased hypoglycemia risk during the treatment period (as described in Section 7.8.2.2).

Dose reduction of allowable OAM therapy during the trial should be properly documented.

In study participants who require rescue therapy, dose increase of allowable OAM therapy is permitted, but the dose and the reason for change must be properly documented in the eCRF.

Guidance for treatment during the safety follow-up period is provided in Section 5.1.1 (Study Period 3: Safety Follow-up, Visit 801).

### **7.7.3. 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 7.7). If started after

screening, these medications should be stopped immediately. In addition, study participants 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 6.3).

#### **7.7.4. 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. Study participants who require >14 consecutive days of therapy with these medications after randomization will be excluded from the PP population for analyses.

#### **7.7.5. 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.

#### **7.7.6. Dyslipidemia Medications**

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

### **7.8. Treatment After the End of the Study**

#### **7.8.1. Treatment After Study Completion**

Investigational Product will not be made available to study participants after conclusion of the study

Beginning on the evening of the last treatment visit (Visit 21 [Week 32] or ET visit), study participants will resume their previous basal insulin therapy. As washout of LY may take up to 10 weeks to complete, previous basal insulin therapy will be instituted using the Riddle algorithm as need based on FBG (Section 7.2.1.2.). For example, no insulin would be required until the study participant's blood glucose increases to >100 mg/dL, and then daily basal insulin would be initiated and adjusted based on weekly algorithm FBG.

#### **Study Participants treated with LY3209590:**

Study participants will receive the last injection of LY3209590 at Week 31 of the study and will switch back to their previously used basal insulin after Visit 21. Since LY3209590 has a half-life of approximately CCI of the original insulin dose and CCI of the original insulin dose. Therefore, a slow up-titration of their previously used basal insulin is necessary to prevent hypoglycemia due to overlapping insulin action. The pre-study basal insulin should be started at a dose of 10 I.U. at Visit 22 with a FBG of above 120 mg/dL for 3 consecutive days or as soon as the study participants FBG is above 180 mg/dL for 3 consecutive days. Thereafter, an

up-titration according to the modified Riddle algorithm or any country specific label should be applied.

### **Study Participants treated with Insulin Degludec:**

Study participants assigned to the insulin degludec treatment arm will switch back to their pre-study basal insulin after Visit 21. If their pre-study Basal insulin was insulin degludec they can continue with the same dose used until Visit 21 of the study. If they switch back 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 21 and titrate under supervision of the investigator using the country-specific label for their pre-study basal insulin.

All study participants will continue to wear a continuous blood glucose monitor during the 5-week follow-up period to ensure a safe transition back to their pre-study basal insulin.

## **7.8.2. Special Treatment Considerations**

### **7.8.2.1. Standards of Medical Care**

Investigators and other study team members are expected to treat study participants according to the nationally established standards of care for diabetes management in respective participating countries, except where that treatment would be in conflict with the protocol-provided treatment requirements. If there are no local 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 study participants' participation in this study.

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 study participants, and their caregivers, if applicable, be well-educated about the signs and symptoms of hyperglycemia (for example, severe thirst, dry mouth, frequent micturition, or dry skin) and hypoglycemia (for example, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders). Study participants should be instructed to contact the investigative site in the event of severe, persistent hyperglycemia or severe hypoglycemia between study visits.

### **7.8.2.2. Management of Increased Hypoglycemia Risk**

The risk associated with the allowable OAMs is low since all but the sulfonylureas are non-secretagogues; therefore, clinically relevant increases in the risk of hypoglycemia due to the OAMs are not expected in this trial. The effects of LY3209590 on hypoglycemia are not known and an objective of the study is to assess the risk of hypoglycemia in study participants receiving LY3209590.

The study uses real-time CGM to continuously monitor potential hypoglycemic events. In case of a hypoglycemic event, study participants will be proactively warned by an alarm and are instructed to immediately ingest rapidly absorbable carbohydrates. This safety measure minimizes the risk of severe hypoglycemic events during the complete study duration.

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 symptomatic hypoglycemia within a 1-week period at any time during the treatment period.

In cases where a study participant experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the study participant 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, unexpected increase in exercise).

Study participants fulfilling the definition of increased risk of hypoglycemia should first decrease their OAM dose (especially SU), followed by discontinuation of OAM therapy, if needed. If the study participant continues to experience hypoglycemic events after the discontinuation of OAM therapy, the investigator should reduce the dose according to the appropriate algorithm (Section 7.2.1.2) or discontinue the study participant from IP.

#### **7.8.2.3. Management of Study Participants with Severe, Persistent Hyperglycemia during the Treatment Period**

An additional therapeutic intervention should be considered in study participants who develop severe, persistent hyperglycemia after randomization based on the following criteria (reference FDA Draft Guidance 2016):

- a) average FPG >270 mg/dL (>15.0 mmol/L) over any 2-week period or longer during the first 6 weeks postrandomization; or
- b) average FPG >240 mg/dL (>13.3 mmol/L) over any 2-week period or longer from Week 6 to Week 12 postrandomization; or
- c) average FPG >200 mg/dL (>11.1 mmol/L) over any 2-week period or longer from Week 12 to Week 18 postrandomization.

Investigators should first confirm that the study participant does not have an acute condition causing severe hyperglycemia and, after the first 12 weeks of the study, that the study participant is fully compliant with the assigned therapeutic regimen. The investigator will decide, in collaboration with the responsible clinical research physician (CRP) and in consultation with the study participant, on an appropriate glucose-lowering intervention (rescue intervention) after considering relevant clinical criteria. In general, insulin degludec will be the preferred rescue therapy for study participants assigned to LY3209590. See [Table BDCM.4](#) for allowed medications. Study participants who receive a new intervention for hyperglycemia management should also continue administering IP for the remaining period in the trial.

#### **7.8.2.4. Emergency Situations**

In emergency situations, it may be necessary for study participants to change their dose of OAM and/or be treated with a non-study insulin. This will be allowed for up to 2 weeks total prior to Visit 21 (Week 32). If multiple situations last longer than 2 weeks total prior to Visit 21 (Week 32), a decision to keep the study participant in the study should be made only after consultation between the investigator and the Lilly CRP. The decision should be documented by a note to the investigator's file.

## 8. Discontinuation Criteria

### 8.1. Discontinuation from Study Treatment

#### 8.1.1. *Permanent Discontinuation from Study Treatment*

Possible reasons leading to permanent discontinuation of IP:

- **Subject Decision**
  - the study participant or the study participant's designee, for example, parents or legal guardian requests to discontinue IP.
- **Discontinuation due to a hepatic event or liver test abnormality.**
  - Study 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 study participant meets one of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8X ULN
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio >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%)
- alkaline phosphatase (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, study participants will be discontinued from the IP in the following circumstances:

- if a study participant is inadvertently enrolled and it is determined that continued treatment with IP would not be medically appropriate (see Section 8.1.3)
- if a study participant 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 a study participant is diagnosed by the investigator with acute or chronic pancreatitis
- if a study participant is diagnosed with C-cell hyperplasia or medullary thyroid carcinoma after randomization

- if the investigator or sponsor decides that the study participant 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.

Study participants discontinuing from the IP study treatment prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

Study participants 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.

### **8.1.2. Temporary Discontinuation from Study Treatment**

In certain situations after randomization, the investigator may need to temporarily discontinue (interrupt) IP (for example, due to an AE or a clinically significant laboratory value). If IP interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 9.2 of this protocol. Investigators should inform the Sponsor that IP has been temporarily interrupted. Every effort should be made by the investigator to maintain study participants 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 will be documented in source documents and entered in the eCRF.

### **8.1.3. Discontinuation of Inadvertently Enrolled Study Participants**

If the sponsor or investigator identify a study participant who did not meet enrollment criteria and was inadvertently enrolled, then the study participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the study participant to continue on study treatment. If the investigator and the sponsor CRP agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled study participant to continue in the study with or without treatment with IP. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

## **8.2. Discontinuation from the Study**

Study participants will be discontinued in the following circumstances:

- if a study participant is diagnosed with any type of diabetes mellitus other than T2DM
- if a female study participant becomes pregnant, enrollment in any other clinical study involving an IP 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 study participant should be discontinued from the study
  - if the study 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
- study participant decision
  - the study participant/study participant's designee, for example, parents or legal guardian requests to be withdrawn from the study

Study participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

### **8.3. 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. Site personnel are expected to make diligent attempts to contact study participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

## 9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

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

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

### 9.1. Efficacy Assessments

#### 9.1.1. Primary Efficacy Assessments

The primary efficacy measure is HbA1c change from baseline to Week 32.

#### 9.1.2. Secondary Efficacy Assessments

- HbA1c change from baseline to Week 12
- Fasting glucose change from baseline to Weeks 12 and 32
- Insulin dose change from baseline to week 12 and 32

#### 9.1.3. Appropriateness of Assessments

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 T2DM.

#### 9.1.4. Body Weight

Body weight will be measured at prespecified time points (see Schedule of Activities, Section 2). Study participants 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 2), weight will be measured twice, with the study participant 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.



## 9.2. Adverse Events

Investigators are responsible for monitoring the safety of study participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if the event may be considered an unanticipated benefit to the study participant.

The investigator is responsible for the appropriate medical care of study participants during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the study participant to discontinue the IP before completing the study. The study participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each study participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, IP, via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to IP, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the IP, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a study participant's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

### 9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged in-study participant hospitalization

- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-study participant hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the study participant has signed the ICF and has received IP. However, if an SAE occurs after signing the ICF, but prior to receiving IP, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Study participants with a serious hepatic adverse event should have additional data collected using the eCRF.

Pregnancy (during 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 to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the study participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

#### **9.2.1.1. Suspected Unexpected Serious Adverse Reactions**

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

## 9.2.2. Adverse Events of Special Interest

### 9.2.2.1. Hypoglycemia

Study participants will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (Visit 801 or ET visit). For that purpose, study participants will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect in study diary appropriate information for each episode of hypoglycemia according to the Schedule of Activities (Section 2). Site personnel will enter this information into the eCRF at visits indicated in the Schedule of Activities (Section 2).

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the PG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips) (American Diabetes Association 2005):

- **Documented symptomatic hypoglycemia** is defined as any time a study participant feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).
- **Asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured PG  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).
- **Probable symptomatic hypoglycemia** is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by a PG concentration  $\leq 70$  mg/dL [ $\leq 3.9$  mmol/L]).
- **Severe hypoglycemia** is defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.
- **Total hypoglycemia** is defined as any event meeting the criteria for documented symptomatic hypoglycemia, asymptomatic hypoglycemia, or probable symptomatic hypoglycemia
- Cases of relative hypoglycemia are defined as symptomatic events during which the person reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but a measured PG concentration  $> 70$  mg/dL ( $> 3.9$  mmol/L) is collected.

For additional analysis, hypoglycemia defined as glucose  $< 54$  mg/dL ( $< 3.0$  mmol/L) will also be considered.

If a hypoglycemic event meets the criteria of severe, 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 study participant should receive additional education, if deemed appropriate. Management of increased risk of hypoglycemia is described in Section 7.8.2.2.

#### **9.2.2.2. Allergic/Hypersensitivity Reactions**

All allergic or hypersensitivity reactions, including injection site reactions, will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. 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 8.1.2). 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 8.1.1 for procedures required in this situation.

#### **9.2.3. Adverse Event Monitoring with a Systematic Questionnaire**

Not applicable.

#### **9.2.4. Complaint Handling**

Lilly collects product complaints on investigational products 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.

Study participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

##### **9.2.4.1. Device Complaint Handling**

Any CGM device complaint should be reported via the manufacturer's instructions for device complaints. A 24-hour toll-free number will be provided to the investigative site personnel in the event that either personnel or study participants have questions regarding the device.

#### **9.3. Treatment of Overdose**

Study drug overdose (more than the specified number of injections) will be reported as an AE. In the event of an overdose, refer to the IB for LY3209590 and/or product label.

#### **9.4. Safety**

##### **9.4.1. 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.

#### **9.4.2. Electrocardiograms**

For each study participant, 12-lead digital ECGs, as well as single and triplicate safety ECGs, will be collected according to the Schedule of Activities (Section 2). Study participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs will be performed prior to collection of any blood samples.

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

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 (for example, 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).

#### **9.4.3. Vital Signs**

Sitting blood pressure (BP) and pulse rate will be measured using automated electronic sphygmomanometer according to the Schedule of Activities (Section 2). 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 2). 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.

#### **9.4.4. Self-monitoring of Blood Glucose Using CGM**

A CGM system will be used in this study for self-measurement of plasma glucose equivalents. This system readings will be used for the purpose of monitoring study participant safety (hypoglycemia) and values shown by the system will be used for SMBG documentation. The system will proactively warn study participants of low blood glucose values. Study participants

should record all hypoglycemia related values read on the CGM device in the study diaries provided. Study participants with missing SMBG values may need to be retrained on the importance of SMBG monitoring.

Study participants will be instructed to take a pre-breakfast (fasting) SMBG reading every morning and 4-point SMBG measurements (consisting of fasting, pre-lunch, pre-dinner, and bedtime blood glucose measurements) once weekly throughout the study, and to record all results in diaries. Study participants will also measure FBG as needed to evaluate symptoms of hypoglycemia.

Study participants will be instructed to perform 6-point SMBG 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 2). The 6-point profile consists of pre-meal and 2-hour postprandial SMBG measurements for the morning, midday, and evening meals in 1 day. Pre-meal measurements should be taken before the study participant begins eating the meal. Study participants should record their glucose measurements in their study diaries which are considered source documents and are to be returned to the investigator at each study visit. Values from the 6-point SMBG profiles will be transferred from the diaries and recorded on the eCRFs.

#### **9.4.5. Continuous Glucose Monitoring**

A CGM system will be provided to participating investigative sites. Study-specific training will be provided to investigative site personnel and study participants. The allowed range of the instrument recording is from 40 mg/dL to 400 mg/dL (2.2 mmol/L to 22.2 mmol/L) in the interstitial fluid (Gross et al. 2000). The results of the continuous monitoring will be unblinded to study participants and investigative site personnel and will be downloaded for transfer to Lilly or designee.

The study participants will be thoroughly trained on sensor insertion and usage, and CGM data/alarm interpretation during the randomization visit. Study participants should self-insert the first sensor at Visit 3 and initiate the CGM system under supervision of the trained site personnel. Thereafter, study participants will be provided with the necessary CGM supplies and will self-insert new sensors when alerted by the system.

The CGM device and sensor will monitor study participant glucose levels. Study participants will be unblinded to the real time CGM monitor readouts and alarms, so corrective action can be taken at the site regarding hypoglycemia prevention.

If problems occur with the CGM monitor or sensor, another sensor may be inserted or a replacement monitoring instrument may be used, as long as the CGM procedures and the subsequent visits continue to fall within the allowable time frames. A sensor or monitoring instrument provided specifically for this study must be used when replacing another sensor or CGM monitor.

#### **9.4.6. Laboratory Tests**

For each study participant, laboratory tests detailed in ([Appendix 2](#)) should be conducted according to the Schedule of Activities (Section 2).

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis, and that occur after the study participant receives the first dose of IP should be reported to Lilly or its designee as an AE via eCRF.

#### **9.4.7. Immunogenicity Assessments**

Venous blood samples of approximately 10 mL will be collected to determine antibody production against LY3209590 as specified in the Schedule of Activities (Section 2). To interpret the results of immunogenicity, a PK sample will be collected at the same time points to determine the concentrations of LY3209590. All samples for immunogenicity should be taken predose when applicable and possible. In the event of drug hypersensitivity reactions (immediate or non-immediate), additional blood samples will be collected for anti-drug antibodies (ADA), PK and exploratory hypersensitivity analyses at the following time points, as close as possible to the onset of the event, at the resolution of the event, and 30 ( $\pm 3$ ) days following the event. Exploratory hypersensitivity samples may be analyzed for markers of basophil/mast cell activation (e.g., tryptase), immune complex formation (e.g., C3 levels) and cytokine release (e.g., IL-6) as appropriate for the clinical presentation. 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.

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of LY3209590 at a laboratory approved by the sponsor. For the detection of anti-LY3209590 antibodies, study participant sera samples will be analyzed using a 3-tiered approach. All samples will be assessed in Tier 1 (screening) for possible presence of ADA. Samples found to produce a signal above or equal to the screening cut point will be assessed in Tier 2 to confirm specificity to LY3209590 (confirmation). Any samples confirmed as specific for LY3209590 will be reported as “detected”. All samples below the screening cut point in Tier 1 or not confirmed in Tier 2 will be reported as “not detected”. All “detected” samples in Tier 2 will be assessed in Tier 3 (titer assessment). In vivo laboratory indicators for glycemic control (blood glucose and HbA1c) will be utilized to detect a potential neutralizing effect of ADA against LY3209590.

Treatment-emergent antidrug antibodies (TE-ADA) are defined in Section [10.3.6](#). A risk-based approach will be used to monitor study participants who develop TE-ADA after treatment with LY3209590. Clinically significant TE-ADA will be defined as any TE-ADA at the follow-up visit with:

- A titer  $\geq 1:640$  or increasing ADA titer at follow-up visit.
- An association of TE-ADA with moderate to severe injection site reaction

Study participants who have clinically significant TE-ADA will be followed with ADA testing (every 3 months for up to 1 year after dose) until the titer reaches a plateau/decreases (if increasing) or remains the same/decreases (if high). A PK sample will continue to be collected at each time point at the investigator's discretion.

Samples will be retained for a maximum of 15 years after the last study participant 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 the LY3209590. Any samples remaining after 15 years will be destroyed.

#### **9.4.8. Other Tests**

Not applicable.

#### **9.4.9. Safety Monitoring**

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. Lilly will also review SAEs within the time frames mandated by company procedures. The Lilly CRP will, as appropriate, consult with the functionally independent Global Study participant Safety therapeutic area physician or clinical scientist.

##### **9.4.9.1. Hepatic Safety Monitoring**

If a study participant experiences elevated ALT  $\geq 3X$  ULN, ALP  $\geq 2X$  ULN, or elevated TBL  $\geq 2X$  ULN, liver testing ([Appendix 4](#)) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), 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 medical monitor. 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 serum ALT to  $\geq 5X$  ULN on 2 or more consecutive blood tests
- elevated serum TBL to  $\geq 2X$  ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to  $\geq 2X$  ULN on 2 or more consecutive blood tests
- study participant discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.



## 9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), 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.

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 by the Sponsor, and stored at a facility designated by the Sponsor.

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

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

## 9.6. Pharmacodynamics

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

## 9.7. Pharmacogenomics

### 9.7.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last study participant visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards impose shorter time limits. 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 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

## 9.8. Biomarkers

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

Serum and plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3209590 pathways associated with T2DM, mechanisms of action of LY3209590 and/or research methods, or in validating diagnostic tools or assay(s) related to T2DM.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last study participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. 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.

## 9.9. Health Economics

No health economic outcomes are planned.

## 10. Statistical Considerations

### 10.1. Sample Size Determination

Approximately 375 study participants will be randomized in a 1:1:1 ratio to LY3209590 in one of two dosing algorithms or insulin degludec treatment arms, assuming a 20% dropout rate resulting in approximately 300 total completers at 32 weeks (100 completers per treatment arm). The sample size was calculated based on the statistical power for the primary and liver safety endpoints.

- The 300 completers will provide 90% statistical power to demonstrate the noninferiority of the pooled LY3209590 arms versus insulin degludec for the change in HbA1c from baseline to 32 weeks (assuming non-inferiority margin is 0.4%, the SD is 1.1% and true mean difference is 0%) using two sided t-test at  $\alpha = 0.1$ .

### 10.2. Analysis Sets

For purposes of analysis, the following populations and analysis sets are defined:

Population and Analysis Set	Description
Enrolled	All study participants who sign informed consent
All randomized study participants	All study participants who are randomly assigned a treatment arm
Efficacy analysis set (EAS)	Data for all randomized study participants who received at least one dose of study medication, excluding data after using rescue medication or stopping study medication (last dose date + xx days). In the event of a treatment error, participants will be analyzed according to the treatment they actually received.
Full analysis set (FAS)	Data for all randomized study participants, regardless of titration, stop of study medication, or rescue.

### 10.3. Statistical Analyses

#### 10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the statistical methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the statistical analyses and the justification for the change will be described in the statistical analysis plan (SAP) and/or clinical study report. Additional exploratory analyses of the data may be performed as deemed appropriate. Analyses will be fully detailed in the SAP.

Statistical analyses (including the primary analysis) will be conducted on the efficacy analysis set population. Safety analyses will be performed on the full analysis set.

No adjustments for multiplicity will be performed.

All tests of treatment effects will be conducted at a two-sided alpha level of 0.1 and/or two-sided 90% confidence interval, unless otherwise stated.

The baseline value used for the analyses will be the last scheduled baseline value obtained for each study participant prior to randomization. ALT, AST, and GGT will be average of 3 assessments as baseline.

The analysis of the main secondary efficacy endpoint and possibly other Bayesian analyses may be computed using Fixed and Adaptive Clinical Trial Simulator software. Remaining summaries and analyses will be performed using the SAS System.

### **10.3.2. Treatment Group Comparability**

#### **10.3.2.1. Study Participant Disposition**

Intention-to-treat population will be used for this analysis. All study participants who discontinue the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment. The discontinuation due to AE will be summarized by adverse event and treatment. The percentage of study participants discontinuing from each treatment will be compared using the Fisher's exact test.

#### **10.3.2.2. Study Participant Characteristics**

Intention-to-treat population will be used for this analysis. Demographic and baseline characteristics will be summarized by treatment group. Categorical variables will be summarized by frequencies and percentages. For categorical variables, comparisons between treatment groups will be assessed using a Pearson chi-square test. Continuous variables will be summarized by mean and SD. For continuous variables, comparisons between the treatment groups will be performed using a 1-way analysis of variance with treatment as the fixed effect.

#### **10.3.2.3. Concomitant Therapy**

Intention-to-treat population will be used for this analysis. Listings and summary of concomitant therapies will be provided by treatment group.

#### **10.3.2.4. Treatment Compliance**

Treatment compliance will be listed using all randomized study participants and summarized using the modified intention-to-treat population. For a given study participant, overall compliance for treatment period is defined as, not missing 2 or more consecutive doses of the assigned treatment, or, missing 4 or more at any point in the study. Study participants who miss 4 or more doses at any point during the study will not be included in the efficacy analysis.

Adherence to the dosing algorithm is required from Visit 3 (Randomization) up to Visit 21 (Week 32, inclusive), although the last scheduled opportunity for dose adjustment will occur at Week 31. Adherence to the dosing algorithm will be assessed based on the number and percentage of investigator-reported prescribed doses that do not follow the investigator-calculated algorithm dose, which represent intentional deviation from the algorithm, and the number and percentage of investigator-calculated doses that are not equal to the sponsor-calculated algorithm doses.

### **10.3.3. Efficacy Analyses**

#### **10.3.3.1. Primary Analyses**

The primary efficacy outcome is HbA1c change from baseline to Week 32 for LY arms. The mixed-effect model repeated measures (MMRM) with BMI strata, treatment, visit, SU (Y/N), and treatment-by-visit interaction as fixed effects, HbA1c baseline as a covariate will be used for the analysis. The within-study participant correlation will be modelled through a variance-covariance structure. The dependent variable will be the post-baseline change from baseline values. The unstructured covariance matrix will be selected initially. There will be no explicit missing data imputation as the missing values are handled implicitly by the MMRM model.

#### **10.3.3.2. Secondary Analyses**

The secondary analysis will be performed on the efficacy analysis set. The main secondary efficacy analysis aims to compare LY versus Insulin Degludec with regarding to HbA1c change from baseline at Week 12 and 32. The estimand of interest is the treatment differences in HbA1c at 12 and 32 weeks while the study participants are on study treatment. The efficacy analysis set (EAS) will be used to calculate the mean difference between treatments. Similar MMRM model will be used for the main secondary analysis. The least-squares (LS) mean differences and the standard errors from each imputed sample will be calculated based on the above model, and the final estimation for the means, standard errors, 90% confidence intervals, and p-values will be reported.

A supplementary analysis will be conducted to evaluate the “treatment policy” estimand, which is defined as the treatment differences in HbA1c at 32 weeks with the randomized treatment based on FAS. The estimator is defined as the mean difference between treatments based on FAS. The missing values will be imputed using multiple imputations. The similar MMRM model will be performed on imputed data and inferences will be drawn based on the framework of multiple imputations (Rubin, 1987).

In addition to the main secondary efficacy analysis of HbA1c, the following secondary efficacy outcomes will be analyzed:

- Body weight and change from baseline to 12 and 32 weeks
- Fasting blood glucose and change from baseline at 12 and 32 weeks

The analyses of the HbA1c change, mean weight change, fasting blood glucose change and SMBG change from baseline will be conducted through MMRM similar to that of the primary efficacy outcome. The corresponding baseline will be used in the model instead of the baseline HbA1c levels. The MMRM model will also include a term for the HbA1c stratification group. The treatment p-value will be used as evidence of difference between LY3209590 and insulin degludec, while the comparison of LS means versus insulin degludec (unadjusted for multiple comparisons) and its 90% confidence interval will provide magnitude and significance of this difference.

### 10.3.3.3. Exploratory Analyses

LY3209590 concentration data will be analyzed using standard nonlinear mixed-effects modeling implemented on the NONMEM software. The relationships between LY3209590 dose and/or concentration and efficacy, tolerability, and safety endpoints will be characterized, such as fasting glucose, SMBG, HbA1c, hypoglycemia, body weight, blood pressure, pulse rate, and corrected QT interval (QTc).

Additionally, the impact of intrinsic and extrinsic study participant factors such as age, weight, gender and renal function on PK and/or PD parameters may be examined as needed. If ADA titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3209590 PK or any relevant PD parameters will also be examined.

### 10.3.4. Safety Analyses

The FAS will be used for safety analyses. Both the overall and the pairwise comparisons of each LY3209590 arm versus insulin degludec will be reported for these safety analyses.

Safety measures include liver biomarkers (ALT), hypoglycemia, vital signs (BP and pulse rate), body weight, TEAEs (including SAEs and AEs of special interest), laboratory measures (including anti-LY3209590 antibodies), and ECGs. Summary statistics will be presented by treatment for the safety measures.

The summary statistics for continuous variables will be sample size, mean, SD, median, minimum, and maximum.

The summary statistics for categorical variables will be sample size, frequency, and percentage.

Exposure to each therapy during the treatment period of the study will be calculated for each study participant and summarized by treatment group.

In addition, the following safety outcomes will be analyzed on the efficacy analysis set population:

- ALT change from baseline to 12 and 32 weeks

The change from baseline of ALT will be analyzed using MMRM model. In addition, Bayesian model will be used to conduct the same analysis. The corresponding baseline will be used in the model instead of the baseline HbA1c levels. The MMRM model will also include a term for the HbA1c stratification group.

Additional analyses, such as concentration-safety laboratory plots, may be performed, if warranted upon review of the data.

#### 10.3.4.1. Adverse Events

Adverse Events will be listed by study participant, actual term, preferred term, severity, and relationship to the treatment. 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 study 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 TEAEs will be presented. The incidence of study 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 CV AEs will be listed by study participant, and if there are a sufficient number of cases they may be summarized by treatment group.

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

Discontinuations due to AE and TEAEs will be listed by study participant and summarized by treatment group.

#### **10.3.4.2. Vital Signs**

Descriptive statistics for the actual measurements and changes from baseline for systolic and diastolic blood pressure and pulse rate will be presented by treatment arm and visit.

Corresponding figures may be presented.

Vital signs will be analyzed using a similar MMRM-based model.

#### **10.3.4.3. Hypoglycemia Episodes**

The rate and incidence analyses will be analyzed. Details will be provided in the SAP. Statistical analysis will be performed for overall total hypoglycemia, documented symptomatic hypoglycemia and nocturnal hypoglycemia. Listing of hypoglycemic episodes and severe hypoglycemic episodes will be presented by visit for each study participant. If a sufficient number of severe hypoglycemic episodes are reported, then incidence summaries and analysis similar to incidence of hypoglycemic episodes will be included.

#### **10.3.4.4. Laboratory Measures**

Summary statistics will be provided for laboratory measures, by treatment group and by visit.

A listing of laboratory measurements for individual study participants will be presented 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, including safety off-treatment visits.

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 laboratory) will be compared to the baseline observation by examining the proportion of study participants whose test values are within and outside the reference ranges.

#### **10.3.4.5. Electrocardiograms**

A listing of the individual and averaged ECG measurements, by study participant, will be produced. This will include the time elapsed between the onset of ventricular depolarization and the end of ventricular repolarization (QT) corrected values described below.

Descriptive statistics for the absolute measurements, outliers, and changes from baseline for selected ECG parameters will be presented by treatment arm. These include the ECG heart rate, and the following intervals: QT and QT corrected for heart rate using Fridericia's formula (QTcF).

In addition, LY3209590 concentration-response analysis of QTcF results will be performed as well as a categorical analysis of absolute and change from baseline QTc intervals. Any additional ECG analyses will be detailed in the SAP.

#### **10.3.4.6. Adverse Events of Special Interest**

Hypoglycemia, major adverse cardiovascular events, and injection site reaction are defined as AESIs.

Descriptive statistics for the AESIs will be presented by treatment group and visit. Continuous responses will be summarized using sample size, mean, SD, median, minimum, and maximum, while categorical responses will be summarized using frequencies and percentages.

If necessary, continuous AESIs will be analyzed using a similar MMRM-based model.

Categorical AESIs will be analyzed using a logistic regression analysis with fixed effects of treatment, and HbA1c strata.

### **10.3.5. 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 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 subject factors, such as age, weight, gender and renal function on PK and/or PD parameters, may be examined. Should ADA be detected from immunogenicity testing, its impact on LY3209590 PK or any relevant PD parameters will also be examined.

### **10.3.6. Evaluation of Immunogenicity**

The frequency of antibody formation to LY3209590 will be determined. Treatment-emergent ADA 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). For the TE ADA+ study participants, the distribution of maximum titers will be described.



The relationship between the presence of antibodies, antibody titers, and clinical parameters (for example, AEs, efficacy measures) may be assessed.

### **10.3.7. Other Analyses**

Detailed analysis plan for CGM will be documented in SAP.

#### **10.3.7.1. Health Economics**

Not applicable.

#### **10.3.7.2. Subgroup Analyses**

Subgroup analyses of important factors, including age, race, ethnicity, gender, duration of diabetes, baseline HbA1c ( $<8.5\%$ ,  $\geq 8.5\%$ ), BMI, and other factors to be specified in the SAP are planned for the key outcomes of HbA1c, insulin dose and incidence and rate of hypoglycemia.

These will be conducted using the analysis of covariance model with strata, treatment, factor, treatment-by-factor interaction as fixed effects, and baseline as covariate.

Covariate analysis of PK and PK/PD may be performed.

Other exploratory subgroup analyses may be performed as deemed appropriate.

### **10.3.8. Interim Analyses**

Interim analyses have been planned for this study. The cancellation or addition of interim analysis will be determined at any time during the study and does not need protocol amendment.

An interim analysis of select safety, efficacy, and PK data is planned when approximately 50% of study participants complete 6 weeks of treatment. Results of interim analysis might be used for adjusting LY3209590 dosing algorithm.

A subsequent interim analysis of select safety, efficacy, and PK data is planned when all study participants complete 12 weeks of treatment. Results of interim analysis will be used to design subsequent studies.

In addition, the study team will perform periodic safety reviews during the study and if safety signals or concerns arise from these reviews, safety data may need to be in an unplanned interim analysis.

Study sites will receive information about interim results ONLY if they need to know for the safety of their study participants.

## 11. References

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## 12. Appendices

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## Appendix 1. Abbreviations and Definitions

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Term	Definition
<b>ADA</b>	antidrug antibodies
<b>AE</b>	adverse event: Any untoward medical occurrence in a study participant or clinical investigation subject 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.
<b>AESI</b>	adverse event of special interest
<b>ALP</b>	alkaline phosphate
<b>ALT/SGPT</b>	alanine aminotransferase/ serum glutamic pyruvic transaminase
<b>AST/SGOT</b>	aspartate aminotransferase/ serum glutamic oxaloacetic transaminase
<b>AUC</b>	area under the curve
<b>blinding/masking</b>	<p>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the study participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the study participant are not.</p> <p>A double-blind study is one in which neither the [study participant/subject] nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.</p>
<b>BMI</b>	body mass index
<b>BP</b>	blood pressure
<b>CGM</b>	continuing glucose monitoring
<b>Complaint</b>	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.
<b>CRP</b>	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.
<b>CSR</b>	clinical study report
<b>CV</b>	cardiovascular
<b>DPP-4</b>	dipeptidyl peptidase-4

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<b>ECG</b>	electrocardiogram
<b>eCRF</b>	electronic case report form
<b>Enroll</b>	The act of assigning a study participant to a treatment. Study participants who are enrolled in the trial are those who have been assigned to a treatment.
<b>Enter</b>	Study participants entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>ERB</b>	Ethics Review Board
<b>ET</b>	early termination
<b>FAS</b>	full analysis set
<b>FBG</b>	fasting blood glucose
<b>FBS</b>	Fasting blood sugar
<b>FPG</b>	fasting plasma glucose
<b>GCP</b>	good clinical practice
<b>GGT</b>	gamma-glutamyl transferase
<b>HbA1c</b>	hemoglobin A1c
<b>ICF</b>	informed consent form
<b>interim analysis</b>	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.
<b>investigational product (IP)</b>	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.
<b>IWRS</b>	interactive web-response system
<b>LS</b>	least squares
<b>LY</b>	LY3209590
<b>MAD</b>	multiple ascending dose
<b>MMRM</b>	mixed-effect model repeated measures
<b>NAFLD</b>	non-alcoholic fatty liver disease
<b>OAM</b>	oral antihyperglycemic medication
<b>OTC</b>	over the counter

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<b>PD</b>	pharmacodynamic
<b>PG</b>	plasma glucose
<b>PK</b>	pharmacokinetics
<b>PP</b>	per-protocol set: The set of data generated by the subset of study participants 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.
<b>QTc</b>	corrected QT interval
<b>QTcF</b>	QT corrected for heart rate using Fridericia's formula
<b>SAD</b>	single-ascending dose
<b>SAE</b>	serious adverse event
<b>SAP</b>	Statistical analysis plan
<b>SC</b>	subcutaneous
<b>SD</b>	standard deviation
<b>SGLT</b>	sodium-glucose cotransporter
<b>SMBG</b>	self-monitoring of blood glucose
<b>SMPG</b>	self-monitored plasma glucose
<b>SU</b>	sulfonylureas
<b>SUSARs</b>	suspected unexpected serious adverse reactions
<b>Screen</b>	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.
<b>T2DM</b>	type 2 diabetes mellitus
<b>TEAE</b>	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, which and does not necessarily have to have a causal relationship with this treatment.
<b>ULN</b>	upper limit of normal

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## Appendix 2. Clinical Laboratory Tests

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**Hematology<sup>a</sup>**

Hemoglobin  
 Hematocrit  
 Erythrocyte count (RBC)  
 Mean cell volume  
 Mean cell hemoglobin  
 Mean cell hemoglobin concentration  
 Leukocytes (WBC)  
 Neutrophils, segmented  
 Lymphocytes  
 Monocytes  
 Eosinophils  
 Basophils  
 Platelets

**Urinalysis<sup>a, c</sup>**

Protein  
 Nitrite  
 Blood  
 Urine leukocyte esterase

**Pregnancy test serum and urine (females only)<sup>a, d</sup>**

Follicle stimulating hormone (females only, to confirm WCBP)

**Endocrine**

C-peptide

**Pancreas (Exocrine)**

Pancreatic amylase  
 Lipase

**Immunogenicity**

Anti-LY3209590

**Clinical Chemistry<sup>a, b</sup>**

Sodium  
 Potassium  
 Chloride  
 Bicarbonate  
 Total bilirubin  
 Direct bilirubin  
 Alkaline phosphatase (ALP)  
 Alanine aminotransferase (ALT)  
 Aspartate aminotransferase (AST)  
 Gamma-glutamyltransferase (GGT)  
 Blood urea nitrogen (BUN)  
 Creatinine  
 Uric acid  
 Calcium  
 Phosphorus  
 Glucose  
 Total protein  
 Albumin  
 Creatine kinase  
 Cholesterol  
 Triglycerides  
 eGFR

**Additional lipids**

HDL cholesterol  
 LDL cholesterol

**Hemoglobin A1c****Free Fatty Acid****Hepatitis B**

Hepatitis B Core Antibody  
 Hepatitis B Surface Antigen  
 Hepatitis B Surface Antibody

**Drug concentration**

LY3209590

**Pharmacogenetic sample**

**Non-pharmacogenetic samples**

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Abbreviations: HDL = high density lipoprotein; LDL = low density lipoprotein; RBC = red blood cells;  
WBC = white blood cells; WCBP = women of child bearing potential.

- a Results will be confirmed by the Central Lab at the time of initial testing.
- b Refer to the Schedule of Activities.
- c All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.
- d Urine pregnancy tests (analyzed on-site) to be performed at Visits 3, 801, and ET and serum pregnancy test (analyzed by central laboratory) to be performed at Visit 1 for women of childbearing potential. Additional pregnancy tests may be performed at the investigator's discretion during the study.



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## **Appendix 3. Study Governance Considerations**

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## **Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process**

### ***Appendix 3.1.1. Informed Consent***

The investigator is responsible for:

- Ensuring that the study participant/study participant's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- Ensuring that informed consent is given by each study participant/study participant's legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- Answering any questions the study participant/study participant's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the study participant/study participant's legal representative's willingness to continue his or her participation in the study.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

### ***Appendix 3.1.2. Recruitment***

Lilly or its designee is responsible for the central recruitment strategy for study participants. Individual investigators may have additional local requirements or processes.

Investigator(s) will be responsible for subject recruitment through local requirements or processes.

### ***Appendix 3.1.3. Ethical Review***

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF,

including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda
- current Investigator Brochure (IB)
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

#### ***Appendix 3.1.4. Regulatory Considerations***

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

- consensus ethics principles derived from international ethics 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

Some of the obligations of the sponsor will be assigned to a third party.

#### ***Appendix 3.1.5. Investigator Information***

Physicians with a specialty in diabetes will participate as investigators in this clinical trial.

Physicians with a specialty in diabetes working in teaching or nonteaching hospitals or outstudy participant setting will participate as investigators in this clinical trial.

#### ***Appendix 3.1.6. Protocol Signatures***

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

#### ***Appendix 3.1.7. Final Report Signature***

The investigator will sign the final clinical study report (CSR) for this study, indicating agreement with the analyses, results, and conclusions of the report.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most analyzable study participants will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

## **Appendix 3.2. Data Quality Assurance**

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

### **Appendix 3.2.1. 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 the eCRF 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 eCRF.

Additionally, clinical outcome assessment (COA) data (questionnaires, scales, self-reported diary data, rating scales, etc.) will be collected by the study participant (investigator site personnel),

via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture system(s) will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive 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 electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

### **Appendix 3.3. Study and Site Closure**

#### ***Appendix 3.3.1. Discontinuation of Study Sites***

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

#### ***Appendix 3.3.2. Discontinuation of the Study***

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

#### ***Appendix 3.4. Publication Policy***

The publication policy for Study I8H-MC-BDCM is described in Clinical Trial Agreement.

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## Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with study participants in consultation with Lilly, or its designee, clinical research physician.

### Hepatic Monitoring Tests

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#### Hepatic Hematology<sup>a</sup>

Hemoglobin  
Hematocrit  
RBC  
WBC  
Neutrophils, segmented  
Lymphocytes  
Monocytes  
Eosinophils  
Basophils  
Platelets

#### Hepatic Chemistry<sup>a</sup>

Total bilirubin  
Direct bilirubin  
Alkaline phosphatase  
ALT  
AST  
GGT  
CPK

#### Haptoglobin<sup>a</sup>

#### Hepatic Coagulation<sup>a</sup>

Prothrombin Time  
Prothrombin Time, INR

#### Hepatic Serologies<sup>a, b</sup>

Hepatitis A antibody, total  
Hepatitis A antibody, IgM  
Hepatitis B surface antigen  
Hepatitis B surface antibody  
Hepatitis B Core antibody  
Hepatitis C antibody  
Hepatitis E antibody, IgG  
Hepatitis E antibody, IgM

#### Anti-nuclear antibody<sup>a</sup>

#### Alkaline Phosphatase Isoenzymes<sup>a</sup>

#### Anti-smooth muscle antibody (or anti-actin antibody)<sup>a</sup>

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

<sup>a</sup> Assayed by Lilly-designated or local laboratory.

<sup>b</sup> Reflex/confirmation dependent on regulatory requirements and/or testing availability.

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## Appendix 5. Methods of Contraception

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### Highly Effective Methods of Contraception:

- Combined oral contraceptive pill or mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence
- Vasectomy for men in clinical trials
- Partner with vasectomy for women in clinical trials
- Essure

### Combination of 2 effective methods of contraception

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge with condom
- Cervical cap with spermicide

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## **Appendix 6. New York Heart Association Cardiac Disease Classification**

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Current classification can be found at

<https://manual.jointcommission.org/releases/TJC2016A/DataElem0439.html>



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## Appendix 7. Dosing Guidance

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LY3209590 will be initiated at a loading dose [CCI] estimated to be comparable to the total daily basal insulin dose already administered prior to randomization. The [CCI] dose are shown in [Table BDCM.5](#). New dosing algorithms developed specifically for LY3209590 will be used by investigators for adjusting fasting glucose to achieve glycemic goals ([Table BDCM.6](#)). In situations where study participant safety is a concern or where dose adjustments have not had the desired therapeutic effect, investigators may only make adjustments to the dose of LY3209590 recommended by the dose-adjustment algorithm after consultation with Lilly.

At the time of site visit or telephone 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 blood glucose value. Adherence to the dosing algorithm provided for this study is required from Visit 3 (randomization) up to Visit 21 (Week 32, inclusive) and will be monitored periodically by the study team. Dose increases may be made no sooner than [CCI] (algorithm #1) or [CCI] (algorithm #2) [CCI] following the last dose increase. There should be no dose increase or decrease if at least [CCI], respectively, have not elapsed since the previous dose increase. Any deviations from this guidance must be approved by Lilly.

LY3209590 dose increase algorithm will be determined based on the mean of the FBG (determined from self-monitoring of blood glucose [SMBG]) [CCI]. Due to the long half-life of LY3209590, the change in fasting glucose response following dose adjustment may take several weeks to reach new level; therefore, less frequent dose adjustment is recommended to minimize prolonged variation in glycemic control.

The insulin dose may not be increased if [CCI]

[CCI]

[CCI]

[CCI]

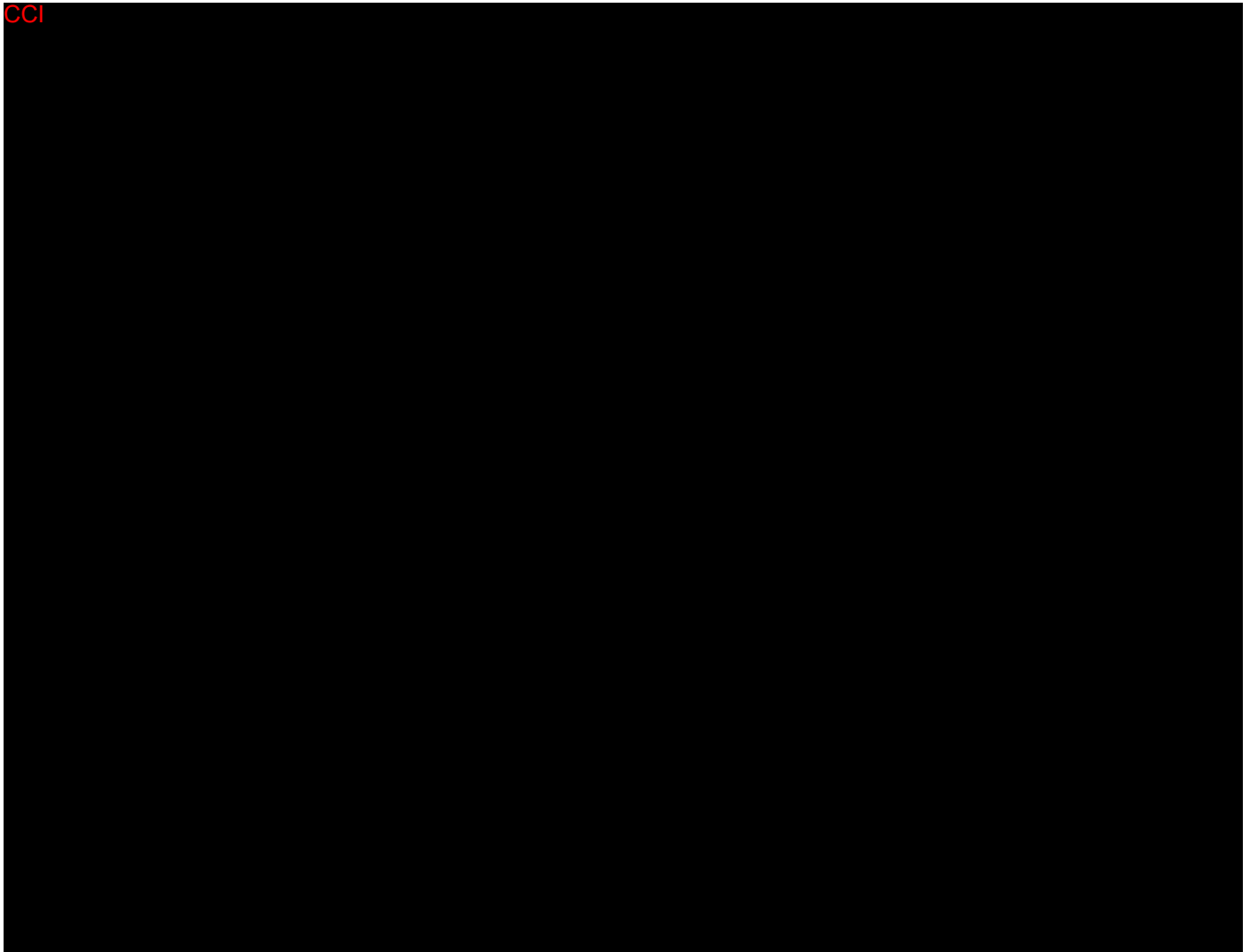
Table BDCM.5 LY3209590 Loading Dose

CC



Table BDCM.6 LY3209590 Titration Algorithm

CCI



Leo Document ID = 918a14c6-c102-4f81-94a2-a4675ac3c540

Approver: PPD )  
Approval Date & Time: 31-Aug-2018 14:54:01 GMT  
Signature meaning: Approved

Approver: PPD )  
Approval Date & Time: 31-Aug-2018 16:06:36 GMT  
Signature meaning: Approved