Protocol I8F-MC-GPGM (b)

Efficacy and Safety of LY3298176 Once Weekly versus Insulin Glargine in Patients with Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4)

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Confidential Information

LY3298176

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1. Synopsis

Title of Study:

Efficacy and Safety of LY3298176 Once Weekly versus Insulin Glargine in Patients with Type 2 Diabetes and Increased Cardiovascular Risk.

Rationale:

Patients with type 2 diabetes mellitus (T2DM) need antihyperglycemic treatment. As the disease progresses, multiple drug treatments are warranted to manage the disease. When oral therapies are insufficient to reach target glycemia, injectable therapies are added. Basal insulins, such as glargine, are frequently used as the first injectable after failure of the oral therapy. Adequately titrated glargine therapy, in combination with oral treatment, frequently achieves the target glycemic level; however, it is frequently associated with weight increase and eventual hypoglycemia. LY3298176 is a 39-amino acid synthetic peptide with agonist activity at both the GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety. It is administered once weekly (QW) by subcutaneous administration. The aim of the present study is to compare the glycemic effect of glargine and LY3298176 in patients with T2DM and elevated risk for cardiovascular disease. The study will also compare the effect of these drugs on weight and their safety profile.

Study I8F-MC-GPGM (GPGM) is a Phase 3, open-label comparator, multicenter, parallel-arm, randomized study to compare the safety and efficacy of 3 maintenance doses of LY3298176 with insulin glargine in patients with T2DM with increased cardiovascular (CV) risk. The primary endpoint will be the mean change in hemoglobin A1c (HbA1c) levels from baseline to 52 weeks.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To demonstrate that QW LY3298176 10 mg and/or 15 mg is noninferior to insulin glargine for change from baseline in HbA1c at 52 weeks	• Mean change in HbA1c
Key Secondary (controlled for type 1 error) <u>Efficacy</u> • To demonstrate that QW LY3298176 5 mg is noninferior to insulin glargine for change from baseline in HbA1c at 52 weeks • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine for change from baseline in weight at 52 weeks • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine for change from baseline in HbA1c at 52 weeks • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin	• Mean change in HbA1c • Mean change in body weight • Mean change in HbA1c

Objectives	Endpoints
glargine for the proportion of patients with HbA1c target values of <7.0% (53 mmol/mol) at 52 weeks	• HbA1c
Additional Secondary (not controlled for type 1 error) Efficacy • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine at 52 weeks	• The mean change in fasting serum glucose (central laboratory) from baseline • The proportion of patients achieving an HbA1c target value of ≤6.5% (48 mmol/mol) and <5.7% (39 mmol/mol) • Mean change in 7-point self-monitored blood glucose profiles from baseline • Proportion of patients who achieved weight loss of ≥5%, ≥10%, and ≥15% from baseline
Safety • To compare the safety of LY3298176 5 mg, 10 mg, and 15 mg LY3298176 to insulin glargine at 52 weeks and at the end of the safety follow-up period, with respect to the following outcomes	• Treatment-emergent adverse events (TEAEs) • Early discontinuations of study drug due to adverse events (AEs) • Adjudicated deaths and nonfatal major CV events • Adjudicated pancreatic AEs • Medullary thyroid carcinoma (MTC), C-cell hyperplasia, and serum calcitonin • Incidence of treatment-emergent LY3298176 anti-drug antibodies and systemic hypersensitivity reactions • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Occurrence of hypoglycemic events • Time to initiation of rescue therapy for severe, persistent hyperglycemia
Pharmacokinetics • To characterize the pharmacokinetics (PK) of LY3298176 5 mg, 10 mg, and 15 mg and evaluate the relationships between LY3298176 exposure and safety, tolerability, and efficacy measures	• Population PK and PD parameters

Summary of Study Design:

Study GPGM is a Phase 3, open-label comparator, multicenter, parallel-arm, randomized study to compare the safety and efficacy of 3 maintenance doses of LY3298176 with insulin glargine in patients with T2DM with increased CV risk. The primary endpoint will be the mean change in HbA1c from baseline to 52 weeks.

Treatment Arms and Duration:

Patients will be randomized in a 1:1:1:3 ratio to receive 5 mg LY3298176, 10 mg LY3298176, 15 mg LY3298176, or insulin glargine. The randomization will be stratified by country, baseline HbA1c concentration (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and sodium-glucose co-transporter-2 inhibitors (SGLT-2i) use (Yes or No).

The study will continue until all of the following criteria are fulfilled.

1) At least 52 weeks from the time of the last patient randomized
2) At least 300 patients assigned to the combined LY3298176 arms reach at least 78 weeks of treatment
3) Approximately 110 patients in this study experience at least 1 component event of the composite CV endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina

Number of Patients:

Approximately 1878 patients will be randomized in a 1:1:1:3 ratio to 5 mg LY3298176 (313 patients), 10 mg LY3298176 (313 patients), 15 mg LY3298176 (313 patients), and insulin glargine (939 patients).

Statistical Analysis:

Efficacy Analyses:

Efficacy and safety will be assessed using the modified intention-to-treat population, which consists of all randomly assigned participants who are exposed to at least 1 dose of study drug. There will be 2 estimands of interest in comparing efficacy of LY3298176 doses with insulin glargine relative to the primary measure of mean change in HbA1c from baseline to 52-week visit. First estimand, the "efficacy" estimand, represents efficacy prior to discontinuation of study drug without confounding effects of rescue therapy for persistent severe hyperglycemia. Second estimand, the "treatment-regimen" estimand, represents the efficacy irrespective of adherence to investigational product or introduction of rescue therapy for persistent severe hyperglycemia.

For the FDA, the primary efficacy assessments will be guided by the "treatment-regimen" estimand. This assessment will analyze change from baseline in HbA1c to 52-week visit using an analysis of covariance (ANCOVA) with terms, treatment, stratification factors: country, SGLT-2i use (Yes or No), and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using full analysis set (FAS) at 52-week visit, which consists of all available change from baseline in HbA1c data at the 52-week visit, irrespective of whether they were obtained while the participants had discontinued the study drug or whether the participant had been given rescue medication. Additionally, data for subjects with missing values will be imputed based on observed data from subjects in the same treatment arm who had their efficacy measure at the Week 52 visit assessed after early discontinuation of study drug and/or initiation of rescue medication (retrieved dropouts). Analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

For all other purposes, the primary efficacy assessments will be guided by the "efficacy" estimand. This assessment will use efficacy analysis set (EAS) which consists of data obtained before the initiation of any rescue therapy and before premature treatment discontinuation. The analysis model for change from baseline in HbA1c assessed over time will be a mixed model for repeated measures (MMRM), with terms: treatment, visit, and treatment-by-visit interaction, stratification factors: country, SGLT-2i use (Yes or No), as fixed effects, and baseline HbA1c as a covariate. An unstructured covariance structure will model relationship of within-patient errors.

Since the two estimands are intended for different purposes, no multiplicity adjustments will be made. For each estimand, the overall type I error rate of primary and key secondary efficacy endpoint assessments relative to each estimand will be controlled at 2-sided 0.05 level.

Additional details, including analysis methods for key secondary endpoints and the strategy for controlling overall type 1 error rate in evaluating primary and key secondary endpoint evaluation to a 2-sided 0.05 significance level, will be provided in the statistical analysis plan (SAP).

Safety Analyses:

Unless specified otherwise, safety assessments will be based on all available data, irrespective of whether they were obtained after the participants had discontinued the study drug or whether the participant had been given rescue medication. Summary statistics will be provided for incidence of TEAEs, serious adverse events, and study discontinuation due to AEs or death during the treatment period. Counts and proportions of subjects experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups. For continuous laboratory analytes, summary statistics will be provided by visit, with statistical comparisons among treatment at each visit conducted using an MMRM analysis. Selected safety analysis (for example, hypoglycemia) will be conducted after excluding data while on rescue therapy. Additional details, including analysis of AEs of special interest, will be provided in the SAP.

2. Schedule of Activities

The Schedule of Activities described below should be followed for all patients enrolled in Study GPGM. However, for those patients whose participation in this study is affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the novel Coronavirus Disease 2019 (COVID-19), please refer to Appendix 8 for additional instructions.

Table GPGM.1. Schedule of Activities

	Study Period I		Study Period II 52 Weeks																					Study Period III Variable							Study Period IV
	Screening Lead in			Treatment Period																											Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**FT V[z]**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**16**	**20**	**23**	**24**	**28**	**32**	**35**	**36**	**42**	**52**	**62**	**72**	**78**	**88**	**104**			**4 week post end of tx**
Allowable Deviation (days)[c]	**-**	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**			**±3**
Fasting Visit[d]			X		X		X				X		X		X	X		X					X	X			X		X	X	X	X
PK only Visit																	X				X											
Telephone Visit						X		X	X			X																				
Informed consent	X																															
Randomization			X																													
Clinical Assessments																																
Medical history[e]	X																															
Physical	X																							X							X	
Height	X																							X								
Weight[f]	X		X				X				X		X		X	X		X				X	X	X	X	X	X	X	X	X	X	X
Waist circumference			X								X				X			X				X		X			X		X	X	X	
ECG[g]			X																				X	X			X		X	X	X	X
Vital signs (2 sitting BP and HR)[g]	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
Dilated fundoscopic exam[h]		X																														
Adverse 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	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X

	Study Period I		Study Period II 52 Weeks																					Study Period III Variable							Study Period IV
	Screening Lead in			Treatment Period																											Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**FT V[z]**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**16**	**20**	**23**	**24**	**28**	**32**	**35**	**36**	**42**	**52**	**62**	**72**	**78**	**88**	**104**			**4 week post end of tx**
Allowable Deviation (days)[c]	**-**	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**			**±3**
Fasting Visit[d]			**X**		**X**		**X**				**X**		**X**		**X**	**X**		**X**					**X**	**X**			**X**		**X**	**X**	**X**	**X**
PK only Visit																	**X**				**X**											
Telephone Visit						**X**		**X**	**X**			**X**																				
Hypoglycemic events 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	X	X
Patient Education																																
Diabetes education[i,j]		X																														
BG meter, SMBG training[j]		X																														
Dispense BG meter/ supplies as needed		X	X	X	X		X			X	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X		
Study drug injection training[j]		X	X																													
Hand out diary and instruct on use		X																						X			X		X	X		
Remind patient about 7-point SMBG[k]		X																		X			X									
Review 7-point SMBG values collected in the diary			X																			X		X								
Dispense study drug			X				X				X		X		X	X		X	X	X		X	X	X	X	X	X	X				
Observe patient Administer LY3298176[j,m]			X																													

	Study Period I		Study Period II 52 Weeks																					Study Period III Variable								Study Period IV
	Screening Lead in			Treatment Period																												Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**FT V[z]**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**16**	**20**	**23**	**24**	**28**	**32**	**35**	**36**	**42**	**52**	**62**	**72**	**78**	**88**	**104**			**4 weeks post end of tx**
Allowable Deviation (days)[c]	**-**	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**			**±3**
Fasting Visit[d]			**X**		**X**		**X**				**X**		**X**		**X**	**X**		**X**					**X**	**X**			**X**		**X**	**X**	**X**	**X**
PK only Visit																	**X**				**X**											
Telephone Visit						**X**		**X**	**X**			**X**																				
Patient returns study drugs and injection supplies				X	X		X			X	X		X		X	X		X	X	X		X	X	X	X	X	X	X	X	X		
Assess study drug compliance				X	X		X			X	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	
Review insulin dose and adjustment per TTT algorithm[n,o]				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		
Assess compliance with insulin dose adjustment TTT algorithm[o]				X	X		X			X	X		X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X		

	Study Period I		Study Period II 52 Weeks																						Study Period III Variable							Study Period IV
	Screening Lead in			Treatment Period																												Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**FTV[z]**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**16**	**20**	**23**	**24**	**28**	**32**	**35**	**36**	**42**	**52**	**62**	**72**	**78**	**88**	**104**			**4 weeks post end of tx**
Allowable Deviation (days)[c]	**-**	**±3**	**± 7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**			**±3**
Fasting Visit[d]			**X**		**X**		**X**				**X**		**X**		**X**	**X**		**X**					**X**	**X**			**X**		**X**	**X**	**X**	**X**
PK only Visit																	**X**				**X**											
Telephone Visit						**X**		**X**	**X**			**X**																				
Laboratory Tests																																
Serum pregnancy test[p]	X																															
Urine pregnancy test[q]			X										X					X				X		X	X	X		X	X	X		
Follicle-stimulating hormone test[r]	X																															
Chemistry panel	X[s]												X					X					X	X			X		X	X	X	X
Fasting serum glucose			X		X		X				X		X		X	X		X					X	X			X		X	X	X	X
Lipid panel			X																				X	X			X		X	X	X	X

	Study Period I		Study Period II 52 Weeks																						Study Period III Variable							Study Period IV
	Screening Lead in			Treatment Period																												Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**FTV[z]**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**16**	**20**	**23**	**24**	**28**	**32**	**35**	**36**	**42**	**52**	**62**	**72**	**78**	**88**	**104**			**4 weeks post end of tx**
Allowable Deviation (days)[c]	**-**	**±3**	**±7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**			**±3**
Fasting Visit[d]			**X**		**X**		**X**				**X**		**X**		**X**	**X**		**X**					**X**	**X**			**X**		**X**	**X**	**X**	**X**
PK only Visit																	**X**				**X**											
Telephone Visit						**X**		**X**	**X**			**X**																				
Urinary albumin/ creatinine ratio			X																				X	X			X		X	X	X	X
Serum creatinine, eGFR (CKD-EPI)[t]	X[s]	X[u]											X					X					X	X			X		X	X	X	X
Calcitonin	X[s]												X					X					X	X			X		X	X	X	X
Hematology	X[s]												X					X					X	X			X		X	X	X	X
HbA1c	X		X				X				X		X		X	X		X					X	X			X		X	X	X	X
Pancreatic amylase, lipase	X[s]												X					X					X	X			X		X	X	X	X
Immuno-genicity[v]			X				X						X					X					X	X			X		X	X	X	X

	Study Period I		Study Period II 52 Weeks																					Study Period III Variable							Study Period IV
	Screening Lead in			Treatment Period																											Safety F/U
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**FTV[z]**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**16**	**20**	**23**	**24**	**28**	**32**	**35**	**36**	**42**	**52**	**62**	**72**	**78**	**88**	**104**			**4 weeks post end of tx**
Allowable Deviation (days)[c]	**-**	**±3**	**± 7**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**	**±3**	**±3**	**±3**	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**			**±3**
Fasting Visit[d]			**X**		**X**		**X**				**X**		**X**		**X**	**X**		**X**					**X**	**X**			**X**		**X**	**X**	**X**	**X**
PK only Visit																	**X**				**X**											
Telephone Visit						**X**		**X**	**X**			**X**																				
PK sample for Immuno-genicity[w]							X						X					X					X	X			X		X	X	X	X
Anti-GAD antibody			X																													
LY PK[x]										X				X			X				X										X	
Pharmaco-genetic stored sample			X																													
Non-Pharmaco-genetic stored sample			X										X					X					X	X							X	

	Study Period I		Study Period II 52 Weeks																					Study Period III Variable							Study Period IV
	Screening Lead in			Treatment Period																											Safety F/U
Visit	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	FTV[z]	ET[b]	801
Week of Treatment	-3	-2	0	1	2	3	4	5	6	7	8	10	12	15	16	20	23	24	28	32	35	36	42	52	62	72	78	88	104			4 weeks post end of tx
Allowable Deviation (days)[c]	-	±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±3	±3	±3	-	±3	±7	±7	±7	±7	±7	±7	±7			±3
Fasting Visit[d]			X		X		X				X		X		X	X		X					X	X			X		X	X	X
PK only Visit																	X				X											
Telephone Visit						X		X	X			X																				
Patient-Reported Outcomes (PROs)[y]																																
APPADL			X																					X						X	
EQ-5D-5L			X																					X						X	
IW-SP			X																					X						X	
DTSQs			X																													
DTSQc																								X							X	

Abbreviations: ADA = anti-drug antibodies; APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; ECG = electrocardiogram;; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Qualtiy of Life-dimensions; ET = early termination; FTV = final treatment visit; F/U = follow-up; GAD = glutamic acid decarboxylase; HbA1c = hemoglobin A1c; HR = heart rate; IW-SP = Impact of Weight on Self Perception; LY=LY3298176; PK = pharmacokinetics; PRO = patient-reported outcome; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SMBG = self-monitored blood glucose; SU = sulfonylurea; TTT = treat-to-target; Tx = treatment.

[a] Baseline assessments must be completed before processing in the interactive web-response system (IWRS).

[b] Patients who are unable or unwilling to continue in the study for any reason will perform an ET visit. If the patient is discontinuing during an unscheduled visit, that visit should be performed as the ET visit. If the patient is discontinuing during a scheduled visit, that visit should be performed as an ET visit. Visit 801 (safety follow-up visit) should be performed 4 weeks after the ET visit as the final study visit.

[c] The visit date is determined in relation to the date of the randomization visit (± the allowed visit window).

[d] On visits 3, 5, 7, 11, 13, 15, 16, 18, 23, 24, 27, 29, ET, and at follow-up (801), patients should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity and before taking study drug(s), metformin (if used), SGLT-2i (if used), SU (if used).

[e] Medical history includes assessment of preexisting conditions (including history of gall bladder disease, cardiovascular disease, and medullary thyroid carcinoma) and substance usage (such as, alcohol and tobacco).

[f] Weight measurements should be obtained per the detailed guidance in the Manual of Operations.

[g] Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required. The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart. BP must be taken with an automated blood pressure machine.

[h] Dilated fundoscopic exam will be performed by an eye care professional (ophthalmologist or optometrist) for all patients between Visit 2 and Visit 3 to exclude patients with proliferative retinopathy and/or maculopathy. The results from this exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. A follow-up dilated fundoscopic exam should be performed when clinically indicated by any adverse event suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF.

[i] Includes counseling on diet and exercise, management of hypoglycemia and hyperglycemia, etc.

[j] All training should be repeated as needed to ensure patient compliance.

[k] Patient is required to collect two 7-point SMBGs on nonconsecutive days prior to the next visit. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime. These SMBG profiles will be collected by the patient within 2 weeks prior to the assigned visits. If 7-point SMBG is not performed, then data from the most recent nonconsecutive 4-point SMBG profiles can be used. If more than 2 SMBG profiles are available, the 2 most recent nonconsecutive profiles should be used.

[l] Patients should administer their first dose of LY3298176 at the end of this visit, after other study procedures and randomization.

[m] LY3298176 patients only.

[n] During the first 8 weeks, the dose adjustment will be determined by the investigator in discussion with the patient by following a TTT algorithm. After Week 8, the dose adjustment will be determined by the patient in a weekly manner and will be reviewed by the investigator at each office visit. Patient will have weekly visits (clinic or phone) in the first 8 weeks and then visits every 2-3 weeks (clinic or phone) until Week 16 in order to improve compliance with the TTT algorithm.

[o] Insulin glargine patients only. A review of the patient's compliance to the TTT algorithm will still be conducted during the telephone Visits 6, 8, 9, and 12, but the patient's compliance for these visits will be collected in the eCRF at Visits 7, 10 and 13 for the period since the previous visit.

[p] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.

[q] A urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of study drug(s) for women of childbearing potential only. Additional pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period.

[r] Follicle-stimulating hormone test performed at Visit 1 for postmenopausal women at least 50 years of age with an intact uterus, without a history of oophorectomy or bilateral tubal ligation, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months.

[s] Screening visit assessment will serve as baseline.

[t] The CKD-EPI equation will be used by the central lab to estimate and report eGFR. For patients who meet inclusion criterion [4] based solely on history of chronic kidney disease and eGFR <60 mL/min/1.73m^2, the eGFR value must be confirmed to be <60 mL/min/1.73m^2 at Visit 2.

[u] This sample is required only for patients who meet inclusion criterion [4] based solely on history of chronic kidney disease and eGFR <60 mL/min/1.73m^2.

[v] In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, PK, and, exploratory biomarker sample.

[w] PK sample for immunogenicity must be collected prior to drug administration.

[x] PK samples will not be collected from patients who were randomized to insulin glargine since it is an open-label study. PK samples will be collected at these visits at time windows of 1 to 24 hours, 24 to 96 hours, OR 120 to 168 hours post dose, as assigned by IWRS. Dependent on the time-windows to which a patient gets assigned, they may be required to come to site for PK-specific visits. Draw PK at ET visit only if patient discontinues study prior to Week 35. Visits 10 and 14 are for all patients, but only those patients assigned to PK will get a PK blood draw. Visits 17 and 21 are for patients assigned to a PK blood draw only.

[y] PROs should be completed before any other study procedures if the patient is not adversely affected by the fasting condition or completed after the patient has sufficiently recovered from the preceding visit procedures.

[z] When the sponsor determines that the study has met the completion criteria, all patients remaining in the study will return to the site for a FTV within approximately 30 days. The safety follow-up visit will be approximately 30 days after the FTV.

Note: Patients will be required to collect a daily BG and a weekly 4-point SMBG.

3. Introduction

3.1. Study Rationale

Type 2 diabetes mellitus (T2DM) is a metabolic condition characterized by impaired glycemic control caused by increased insulin resistance and successive beta-cell failure and consequently inadequate insulin secretion. Type 2 diabetes mellitus is frequently associated with comorbidities such as increased weight or obesity, hypertension, and increased blood lipoprotein concentrations. Patients with T2DM have a higher risk for cardiovascular diseases (CVDs) particularly arteriosclerotic diseases in the heart and in the central nervous system. In case of prevalent arteriosclerotic diseases and/or chronic kidney diseases (CKD) of T2DM patients, the likelihood of a subsequent, life-threatening major cardiovascular (CV) event is very high, up to 2% to 4%/year (Haffner et al. 1998). To prevent these, complex medical therapy is warranted beyond the necessary changes in lifestyle and diet. Among others, patients have to achieve a tight glycemic control by combination of various antihyperglycemic medications (American Diabetes Association 2017). The diabetes therapy usually starts with lifestyle and diet changes followed by 1 or more oral medications. When oral antihyperglycemic therapies are insufficient to reach the therapy goal of target glycemia, injectable therapies are added to them. Insulins, especially basal insulins, like glargine, are basic injectable treatments after failure of the oral therapy. Adequately titrated glargine therapy, in combination with oral treatment, frequently achieves the target glycemic level. Glargine therapy, however, is frequently associated with weight increase and eventual hypoglycemia. LY3298176 is a 39-amino acid synthetic peptide with agonist activity at both the GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety. It is administered once weekly (QW) by subcutaneous (SC) administration. The aim of the present study is to compare the glycemic effect of glargine and LY3298176 in patients with T2DM and elevated risk for CVD. In addition, the number of major cardiovascular outcome events (MACE-4) to be collected in the study with high CV risk patients, will largely contribute to establishing the cardiovascular safety of LY3298176 prior to submission for license, as requested by the regulatory agencies. The study could also compare the effect of these drugs on weight loss and their safety profile.

Study I8F-MC-GPGM (GPGM) is a Phase 3, open-label comparator, multicenter, parallel-arm, randomized study to compare the safety and efficacy of 3 maintenance doses of LY3298176 with insulin glargine in patients with T2DM with increased CV risk. The primary endpoint will be the mean change hemoglobin A1c (HbA1c) from baseline to 52 weeks.

3.2. Background

Three LY3298176 clinical trials have completed dosing and analysis: a Phase 1 study, Study I8F-MC-GPGA (GPGA), and 2 Phase 2 studies, Study I8F-MC-GPGB (GPGB) and I8F-MC-GPGF (GPGF).

Phase 1 Study GPGA was a combination of single ascending dose (SAD) and multiple ascending dose study in healthy subjects and a multiple dose study in patients with T2DM. Study GPGA investigated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of

LY3298176 administered as SC injections. A total of 142 subjects (89 healthy subjects and 53 patients with T2DM) received at least 1 dose of treatment. Doses of LY3298176 ranged from 0.25 mg to 8 mg in the SAD (with maximum tolerated dose achieved at 5 mg); multiple doses from 0.5 mg to 4.5 mg QW; and titrated doses up to 10 mg QW for 4 weeks in healthy subjects; and multiples doses at 0.5 mg and 5 mg QW and titrated to 15 mg QW for 4 weeks in T2DM patients.

LY3298176 was better tolerated by patients with T2DM than healthy subjects. Doses higher than 5 mg were better tolerated when attained via escalation. Maximum tolerated dose of LY3298176 in healthy subjects following single-dose administration was 5 mg. A dose of 15 mg LY3298176 was administered in patients with T2DM by accelerated dose escalation over 4 weeks (5/5/10/15 mg) and while considered to be safe, was associated with high incidence of GI events.

Gastrointestinal (GI) adverse events (AEs) (nausea, vomiting, diarrhea, decreased appetite, abdominal distension) were the most frequently reported events by both healthy subjects and patients with T2DM and were dose related. Most AEs were mild in severity, few were moderate, and none were reported as severe. There were no apparent trends in chemistry, hematology, or urinalyses. A few subjects experienced elevations in lipase and/or amylase levels, but these episodes were not associated with drug-related risk of pancreatitis.

The safety and tolerability and PK/PD profiles of LY3298176 at doses and escalation regimens administered in this phase 1 study supported further development of LY3298176 for QW dosing in patients with T2DM.

Phase 2 studies have evaluated the efficacy, tolerability, and safety of LY3298176 in patients with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated AEs of LY3298176 are to be found in the Investigator's Brochure (IB).

In addition, detailed information about the known and expected benefits and risks of insulin glargine may be found in the insulin glargine package insert (Basaglar USPI, 2015 [WWW]).

4. Objectives and Endpoints

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

Table GPGM.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To demonstrate that QW LY3298176 10 mg and/or 15 mg is noninferior to insulin glargine for change from baseline in HbA1c at 52 weeks	• Mean change in HbA1c
Key Secondary (controlled for type 1 error) Efficacy • To demonstrate that QW LY3298176 5 mg is noninferior to insulin glargine for change from baseline in HbA1c at 52 weeks • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine for change from baseline in weight at 52 weeks • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine for change from baseline in HbA1c at 52 weeks • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine for the proportion of patients with HbA1c target values of <7.0 (53 mmol/mol) at 52 weeks. **Additional Secondary (not controlled for type 1 error)** Efficacy • To demonstrate that QW LY3298176 5 mg, 10 mg, and/or 15 mg is superior to insulin glargine at 52 weeks	• Mean change in HbA1c • Mean change in body weight • Mean change in HbA1c • HbA1c • The mean change in fasting serum glucose (central laboratory) from baseline • The proportion of patients achieving an HbA1c target value of ≤6.5% (48 mmol/mol), and <5.7% (39 mmol/mol) • Mean change in 7-point self-monitored blood glucose (SMBG) profiles from baseline • Proportion of patients who achieved weight loss of ≥5%, ≥10%, and ≥15% from baseline
Safety	

• To compare the safety of LY3298176 5 mg, 10 mg, and 15 mg LY3298176 to insulin glargine at 52 weeks, and at the end of the safety follow-up period, with respect to the following outcomes:	• Treatment-emergent adverse events (TEAEs) • Early discontinuations of study drug due to AEs • Adjudicated deaths and nonfatal major CV events • Adjudicated pancreatic AEs • Medullary thyroid carcinoma (MTC) and serum calcitonin • Incidence of treatment-emergent (TE) LY3298176 anti-drug antibodies (ADA) and systemic hypersensitivity reactions • Mean change in systolic and diastolic blood pressure and heart rate from baseline • Occurrence of hypoglycemic events • Incidence of initiation of rescue therapy for severe, persistent hyperglycemia
<u>Pharmacokinetics</u> • To characterize the PK of LY3298176 5 mg, 10 mg, and 15 mg and evaluate the relationship between LY3298176 exposure and safety, tolerability, and efficacy measures	• Population PK and PD parameters
Tertiary/Exploratory • To characterize long-term glycemic control with LY3298176 5 mg, 10 mg, and 15 mg • To compare LY3298176 5 mg, 10 mg, and 15 mg to insulin glargine with respect to the following:	• HbA1c • Change in lipids (total cholesterol, high-density lipoproteins, low-density lipoproteins, very low-density lipoproteins, and triglycerides) from baseline • Changes from baseline in mean body mass index (BMI) • Change in waist circumference • Biomarkers • Patient-Reported Outcomes (European Quality of Life – dimensions [EQ-5D-5L], Ability to Perform Physical Activities of Daily Living [APPADL], Impact of Weight on Self-Perception [IW-SP], status (s) and change (c) versions of Diabetes Treatment Satisfaction Questionnaire (DTSQ)

5. Study Design

5.1. Overall Design

Study GPGM is a Phase 3, open-label comparator, multicenter, parallel-arm, randomized study to compare the safety and efficacy of 3 maintenance doses of LY3298176 with insulin glargine in patients with T2DM with increased CV risk. The primary endpoint will be the mean change HbA1c from baseline to 52 weeks.

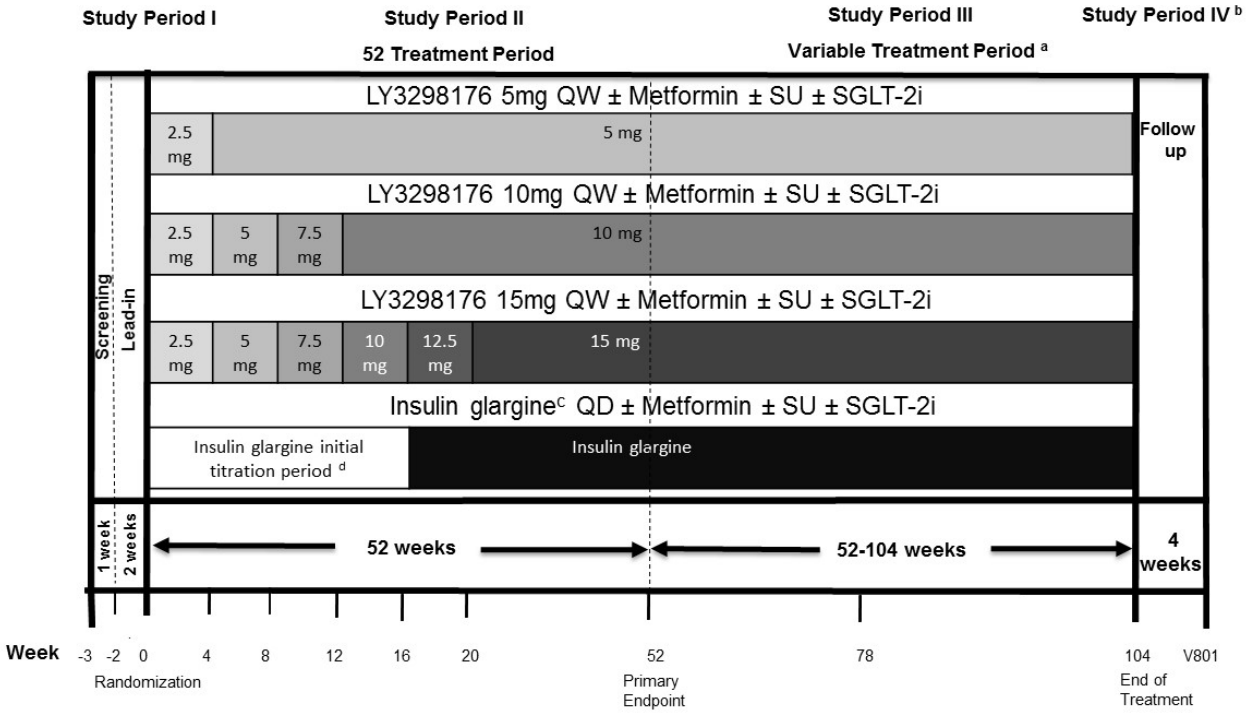
Patients should be on a stable dose (no dose change for at least 90 days) of at least 1 and no more than 3 oral antihyperglycemic medications: metformin, sodium-glucose co-transporter-2 inhibitors (SGLT-2is), or sulfonylureas. Patients will be randomized in a 1:1:1:3 ratio to receive 5 mg LY3298176, 10 mg LY3298176, 15 mg LY3298176, or insulin glargine. The randomization will be stratified by country, baseline HbA1c concentration (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and SGLT-2i use (Yes or No).

The study will continue until all of the following criteria are fulfilled:

1) At least 52 weeks from the time of the last patient randomized,
2) At least 300 patients assigned to the combined LY3298176 arms reach at least 78 weeks of treatment,
3) Approximately 110 patients in this study experience at least 1 component event of the composite CV endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina.

The starting dose of insulin glargine will be 10 IU/day at bedtime, titrated to a fasting blood glucose (FBG) <100 mg/dL, following a treat-to-target algorithm (Riddle et al. 2003). Patients will titrate the insulin glargine dose in a weekly manner and will make the dose decision with the investigator for the first 8 weeks (phone or clinic visit). From Week 8 to Week 16, patients will have a phone or clinic visit every other week.

Figure GPGM.1 illustrates the study design.



Abbreviations: QD = once daily; QW = once weekly; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea.

a Patients will be on study drug for at least 12 months and will receive no more than months of treatment.

b All patients will perform a Visit 801 4 weeks after their last treatment visit.

c The starting dose of insulin glargine will be 10 IU/day at bedtime, titrated to a FBG <100 mg/dL, following a TTT algorithm (Riddle et al. 2003).

d Patients will titrate insulin glargine dose in a weekly manner and will make the dose decision with the investigator for the first 8 weeks (phone or clinic visit). From Week 8 to Week 16, patients will continue the titration by a phone consultation or clinic visit every other week, with 3 weeks between Visits 13 and 14.

Figure GPGM.1. Illustration of study design for Clinical Protocol I8F-MC-GPGM.

Study Period I (screening and lead-in)

Screening (Visit 1)

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2. Patients who meet all applicable inclusion criteria and none of the applicable exclusion criteria at Visit 1 will continue on their prestudy therapy until Visit 2.

Lead-in (Visit 2 to Visit 3)

At Visit 2, the screening laboratory results will be reviewed and patient eligibility will be established. For those patients meeting all other eligibility requirements, a dilated fundoscopic exam, performed by an ophthalmologist or optometrist, must be completed between Visit 2 and Visit 3 to ensure patients with proliferative retinopathy or maculopathy are identified and not enrolled. During the lead-in period, eligible patients should continue their prestudy therapy (all oral medications at the same dose), in order to allow reliable assessment of HbA1c at baseline (Visit 3). During this period, patients will be trained on disease monitoring and disease management procedures, study diaries, and study procedures.

Study Period II (52-week treatment period)

Randomization (Visit 3)

At Visit 3, patients will perform all required baseline study procedures (including the collection of all baseline laboratory measures) prior to randomization and prior to taking the first dose of study drug. Patients will be randomized in a 1:1:1:3 ratio to receive 5 mg LY3298176, 10 mg LY3298176, 15 mg LY3298176, or insulin glargine. The randomization will be stratified by country, baseline HbA1c concentration (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and SGLT-2i use (Yes or No).

Immediately after randomization, the patient will inject the first dose of LY3298176 at the study site, according to the dose escalation regimen described below. Patients randomized to the insulin glargine arm will administer insulin glargine per the investigators' discretion. The date and time of the first dose of study drug should be recorded on the electronic case report form (eCRF).

Following randomization, patients will participate in a 52-week treatment period.

Postrandomization period (end of Visit 3 to Visit 24):

The starting dose of LY3298176 will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study low-dose arm. For the 10-mg arm, the starting dose of LY3298176 will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg arm, the starting dose of LY3298176 will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5-15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

The initial dose of insulin glargine will be 10 IU/day at bedtime, titrated to a FBG <100 mg/dL, following a treat-to-target (TTT) algorithm (Riddle et al. 2003) (see Section 7.2.1.2, Table GPGM.4).

Study Period III (variable treatment period)

Long-term safety period (Visit 25 to Visit 29):

Some patients will continue to receive LY3298176 or insulin glargine for up to, but not longer than, 24 months, as determined by the sponsor.

When the sponsor determines that the study completion criteria have been met, all patients will return to the site for a final treatment visit (FTV) within approximately 30 days. Patients who attend Visit 29 (24 months) or the FTV are considered to have completed the treatment period.

Study Period IV (safety follow-up period)

Safety follow-up (Visit 801) visits:

All patients who complete the treatment period are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after their last visit. Patients discontinuing the study early and performing an early termination (ET) visit will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit. During the safety follow-up period, patients will not receive study drug. Patients will be treated with another glucose-lowering intervention decided upon by the investigator. Initiation of new antihyperglycemic therapy for the safety follow-up period will not be classified as "rescue therapy." All antihyperglycemic medications will be entered on the eCRF specified for this purpose. Patients are also required to return any remaining study diaries to the study site at the end of this period.

Study Procedures

Patients will perform study procedures listed in the Schedule of Activities (Section 2).

Patients will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments. Prohibited medications include GLP-1 receptor agonists, amylin analogs, and dipeptidyl peptidase-4 (DPP-4) inhibitors (see Section 7.7).

Pharmacokinetic samples will be collected from the first 150 patients at each LY3298176 dose, all patients aged ≥70 years, and all patients with severe renal impairment or end-stage renal disease (ESRD) (estimated glomerular filtration rate [eGFR] <30 mL/min) (see Section 9.5).

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Sections 7.2.1.2 and 9.2.2.2) will receive a new glucose-lowering intervention ("rescue therapy") and will also continue to administer study drug. Patients who need hyperglycemic rescue therapy will continue in the trial until they complete all study visits.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

A total of approximately 1878 patients will be randomized in a 1:1:1:3 ratio to 5 mg LY3298176 (313 patients), 10 mg LY3298176 (313 patients), 15 mg LY3298176 (313 patients), and insulin glargine (939 patients).

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 patient.

5.4. Scientific Rationale for Study Design

Study GPGM is designed to determine the comparative benefits and risks of QW LY3298176 5 mg, 10 mg, or 15 mg versus insulin glargine in patients with T2DM with increased CV risk.

An active comparator rather than placebo was selected for this trial because it includes patients with uncontrolled T2DM despite of oral antihyperglycemic therapies (7.5% [58 mmol/mol] to 10.5% [91 mmol/mol], inclusive) and increased risk for CVDs who will be studied for a longer period, up to 2 years. To ensure a valid comparison of the randomized study treatments, it is important that insulin glargine is titrated optimally throughout the entire study. Patients will be required to use a TTT algorithm, which has been shown to be effective in enabling a high proportion of patients with T2DM to achieve their therapeutic targets when treated with insulin glargine (Riddle et al. 2003) as described in Section 7.2.1.2.

To minimize the potential confounding effect of changes to concomitant medications, patients will be permitted to use concomitant medications that they require during the study. Medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments will not be allowed (see Section 7.7).

The planned duration of treatment for the primary endpoint at 52 weeks is considered appropriate to assess the full effects and benefit/risk of each maintenance dose of LY3298176 compared with the other LY3298176 doses on both glycemic control and body weight. The variable treatment duration of up to, but not longer than 104 weeks, will provide sufficient 18-month patient exposures to meet regulatory requirements and to provide sufficient numbers of patients with a major adverse CV event (MACE-4: CV death, myocardial infarction, stroke, or hospitalization for unstable angina) for the meta-analysis to rule out excess CV risk.

5.5. Justification for Dose

LY3298176 doses of 5 mg, 10 mg, and 15 mg administered subcutaneously QW will be evaluated in this study.

These doses and associated escalation schemes were selected based on assessment of safety, efficacy (glycemic and weight loss benefit), and GI tolerability data followed by exposure response modeling of data in T2DM patients in Phase 1 and 2 studies. Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4-week would permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

The maximum proposed dose of 15 mg maintains an exposure multiple of 1.6 to 2.4 to the no-observed adverse effect level doses in 6-month monkey and rat toxicology studies.

The selected dose and escalation scheme would enable further evaluation of benefit/risk considerations for 5 mg, 10 mg, and 15 mg doses of LY3298176.

6. Study Population

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

6.1. Inclusion Criteria

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

Type of Patient and Disease Characteristics

[1] Have been diagnosed with T2DM based on the World Health Organization classification or other locally applicable diagnostic standards

Patient Characteristics

[2] Have HbA1c between ≥7.5% (58 mmol/mol) and ≤10.5% (91 mmol/mol) at screening as determined by the central laboratory at Visit 1

[3] On stable treatment with unchanged dose of at least 1 and no more than 3 oral antihyperglycemic drugs, which may only include metformin, SGLT-2i, and/or sulfonylurea for at least 3 months before Visit 1

[4] Increased risk of CV events as defined by at least 1 of the following (a – e):

a) Coronary heart disease documented as having any of the following:
   1) History of acute myocardial infarction (ST elevation or non-ST elevation)
   2) Stenosis of ≥50% in at least 1 major (left main, left anterior descending, ramus intermedius, left circumflex, right) coronary artery as determined by cardiac imaging
   3) Coronary calcium score ≥300
   4) Stable angina pectoris treated with anti-anginal medication
   5) Asymptomatic cardiac ischemia documented by cardiac imaging on exercise or pharmacological stress test
   6) History of coronary revascularization (percutaneous coronary intervention or coronary artery bypass surgery)

OR

b) Peripheral arterial disease presumed to be of atherosclerotic origin documented as a history of any of the following:
   1) Current or intermittent claudication
   2) Resting limb ischemia
   3) Stenosis of >50% in an iliac, femoral, popliteal, or subclavian artery
   4) An ankle-brachial index ≤0.90
   5) Peripheral arterial revascularization or amputation due to atherosclerotic vascular disease
   6) Asymptomatic carotid artery stenosis ≥70%
   7) Carotid artery revascularization

8) Abdominal aortic aneurysm

OR

c) Cerebrovascular disease presumed to be of atherosclerotic origin documented as a history of ischemic stroke or transient ischemic attack (TIA). Patients with a history of TIA must be age ≥50 years.

NOTE: Does not include stroke or TIA due to nonatherosclerotic causes, for example, hypertension, embolism, or hemorrhagic stroke

OR

d) Age ≥50 years, history of CKD, and an estimated glomerular filtration rate <60 mL/min/1.73m^2 (CKD-Epidemiology[CKD-EPI]) on consecutive measurements (Visit 1 and Visit 2)

OR

e) Age ≥50 years and congestive heart failure (CHF) documented as a history of CHF by the New York Heart Association Functional Classification II to III

[5] Are of stable weight (± 5%) ≥3 months prior to Visit 1 and agree to not initiate an intensive 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

[6] Have a BMI ≥25 kg/m^2 at Visit 1

[7] Eighteen years or older at the time of signing informed consent

Male patients:

Male patients should be willing to use reliable contraceptive methods throughout the study and for at least 3 months after last injection

Female patients:

Female patients not of childbearing potential due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or menopause.

Women with an intact uterus are deemed postmenopausal if they are 45 years old, and

- have not taken hormones or oral contraceptives within the last year and had cessation of menses for at least 1 year

OR

- have had at least 6 months of amenorrhea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL).

Female patients of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must

- test negative for pregnancy at Visit 1 based on a serum pregnancy test

AND

- if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the trial and for 30 days thereafter
- not be breastfeeding

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

- perform SMBG (up to 7 measures in a day)
- learn how to self-inject treatment (LY3298176 or insulin glargine), 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 study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)
- are willing and able to inject study drug QW/once daily
- maintain a study diary, as required for this protocol
- have a sufficient understanding of one of the provided languages of the country such that they will be able to complete the patient questionnaires

Informed Consent

[9] Have given written informed consent to participate in this study in accordance with local regulations and the Ethical Review Board (ERB) governing the study site

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions

[10] Have type 1 diabetes mellitus (T1DM)

[11] Had chronic or acute pancreatitis any time prior to study entry (Visit 1)

[12] Have a history of proliferative diabetic retinopathy or diabetic maculopathy (a dilated fundoscopic exam, performed by an ophthalmologist or optometrist between Visit 2 and Visit 3, is required to confirm eligibility) or nonproliferative diabetic retinopathy that requires acute treatment

[13] Have a history of ketoacidosis or hyperosmolar state/coma

[14] Have had 1 or more episode of severe hypoglycemia and/or 1 or more episode of hypoglycemia unawareness within the 6 months prior to Visit 1

[15] Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect GI motility

[16] New York Heart Association Functional Classification IV congestive heart failure

[17] Have any of the following CV conditions within 2 months prior to Visit 1: acute myocardial infarction, cerebrovascular accident (stroke), or hospitalization for CHF

[18] Have acute or chronic hepatitis, signs or symptoms of any other liver disease, or an alanine aminotransferase (ALT) level >3.0 the upper limit of normal (ULN) for the reference range, as determined by the central laboratory. Patients with nonalcoholic fatty liver disease are eligible to participate only if their ALT level is ≤3.0 the ULN for the reference range

[19] Have evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxicosis or adrenal crises), in the opinion of the investigator

[20] Have family or personal history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2

[21] Have a serum calcitonin level of

(a) ≥20 ng/L at Visit 1, if eGFR ≥60 mL/min/1.73m^2

(b) ≥35 ng/L at Visit 1, if eGFR <60 mL/min/1.73m^2

[22] Have evidence of significant, active autoimmune abnormality (for example, lupus, rheumatoid arthritis) that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 12 months.

[23] Known or suspected hypersensitivity to trial product(s) or related products

[24] History of hypersensitivity to insulin glargine

[25] Have had a transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant

[26] Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years

[27] Have a history of any other condition (such as known drug, alcohol abuse, or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol

[28] Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease)

Prior/Concomitant Therapy

[29] Have a history of insulin therapy except for the use of insulin for treatment of gestational diabetes or acute, temporary use of insulin (≤14 days), for example, for acute illness, hospitalization, elective surgery

[30] Treatment with any glucose-lowering agent(s) other than stated in the inclusion criteria (including DPP-4 inhibitors and GLP-1 receptor agonists) in a period of 3 months before screening prior to Visit 1

[31] Are receiving chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations) or have received such therapy within 1 month of Visit 1

[32] Have been treated with drugs that promote weight loss (for example, Saxenda [liraglutide 3.0 mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion], or similar other body weight loss medications including over-the-counter [OTC] medications [for example, allī®]) within 3 months prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3)

Prior/Concurrent Clinical Trial Experience

[33] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[34] Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed

[35] Have previously completed or withdrawn from this study or any other study investigating LY3298176

Other Exclusions

[36] 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

[37] Are Lilly employees

[38] Are unwilling or unable to comply with completing a diary to record data from the subject

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.

Patients should continue their usual exercise habits and generally follow a healthy meal plan (with consistent meal size and time of day) throughout the course of the study. Dietary counseling may be reviewed throughout the study, as needed. Per inclusion criterion [5] (Section 6.1), patients should not initiate during the study an organized diet and/or exercise weight reduction program 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.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) must not be rescreened.

7. Treatments

7.1. Treatments Administered

Patients will be randomized in a 1:1:1:3 ratio to receive LY3298176 5 mg, LY3298176 10 mg, LY3298176 15 mg, or insulin glargine. LY3298176 will be administered QW as SC injection in patients with T2D who are already treated with a stable dose of at least 1 and no more than 3 oral antihyperglycemic medications: metformin, sodium-glucose co-transporter-2 inhibitors, or sulfonylureas.

Table GPGM.3 shows the randomized treatments for the entire treatment period.

The starting dose of LY3298176 will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study low-dose arm. For the 10-mg arm, the starting dose of trizepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg arm, the starting dose of LY3298176 will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5 to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

The starting dose of insulin glargine will be 10 IU/day at bedtime, titrated to a FBG <100 mg/dL, following a treat-to-target algorithm (Riddle et al. 2003). Patients will titrate the insulin glargine dose in a weekly manner and will make the dose decision with the investigator for the first 8 weeks (phone or clinic visit). For further dose titration, from Week 8 to Week 16, patients will have a phone or clinic visit every other week.

Table GPGM.3. LY3298176 Treatment Regimens

Treatment Group						Treatment Period Interval
	Weeks 0 to 3	Weeks 4 to 7	Weeks 8 to 11	Weeks 12 to 15	Weeks 16 to 19	Weeks 20 to 104
15 mg LY3298176	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg →
10 mg LY3298176	2.5 mg	5 mg	7.5 mg	10 mg →		
5 mg LY3298176	2.5 mg	5 mg →				

Note: All doses will be administered QW using a single-dose prefilled syringe.

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

- explaining the correct use of the investigational agent(s) to the patient
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection as well as records of interruptions in study drug administration

- patient should be instructed to discard all used syringes for LY3298176 or pens for insulin glargine in a closeable, puncture-resistant container and dispose according to local regulations

7.1.1. Packaging and Labeling

The sponsor will provide LY3298176 in prefilled syringes and insulin glargine in prefilled pens. These will be dispensed via an interactive web-response system (IWRS). Prefilled syringes and prefilled pens will be packaged in cartons to be dispensed. Clinical trial materials will be labeled according to the country's regulatory requirements.

7.1.2. Medical Devices

The combination products provided for use in the study are LY3298176 investigational prefilled syringe and a marketed insulin glargine prefilled pen.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to 1 of the study treatment arms at Visit 3. Assignment to treatment arms will be determined by a computer-generated random sequence using an IWRS. Patients will be randomized in a 1:1:1:3 ratio to receive 5 mg LY3298176, 10 mg LY3298176, 15 mg LY3298176, or insulin glargine. The randomization will be stratified by country, baseline HbA1c concentration (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and baseline SGLT-2i use (Yes or No).

7.2.1. Selection and Timing of Doses

7.2.1.1. LY3298176

Assignment to LY3298176 (3 doses) or insulin glargine will occur at randomization.

There are no restrictions on the time of day each weekly dose of LY3298176 is given, but it is advisable to administer the SC injections on the same day and same time each week. The actual date and time of all dose administrations will be recorded by the patient. If a dose of LY3298176 is missed, the patient should take it as soon as possible unless it is within 72 hours of the next dose, in which case, that dose should be skipped and the next dose should be taken at the appropriate time.

7.2.1.2. Insulin Glargine

Dosing for patients randomized to insulin glargine will start at 10 units once daily. Patients should administer their daily doses at the time of day agreed upon between the patient and the investigator, typically before bedtime. Patients assigned to the insulin glargine treatment arm will be instructed to adjust insulin glargine doses to a target FBG of <100 mg/dL (5.6 mmol/L) based on the median value of the last 3 self-monitored fasting blood glucose (SMBG) values according to the schedule below (Riddle et al. 2003). Insulin glargine dose adjustments should occur once in a week. After Week 8, patients will continue to adjust insulin glargine per the titration algorithm; the insulin glargine dose will be also reviewed and revised, as needed, at subsequent office visits. There will be no central oversight of insulin glargine titration. Add-on

glycemic rescue therapy should be initiated for patients who met prespecified criteria for severe, persistent hyperglycemia, and further titration of glargine cannot control the condition (see Table GPGM.4).

Table GPGM.4. Titration of Insulin Glargine

Median Fasting Blood Glucose[a]		Adjustment of Insulin Glargine
mg/dL	mmol/L	
≤70	≤3.9	Decrease by 2 to 4 units[b,c]
71 to 99	4.0 to 5.5	No adjustment
100 to 119	5.6 to 6.6	Increase by 2 units
120 to 139	6.7 to 7.7	Increase by 4 units
140 to 179	7.8 to 9.9	Increase by 6 units
≥180	≥10.0	Increase by 8 units

Abbreviation: SMBG = self-monitored blood glucose.

[a] Based on the last 3 self-monitored fasting blood glucose (SMBG) values.

[b] Dose should also be decreased by 2 to 4 units in the following situations:

- If multiple episodes of nonsevere hypoglycemia were recorded during the assessment period at any time during the day; and/or
- If at least 1 episode that met the criteria for severe hypoglycemia (events requiring assistance to administer therapy) or was associated with self-monitored blood glucose (SMBG) value <54 mg/dL (<3.0 mmol/L) was recorded during the assessment period.

[c] If only 1 hypoglycemic episode with SMBG value ≥54 mg/dL (≥3.0 mmol/L) and ≤70 mg/dL (≤3.9 mmol/L) was recorded, insulin dose should not be changed.

Source: Riddle et al. 2003.

7.3. Blinding

This trial is open-label due to the differences in dosing schedule, titration, and devices between QW LY3298176 and once-daily insulin glargine.

7.4. Dosage Modification

7.4.1. Study Drugs

Details about dose administration of LY3298176 during the study are described in Sections 7.2.1 and 8.1.2.

Insulin glargine will be adjusted according to the TTT method (see Section 7.2.1.2, Table GPGM.4).

7.4.2. Reduction and/or Discontinuation of Concomitant Antihyperglycemic Medications

Temporary discontinuation of concomitant antihyperglycemic medications <14 consecutive days is allowed for certain clinical situations (for example, severe dehydration, elective surgery, or need for radiologic exam involving IV iodinated contrast dye).

In the event of a hypoglycemic episode(s) (clinical symptoms of hypoglycemia and/or blood glucose (BG)-confirmed symptomatic BG hypoglycemia [glucose concentration ≤3.1 mmol/L

[{56 mg/dL}]), in patients on any oral treatment combination containing sulfonylurea, the sulfonylurea dosage should be reduced or discontinued. In patients not on sulfonylurea (anymore) but on dual oral treatment of metformin and SGLT-2i, in case of (further) hypoglycemic episode(s), the dose of metformin should be reduced or discontinued prior to reducing/discontinuing SGLT-2i. When hypoglycemia develops in patients on any oral monotherapies, the dose of this oral medication should be reduced or discontinued. For further information see Section 9.2.2.1.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his or 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 the study drug in a locked and secure environment. Please refer to the study drug label for specific storage conditions. Patients will receive insulated bags with cooling gel packs for use in transporting the study drug carton from the site to home.

Study site staff must regularly assess whether the patient is correctly administering the assigned study drug and storing the study drug according to the provided instructions.

7.6. Treatment Compliance

Study drug compliance will be determined by the following:

- Study drug administration data will be recorded by the patient and reviewed by the investigator at each study visit.
- The patients will be instructed to return any unused study drug and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

In the 3 LY3298176 treatment arms, as well as the insulin glargine arm, treatment compliance for each visit interval is defined as taking at least 75% of the required doses of study drug. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

In addition to the assessment of a patient's compliance with the study drug administration, other aspects of compliance with the study treatments will be assessed at each visit based on the patient's adherence to the visit schedule, compliance with the concomitant antihyperglycemic medication regimen, completion of study diaries, the results of home BG monitoring, and any other parameters the investigator considers necessary.

Initially, patients considered to be poorly compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

7.7. Concomitant Therapy

Patients will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments. Prohibited medications include GLP-1 receptor agonists, amylin agonists, and DPP-4 inhibitors. The list of excluded medications and procedures is provided in the Manual of Operations. Other medications for glycemic control for patients meeting severe persistent hyperglycemia criteria for rescue may be added during the study at the investigator's discretion. Patients on the insulin glargine arm should receive other antihyperglycemic medication only when further dose adjustment of glargine cannot control the persistent hyperglycemia.

Short-term insulin use is allowed for certain clinical situations (for example, elective surgery, during hospitalization, hyperosmolar states). Rescue therapy with other glucose-lowering agents, including basal or rapid acting insulins, may be medically indicated in certain situations after randomization due to severe, persistent hyperglycemia or early discontinuation of study treatment. If insulin is prescribed as a rescue therapy, it must be differentiated from short-term use of insulin therapy for medical emergencies when reported in the eCRF.

Investigative site staff will inform patients that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study. This may not be possible when initiated for treatment of medical emergencies, in which case, the patient will inform the investigator or a designated site staff member as soon as possible. Any additional medication initiated during the course of the study (including OTC drugs, such as paracetamol or aspirin) must be documented, and the name of the drug and the date(s) of administration must be recorded on the "Concomitant Medications" section of the eCRF.

All nonstudy medications will be recorded on the eCRF at all visits.

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

7.7.1. Management of Patients with Gastrointestinal Symptoms

In the Phase 2 program, the most commonly reported treatment-emergent adverse events (TEAEs) for patients receiving LY3298176 were nausea, vomiting, and diarrhea.

The LY3298176 dose escalation scheme has been designed to minimize the development of intolerable GI symptoms. The escalation period is considered to be 24 weeks, which allows 20 weeks to escalate to 15 mg and additional 4 weeks to reach steady state. During the dose escalation period, every effort should be made by the investigator to be able to escalate and maintain patients on the corresponding study drug dosage.

To mitigate GI symptoms and manage patients with intolerable GI AEs, the investigator should:

- Advise patients to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
- Prescribe symptomatic medication (for example, anti-emetic or anti-diarrheal medication) per local country availability and individual patient needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
- Temporarily interrupt LY3298176 (omit 1 dose, the patient will take 3 of 4 doses at that dose level). The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF.
- After the interruption, restart at the same dose with the patient taking medication to alleviate their GI symptoms (Section 8.1.2).

If intolerable GI symptoms or events persist despite the above measures, the investigator may decide to continue treatment at a lower, tolerated maintenance dose of LY3298176 (5 mg or 10 mg).

- Patients at 5 mg or lower will be discontinued from LY3298176.
- Patients at 7.5 mg or 10 mg will decrease the dose to 5 mg.
- Patients at 12.5 mg or 15 mg will decrease the dose to 10 mg.

If de-escalation of the LY3298176 dose is necessary, the investigator will use the IWRS to receive the appropriate LY3298176 dispensing information. If de-escalation is needed between scheduled visits, the IWRS will have unscheduled visits (for example, Visit 13a) dedicated to provide dispensing information for patients whose dose has been de-escalated. Those patients who have their dose de-escalated, will not be escalated again. The dose can be de-escalated only once. After that, the patients will have to discontinue LY3298176 if intolerable GI AE persists. Please see the Manual of Operations for more detailed instructions.

If intolerable persistent GI symptoms occur after 24 weeks, the investigator should take the above measures to keep the patient on study treatment. However, after the escalation period (Week 24), dose decreases will not be permitted.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

LY3298176 will not be made available after conclusion of the study to patients.

7.8.2. Special Treatment Considerations

Investigators will be trained on how to apply decision criteria for the timing and method of intervention in patients who do not reach glycemic targets during the treatment period. An additional therapeutic intervention should be considered for patients with persistent hyperglycemia as described in Section 9.2.2.2.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Patient Decision**
  - The patient requests to discontinue investigational product.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the electronic case report form (eCRF).

  Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:

  - ALT or aspartate aminotransferase (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 (INR) >1.5
  - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - 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, patients will be discontinued from the investigational product in the following circumstances:
  - If a patient is inadvertently enrolled and it is determined that continued treatment with study drug would not be medically appropriate (see Section 8.1.3)
  - Acute or chronic pancreatitis
  - If a patient is diagnosed with MTC after randomization
  - If a patient is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
  - Any significant study drug-related hypersensitivity reaction
  - Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken

- If female patient becomes pregnant
- If a patient is diagnosed with T1DM

Patients who stop the study drug permanently may receive another glucose-lowering intervention (Section 7.4.2) and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements.

Patients discontinuing from the investigational product 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.

8.1.2. Temporary Interruption of Study Treatment

In certain situations after randomization, the investigator may need to temporarily interrupt study drug. Every effort should be made by the investigator to maintain patients on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so.

- If the number of doses missed is ≤2, the treatment can be restarted at the same dose, if the drug was well tolerated prior to discontinuation.
- If the number of missed doses is ≥3, then the treatment should be restarted at 5 mg irrespective of the dose the patient was receiving before the interruption and subsequently, escalated as required by protocol (See Manual of Operations for further details).

If study drug 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. If the study drug interruption is due to intolerable persistent GI AE (for example, nausea, vomiting, or diarrhea), the patients should be treated as suggested in Section 7.7.1.

The data related to temporary interruption of study treatment will be entered on the eCRF.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor clinical research physician (CRP) agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. 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

In order to minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep patients in the study irrespective of the following:

- adherence to study drug
- adherence to visit schedule
- missing assessments
- study drug discontinuation due to AE (Section 8.1.1)
- development of comorbidities
- development of clinical outcomes

The circumstances listed above are not valid reasons for discontinuation from the study.

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- If a female patient becomes pregnant
- If a patient is diagnosed with T1DM
- patient requests to be withdrawn from the study

Patients who agree to provide information relevant to any trial endpoint at the end of the study are not considered to have discontinued from the study.

A patient who withdraws consent and clearly indicates that there will be no further contact of any kind with the site will be considered to have discontinued from the study.

Prior to early study discontinuation, the patient will discontinue study drug and will have end-of-study procedures (ET visit) performed as shown in the Schedule of Activities (Section 2). During the ET visit, the patient may be prescribed an appropriate glucose-lowering regimen and glucose self-monitoring plan. Visit 801 (safety follow-up visit) should be performed approximately 4 weeks after the ET visit as the final study visit.

Patients 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 patient 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. Every attempt will be made to minimize the number of patients considered lost to follow-up at the end of the study. Patients will be informed about the importance of completing the study and providing updated contact information to the study site when necessary.

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 and Procedures

The primary efficacy measurement in this study is mean change in HbA1c from baseline to 52 weeks, as determined by the central laboratory. Blood samples for HbA1c measurements will be collected at specific clinic visits as summarized in the Study Schedule.

9.1.2. Secondary Efficacy Assessments and Procedures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule.

- Change in HbA1c from baseline
- Change in weight from baseline
- Proportion of patients achieving a target HbA1c <7% (53 mmol/mol)

9.1.3. Exploratory Efficacy Assessments and Procedures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule.

- Fasting serum glucose measured in the central laboratory (actual values and change from baseline)
- Seven-point SMBG profile (actual values and change from baseline to prespecified time points). Patients will be asked to perform two 7-point SMBG profiles over a 24-hour period, on nonconsecutive days, during the 14-day period prior to each visit, according to the Study Schedule. The 7-point profile consists of pre-meal and 2-hour postprandial SMBG measurements for the morning, midday, and evening meals in one day, and at bedtime. Pre-meal measurements should be taken before the patient begins eating the meal. Patients should record their glucose measurements in their patient diaries, which are considered source documents and are to be returned to the investigator at each study visit. Values from the 7-point SMBG profile will be transferred from the diary and recorded on the eCRF.
- Change waist circumference from baseline

9.1.4. 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.

9.2. Adverse Events

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

The investigator is responsible for the appropriate medical care of patients 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 investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves or stabilizes with appropriate diagnostic evaluation. 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 informed consent form (ICF) is signed, study site personnel will record via the electronic case report form (eCRF) the occurrence and nature of each patient'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. For each AE, the onset and duration, the seriousness and severity, and the actions taken with respect to study treatment will be recorded. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via the CRF.

Procedures and assessments performed prior to Visit 3 are considered screening procedures. The results of these procedures and assessments should be considered pre-existing conditions and should be reported as medical history or concomitant illness.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, 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 investigational product, study device, and/or study procedure and the AE.

The investigator answers Yes or 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 patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via the CRF, 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 inpatient 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 patient 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 inpatient 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 patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, 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. Patients with a serious hepatic AE should have additional data collected using the eCRFs (Section 9.4.5.1).

Pregnancy (during maternal or paternal exposure to investigational product) 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 patient disposition eCRF 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 or 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 investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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

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

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 blood-equivalent glucose meters and strips) in accordance with the 2017 American Diabetes Association position statement on glycemic targets (American Diabetes Association 2017):

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of ≤70 mg/dL (≤3.9 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured BG ≤70 mg/dL (≤3.9 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available but with a measured BG ≤70 mg/dL (≤3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <54 mg/dL (<3.0 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured BG <54 mg/dL (<3.0 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available but with a measured BG <54 mg/dL (<3.0 mmol/L).

Severe hypoglycemia (Level 3):

- **Severe hypoglycemia** is defined as an episode with severe cognitive impairment 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. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

Nocturnal hypoglycemia:

- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

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

To avoid duplicate reporting, all consecutive BG values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

9.2.2.2. Severe, Persistent Hyperglycemia

Add-on glycemic rescue therapy will be allowed for patients who meet any of the following prespecified criteria for severe, persistent hyperglycemia. In this case, the investigator determines if a new intervention is warranted, after noncompliance with the assigned therapeutic regimen is ruled out as the reason for hyperglycemia. Patients should continue administering assigned study drugs (insulin glargine or LY3298176). The criteria are as follows:

a) average daily BG from the QW 4-point SMBG profile >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period any time during the first 8 weeks post randomization;
   OR
b) average daily BG from the QW 4-point SMBG profile >240 mg/dL (>13.3 mmol/L) over a consecutive 2-week period at any time 8 to 16 weeks post randomization;
   OR
c) average daily BG from the QW 4-point SMBG profile >200 mg/dL (>11.1 mmol/L) over a consecutive 2-week period at any time beyond the first 16 weeks post randomization.
   OR
d) HbA1c ≥8.5% (69 mmol/mol) on 2 consecutive measurements separated by at least 8 weeks at any time beyond the first 24 weeks post randomization

Investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that they do not have an acute condition that is raising their BG. For patients in the insulin glargine arm, the above-described criteria for severe, persistent hyperglycemia will only be applicable after Week 12. The first choice before initiating any rescue therapy for those patients during the initial 12 weeks will be to follow the TTT algorithm and to increase the dose

of insulin glargine. This approach is recommended as first measure during the entire study course. For patients who meet criteria for severe persistent hyperglycemia, the investigator will decide, in consultation with the patient, on an appropriate glucose-lowering intervention (rescue therapy). Investigators should follow national standards of care for diabetes management in respective participating countries or the American Diabetes Association/ European Association for the Study of Diabetes guidance (Inzucchi et al. 2015). Glucagon-like peptide-1 receptor agonists, basal insulins, amylin analogs, and DPP-4 inhibitors are prohibited medications and must not be included in the rescue intervention (with the exception of basal insulin in the LY3298176 arm). Patients who receive a new intervention should also continue administering study drugs for the remaining period in the trial.

9.2.2.3. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with LY3298176, including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases) (Banks and Freeman 2006; Koizumi et al. 2006); the pain is often associated with nausea and vomiting)
- serum amylase (total and/or pancreatic) and/or lipase ≥3X ULN
- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with LY3298176 but will continue in the study on another glucose-lowering regimen. The most appropriate diabetes therapeutic regimen will be decided by the investigator based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

Each patient will have measurements of p-amylase and lipase (assessed at the central laboratory) as shown on the Schedule of Activities (Section 2) to assess the effects of the investigational doses of LY3298176 on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients

(Nauck et al. 2017; Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3X ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the patient's overall clinical condition. Only cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee (CEC). In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page by study site. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

9.2.2.4. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN-2 will be excluded from the study. The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy including MTC and papillary carcinoma and measurements of calcitonin. This data will be captured in specific eCRFs. The purpose of calcitonin measurements is to assess the potential of LY3298176 to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Patients with eGFR ≥60 mL/min/1.73m^2 at Baseline

Patients who develop serum calcitonin increases ≥50% over the screening value AND an absolute value ≥20 ng/L and <35 ng/L will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be encouraged to undergo additional endocrine assessment and longer term follow-up by an endocrinologist to exclude a serious adverse effect on the gland.

Patients with an increase in serum calcitonin ≥50% over the screening value AND an absolute value ≥35 ng/L will be recommended to immediately undergo additional endocrine assessments and longer term follow-up by an endocrinologist. If a patient's labs meet this criteria, these clinically significant labs should be recorded as an AE.

For patients who require additiona QC Did not see in Amendment summary nor Revised Protocol Sections l endocrine assessment because of increased calcitonin concentration per criteria provided in this section, data from the follow-up assessment will be collected in the specific section of the eCRF.

Patients with eGFR <60 mL/min/1.73m^2 at Baseline

LY3298176 should be discontinued (after first confirming the value) if postrandomization calcitonin value is ≥35 ng/L and has increased at least 50% over baseline. A consultation with a thyroid specialist (if not available, an endocrinologist) should be obtained.

If the increased calcitonin value (≥35 ng/L and increases by ≥50% compared to baseline) is observed in a patient who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped and calcitonin levels should be measured after an appropriate washout period.

For patients who require additional endocrine assessment because of increased calcitonin concentration per criteria provided in this section, data from the follow-up assessment will be collected in the specific section of the eCRF.

9.2.2.5. Major Adverse Cardiovascular Events

Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment. The nonfatal CV AEs to be adjudicated include MI; 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.

9.2.2.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Patients who develop any event from these groups of disorders should undergo an electrocardiogram (ECG) which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 9.2.1 must be reported as SAEs.

9.2.2.7. Hypersensitivity Events

All allergic or hypersensitivity 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 study drug(s) via the eCRF created for this purpose. Additional samples should also be collected as outlined in Section 9.4.4. Study drug(s) should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug(s). Study drug(s) may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug(s) is permanently discontinued, the patient will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the patient's clinical status, and will continue in the trial to collect all planned efficacy and safety measurements.

9.2.2.7.1. Injection Site Reactions

Injection site reactions will be collected on the eCRF separate from the hypersensitivity reaction eCRF. At the time of AE occurrence in the LY3298176 arm, samples will be collected for measurement of LY3298176 ADA and LY3298176 concentration.

9.2.2.7.2. Anti-Drug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 9.4.4.

9.2.2.8. Diabetic Retinopathy Complications

Dilated retinal fundoscopic exam will be performed by an eye care professional (ophthalmologist or optometrist) for all patients between Visit 2 and Visit 3 to exclude patients with proliferative retinopathy and/or maculopathy. The results from this exam will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy.

A follow-up, dilated fundoscopic exam should be performed when clinically indicated by any adverse event suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF.

9.2.2.9. Hepatobiliary Disorders

All events of TE biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 9.4.5.1 and Appendix 4.

9.2.2.10. Severe Gastrointestinal Adverse Events

LY3298176 may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form. For detailed information concerning the management of GI AEs, please refer to Section 7.7.1.

9.2.2.11. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. GI AEs have been reported with LY3298176, including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 receptor agonists (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Patients should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

9.2.2.12. Metabolic Acidosis, Including Diabetic Ketoacidosis

Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been reported rarely in patients with T2DM. Patients who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, SGLT2is should be discontinued (if used), patients should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

Lactic acidosis has been reported rarely in patients with T2DM associated with use of metformin, excessive alcohol intake, and decreased renal function. Routine bicarbonate assessment will be performed during the course of the study. If lactic acidosis is suspected, metformin should temporarily be discontinued (if used) until the resolution of the event.

9.2.2.13. Amputation/Peripheral Revascularization

All cases of amputation and peripheral revascularization should be reported as an AE.

9.2.2.14. Major Depressive Disorder/Suicidal Ideation

The prevalence of depressive symptoms and disorders is increased in patients with T1DM or T2DM (ADA 2017). Any AE of major depressive disorder or suicidal ideation should be reported.

9.2.3. 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, to monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

Study drug overdose (more than the specified number and dose of injections) will be reported as an AE. In the event of overdose, refer to the IB for LY3298176 and/or Product Label for insulin glargine (Basaglar USPI, 2015 [WWW]).

9.4. Safety

9.4.1. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations included in Manual of Operations for the study.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate subject management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via the eCRF.

All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist 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 a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via the eCRF.

9.4.3. Laboratory Tests

For each patient, 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 patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via the eCRF.

9.4.4. Immunogenicity Assessments

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against LY3298176 as specified in the Schedule of Activities (Section 2).

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against the LY3298176. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity sample. All samples for immunogenicity should be taken predose when applicable and possible. In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected (including ADA, PK, and, exploratory immune safety sample) as close to the onset of the event as possible, at the resolution of the event, and 30 days following the onset of the event. 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 ADAs in the presence of the LY3298176 at a laboratory approved by the sponsor. Sample collected at Visit 801 will assess immunogenicity at washout of LY3298176 (5 half-lives post end of treatment).

Treatment-emergent ADAs are defined in Section 10.3.6.

Samples with LY3298176 ADA detected will be titered and evaluated for their ability to neutralize the activity of assigned treatment (LY3298176-neutralizing antibodies). Samples with LY3298176 ADA detected will also be tested for cross-reactive binding to native GIP and GLP-

1, and, if such is detected, then for neutralizing antibodies against native GIP and GLP-1, respectively.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and Ethical Review Boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY3298176. Any samples remaining after 15 years will be destroyed.

9.4.5. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.5.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study 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 ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected from the first 150 patients in each LY3298176 arm, all patients aged ≥70 years, and all patients with severe renal impairment or ESRD (eGFR<30 mL/min).

Plasma LY3298176 concentrations will be determined from blood samples obtained from patients receiving LY3298176 treatment. Blood samples for PK assessment will be collected after 7, 15, 23, and 35 weeks of LY3298176 treatment per the Study Schedule or at early termination (reference to SoA). Each patient will be assigned via IWRS to one of the sampling PK time windows of 1 to 24 hours, 24 to 96 hours, or 120 to 168 hours post dose at Weeks 7, 15, 23, and 35.

The date and time of the most recent SC injection administered prior to collecting the sample must be recorded on the eCRF from the study diaries.

The date and time at which each sample was drawn must be recorded on the laboratory accession page.

Concentrations of LY3298176 will be assayed using a validated liquid chromatography mass spectrometry (LC/MS) method.

Bioanalytical samples collected to measure LY3298176 concentrations will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Samples to assess the PD properties of LY3298176 are included in the efficacy measures and not applicable in this section.

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.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3298176 and to investigate genetic variants thought to play a role in T2DM. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study or for a shorter period if local regulations and/or Ethical Review Boards (ERBs)/investigational review boards (IRBs) 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 LY3298176 or after LY3298176 become(s) 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 patient response (including safety), and

clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including proteins, lipids, and other cellular elements.

Serum and plasma samples for nonpharmacogenetic 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 LY3298176, pathways associated with T2DM, mechanism of action of LY3298176, and/or research method or in validating diagnostic tools or assay(s) related to T2DM.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last patient 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 course of the development and commercialization of both study drugs.

9.9. Health Economics

The following questionnaires will be completed by the patients at specific clinic visits according to the Schedule of Events (Section 2). At these visits, the questionnaires should be completed before the patient has discussed their medical condition or progress in the study with the investigator and/or site staff and before any other study procedures if the patient is not adversely affected by their fasting condition.

9.9.1. European Quality of Life (EQ-5D-5L)

Generic HR-QoL will be assessed using the EQ-5D-5L (EQ-5D; EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3251 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. In conjunction with the health state data, it provides a composite picture of the respondent's health status.

The EQ-5D-5L is used worldwide and is available in more than 170 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide (EuroQoL Group 2015).

9.9.2. Ability to Perform Physical Activities of Daily Living (APPADL)

The Ability to Perform Physical Activities of Daily Living (APPADL) questionnaire contains 7 items that assess how difficult it is for patients to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs (Hayes et al. 2011; Hayes et al. 2012). Items are scored on a 5-point numeric rating scale, where 5 = "not at all difficult" and 1 = "unable to do." A raw overall score is calculated by simply summing the scores of the 7 items, and a transformed overall score is obtained by linearly transforming the raw overall score to a 0 to 100 scale. A higher raw overall score and a higher transformed overall score are indicative of better ability to perform activities of daily living.

9.9.3. Impact of Weight on Self-Perception Questionnaire (IW-SP)

The Impact of Weight on Self-Perception (IW-SP) questionnaire contains 3 items that assess how often the patients' body weight affects how happy they are with their appearance and how often they feel self-conscious when out in public (Hayes and DeLozier 2015). Each item is rated on a 5-point scale ranging from "always" to "never." Total scores for the IW-SP are derived by summing the item scores and dividing by the number of items. The score can also be transformed to a range from 0 to 100. Higher IW-SP scores correspond to better self-perception (Hayes and DeLozier 2015).

9.9.4. Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The status (s) and change (c) versions of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) will be used during the study to assess the patients' satisfaction with their diabetes treatment and the perceived frequency of hyperglycemia and hypoglycemia. The questionnaire contains 8 items (Bradley 1994). Each item is rated on a 7-point Likert scale. Six items (1 and 4 through 8) are summed to produce a measure of treatment satisfaction ranging from 0 "very dissatisfied" to 6 "very satisfied." The remaining 2 items (2 and 3) are treated individually. Item 2 measures the perceived frequency of hyperglycemia on a scale ranging from 0 "none of the time" to 6 "most of the time," and Item 3 measures the perceived frequency of hypoglycemia on the same scale. The change version has the same 8 items as the status version with a small alteration of the wording of Item 7. The DTSQc response options differ from those of the DTSQs to produce measures of relative change rather than absolute satisfaction.

10. Statistical Considerations

10.1. Sample Size Determination

Patients will be randomized in a 1:1:1:3 ratio to 5 mg LY3298176, 10 mg LY3298176, 15 mg LY3298176, and insulin glargine to optimize CV risk assessment of LY3298176.

Although the primary objective is to establish noninferiority, sample size selection is guided by the objective of establishing superiority of each LY3298176 dose to insulin glargine relative to the reduction in mean HbA1c change from baseline at 52 weeks from randomization irrespective of adherence to investigational product or introduction of rescue therapy for persistent severe hyperglycemia ("treatment-regimen" estimand).

The sample size determination assumes that evaluation of superiority of 10 mg LY3298176 and 15 mg LY3298176 to insulin glargine will be conducted in parallel, each at a 2-sided significance level of 0.025 using a 2-sample t-test. Additionally, a 0.30% superior mean HbA1c reduction from baseline at 52 weeks from randomization for 10 mg LY3298176 and 15 mg LY3298176 compared to insulin glargine and a common standard deviation (SD) of 1.3% are assumed for statistical power calculations. Under the assumptions above, randomizing 1878 patients in a 1:1:1:3 ratio to 5 mg LY3298176 (313 patients), 10 mg LY3298176 (313 patients), 15 mg LY3298176 (313 patients), and insulin glargine (939 patients) provides 90% power to demonstrate superiority of each LY3298176 dose to insulin glargine.

The chosen sample size and randomization ratio also provides >90% power to establish superiority of 10 mg LY3298176 and 15 mg LY3298176 doses to insulin glargine in absence of confounding effects of rescue therapy for persistent severe hyperglycemia ("efficacy" estimand). For comparison of each LY3298176 dose to insulin glargine using data collected prior to the initiation of any rescue medication or premature treatment discontinuation, conducted in parallel using a 2-sample t-test, each at a 2-sided significance level of 0.025, a 0.30% superior mean HbA1c reduction compared to insulin glargine, a common SD of 1.1%, and no more than 28% initiate of any rescue antihyperglycemic medication or prematurely discontinue study drug by 52 weeks are assumed.

The trial is designed to contribute toward a meta-analysis across Phase 3 trials demonstrating that LY3298176 treatment is not associated with excessive CV risk. The anticipated treatment allocation of pooled LY3298176 versus pooled comparator is 3:1 in other LY3298176 Phase 3 clinical trials. The primary measure of CV risk is the hazard rate of CEC that confirmed 4-component MACE-4: CV death, myocardial infarction (MI), stroke, and hospitalization for unstable angina. Under the assumption of no increase or decrease in CV risk with LY3298176 compared to pooled comparator, approximately 133 patients with MACE-4 events are required to have 90% power to ensure that the upper 95% confidence limit for the hazard ratio is less than 1.8 in the meta-analysis. Assuming 33 to 40 patients with MACE-4 events per 1000 patient years of exposure and 2% reduced exposure due to lost to follow-up, patients followed for an average of 18 to 22 months is expected to result in 110 patients with MACE-4 events.

10.2. Populations for Analyses

For purposes of analysis, the following analysis sets are defined in Table GPGM.5 below:

Table GPGM.5. Description of Analysis Sets

Analysis Set	Description
Screened patients	All participants who sign informed consent
Randomized patients	All patients who are randomly assigned a treatment arm
modified intention-to-treat (mITT) set	All randomly assigned participants who are exposed to at least 1 dose of study drug.
Efficacy analysis set (EAS)	Data obtained during Study Period II and III from mITT, excluding data after initiating rescue antihyperglycemic medication or stopping study drug (last dose date + 7 days). In the event of a treatment error, participants will be analyzed according to the treatment they were randomized.
Full analysis set (FAS)	Data obtained during Study Period II and III from mITT, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.
Safety analysis set (SAS)	Data obtained during both Study Period II, III, and IV from mITT, regardless of adherence to study drug or initiation of rescue antihyperglycemic medication.

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

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) will be calculated at 95%, 2-sided. In statistical summaries and analyses, patients will be analyzed as randomized.

There will be 2 estimands of interest in comparing efficacy of LY3298176 doses with insulin glargine. First estimand, the "efficacy" estimand, represents efficacy prior to discontinuation of study drug without confounding effects of antihyperglycemic rescue therapy. Second estimand, the "treatment-regimen" estimand, represents the efficacy irrespective of adherence to study drug or initiation of rescue antidiabetic drugs.

The primary efficacy assessment, guided by the "efficacy" estimand, will be conducted using EAS. The primary efficacy assessment, guided by the "treatment-regimen" estimand, will be conducted using FAS. As they are intended for different purposes, no multiplicity adjustments will be made for conducting 2 primary efficacy assessments.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3298176 doses with insulin glargine irrespective of adherence to study drug or initiation of

antihyperglycemic rescue therapy. Thus, safety analysis will be conducted using safety analysis set (SAS). Selected safety analysis may be conducted after excluding data on rescue therapy.

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment arms relative to continuous measurements assessed over time will be a mixed model for repeated measures (MMRM), with terms: treatment, visit, and treatment-by-visit interaction, country, SGLT-2i use (Yes or No), and baseline measurement as a covariate. An unstructured covariance structure will model relationship of within-patient errors.

Kaplan-Meier method will be used for estimation of cumulative event-free survival rates over time, and cox proportional hazards regression analysis will be used to compare hazard rates among treatments.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Fisher's exact test will be used to examine the treatment difference in categorical outcomes. Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. Summary statistics for discrete count measures will include sample size, mean, SD, median, minimum, and maximum. The negative binomial regression model will be used for the treatment comparison of discrete count measures.

Other statistical methods may be used, as appropriate, and details will be documented in the SAP.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Frequency counts and percentages of all patients screened, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing of randomized patients not receiving study drug will be provided. Of the patients in modified intention-to-treat (mITT) set, frequency counts and percentages of patients completing the study, prematurely discontinuing the study, including reason for premature discontinuation, will be presented by treatment groups. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment group will be provided.

10.3.2.2. Patient Characteristics

Demographic, medical history, and concomitant illness will be summarized by treatment group, using the mITT set.

10.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by anatomical therapeutic chemical classification and treatment arm using the mITT set. In particular, the incidence of initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint. Dose modifications of oral antihyperglycemic therapy will also be compared between treatment arms.

10.3.2.4. Treatment Compliance

Of the patients in mITT set, frequency counts and percentages of patients prematurely discontinuing study drug, including reason for premature discontinuation, will be presented by treatment groups. A Kaplan-Meier analysis of time from randomization to premature study drug discontinuation by treatment group will be provided.

Treatment compliance for each visit interval is defined as taking at least 75% of required injections of study drugs. Frequency counts and percentages of patients compliant to study drug will be summarized by treatment arms and visits using the mITT set.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

As indicated in Section 10.3.1, there will be 2 primary efficacy analyses conducted to establish noninferiority of 10 mg LY3298176 and 15 mg LY3298176 to insulin glargine relative to mean change in HbA1c from baseline to 52-week visit.

For the FDA, the primary efficacy analysis will be guided by the "treatment-regimen" estimand defined in Section 10.3.1. This assessment will analyze change in HbA1c values obtained at 52-week visit using an analysis of covariance (ANCOVA) with terms, treatment, stratification factors, and baseline HbA1c as a covariate. Missing change in HbA1c from baseline values at 52-week visit will be imputed based on observed changes in HbA1c from baseline values at the visit from patients in the same treatment arm who had their efficacy assessed after early discontinuation of study drug and/or initiation of rescue antihyperglycemic medication. With the aid of the ANCOVA, 2-sided 97.5% CI for the difference in mean change in HbA1c from baseline to 52-week visit between 10 mg LY3298176 and insulin glargine as well as between 15 mg LY3298176 and insulin glargine will be constructed. Analysis will be conducted with multiple imputations, and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987). If the upper limit of the CI is below 0.3%, LY3298176 dose will be declared noninferior to insulin glargine.

For all other purposes, the primary efficacy analysis will be guided by the "efficacy" estimand defined in Section 10.3.1. This assessment will be conducted using EAS. The primary analysis model for HbA1c measurements over time will be an MMRM. The response variable of MMRM will be change in HbA1c from baseline values obtained at each scheduled postbaseline visit. The independent variables of the MMRM model are treatment group (5 mg LY3298176, 10 mg LY3298176, 15 mg LY3298176, and insulin glargine), visit, and treatment-by-visit interaction, country, SGLT-2i use (Yes or No), and baseline HbA1c as a covariate. An unstructured covariance structure will model relationship of within-patient errors. If the analysis fails to converge, the following variance-covariance matrix will be used (in order) until convergence is achieved: heterogeneous compound symmetry, compound symmetry, and first-order autoregressive. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. With the aid of the MMRM analysis, 2-sided 97.5% CI for the difference in mean change in HbA1c from baseline to 52-week visit between 10 mg LY3298176 and insulin glargine as well as between 15 mg LY3298176 and insulin glargine will be constructed. If the

upper limit of the CI is below 0.3%, LY3298176 dose will be declared noninferior to insulin glargine.

10.3.3.2. Secondary Analyses

The secondary study objectives subject to type 1 error rate control are as follows:

- noninferiority of 5 mg LY3298176 dose to insulin glargine relative to mean change in HbA1c from baseline to 52-week visit
- superiority of each LY3298176 dose to insulin glargine relative to mean change in HbA1c from baseline to 52-week visit
- superiority of each LY3298176 dose to insulin glargine relative to mean change in body weight from baseline to 52-week visit
- superiority of each LY3298176 dose to insulin glargine relative to proportion of patients achieving target value of HbA1c <7% at 52-week visit

Type 1 error-controlled strategy for primary and secondary endpoints will be described in the SAP. All type 1 error-controlled secondary efficacy analyses will be conducted relative to both estimands, the "efficacy" estimand and the "treatment-regimen" estimand.

Analysis of change from baseline in body weight at 52-week visit will be conducted in a manner similar to the primary efficacy analyses with change in body weight from baseline as the response variable, baseline HbA1c category (≤8.5%, >8.5%) in place of baseline HbA1c, and baseline body weight as a covariate.

Comparisons among treatments relative to proportion of patients achieving HbA1c target value of <7.0% (53 mmol/mol) at 52-week visit will be conducted using a logistic regression analysis with terms treatment, country, SGLT-2i use (Yes or No), and baseline HbA1c as a covariate. In the analysis of patients achieving HbA1c target value relative to the "efficacy" estimand, subjects with missing values at 52-week visit will be excluded. In the analysis of patients achieving HbA1c target value relative to the "treatment-regimen" estimand, missing values at 52-week visit will be imputed based on observed data at respective visits from patients in the same treatment arm who had their efficacy assessed after early discontinuation of study drug and/or initiation of rescue medication. Analysis will be conducted with multiple imputations and statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

10.3.3.3. Tertiary/Exploratory Analyses

All exploratory efficacy analysis will be guided by "efficacy" estimand and will be conducted using EAS. Details will be provided in the SAP.

10.3.4. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3298176 doses with insulin glargine irrespective of adherence to study drug or initiation of rescue therapy. Thus, safety analysis will be conducted using Safety Analysis Set. Selected safety analysis will be conducted after excluding data on rescue therapy.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized MedDRA Queries. Summary statistics will be provided for incidence of TEAEs, serious adverse events (SAEs), study discontinuation due to AEs, study drug discontinuation due to AEs, deaths, and other CV endpoints. Counts and proportions of subjects experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

10.3.4.1. Hypoglycemic Events

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia in each category (either total or nocturnal) will be compared between LY3298176 doses and insulin glargine using negative binomial regression analysis. Summaries and analysis will be repeated excluding data following initiation of rescue antihyperglycemic therapy.

10.3.4.2. Gastrointestinal Events

Summaries and analyses for incidence and severity of nausea, vomiting, and diarrhea will be provided by each treatment.

10.3.4.3. Adjudicated Cardiovascular Events

Listing of deaths, myocardial infarctions, strokes, and hospitalization for unstable angina confirmed by an independent CEC will be provided. The dates of randomization, event, first dose and last dose of study drug, and time from randomization to event will be listed.

10.3.4.4. Central Laboratory Measures, Vital signs, and Electrocardiograms

Values and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. The analysis model to make comparisons among treatment arms relative to continuous change from baseline values assessed over time will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction, country, baseline SGLT-2i use (Yes or No), and baseline measurement as a covariate. An unstructured covariance structure will model relationship of within-patient errors.

The percentages of patients with treatment-emergent abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups by using Fisher's exact test. A treatment-emergent abnormal value is defined as a change from normal value at baseline to an abnormal value at any time during the follow-up. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time during Periods II, III, and IV. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during Periods II, III, and IV. High limit and low limit will be provided in SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

LY3298176 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. The relationships between LY3298176 dose and/or concentration and efficacy, tolerability, and safety endpoints will be characterized.

Additionally, the impact of intrinsic and extrinsic patient factors such as age, weight, gender, and renal function on PK and/or PD parameters may be examined as needed. If anti-drug antibody titers are detected from immunogenicity testing, then the impact of immunogenicity titers on LY3298176 PK or any relevant PD parameters may also be examined.

10.3.6. Evaluation of Immunogenicity

The frequency and percentage of patients with preexisting ADA, with TE ADA, and with neutralizing TE ADA to LY3298176 will be tabulated by LY3298176 dose. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA patients, the distribution of maximum titers will be described by LY3298176 dose. The frequency of neutralizing antibodies to LY3298176 and/or cross-reactive and neutralizing antibodies to endogenous counterparts will be tabulated in TE ADA+ patients.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3298176 may be assessed.

10.3.7. Other Analyses

10.3.7.1. Health Economics

Analyses of actual and change from baseline in patient-reported outcome (PRO) scores will be conducted using linear models with baseline PRO scores, treatment and other factors that may be considered relevant. These variables will be specified in the SAP.

10.3.7.2. Subgroup Analyses

Subgroup analyses of mean change in HbA1c from baseline to Visit 18 will be provided by age, race, ethnicity, gender, duration of diabetes, baseline HbA1c (≤8.5%, >8.5%), and baseline SGLT-2i use (Yes or No).

10.3.8. Interim Analyses

No interim analyses of efficacy (eg, HbA1c and body weight) are planned for this study.

A data monitoring committee (DMC) will have the responsibility to review unblinded interim analysis results in order to monitor the safety of the patients in the study. A sponsor statistical analysis group external to the study team will perform the data analysis for the DMC. As no efficacy analyses are planned by the DMC, the family-wise error rate for the efficacy analysis of the current protocol will not be affected by any of these interim analyses; hence, no alpha spending is necessary. The DMC will perform safety reviews periodically. Detailed information regarding safety reviews will be described in the program DMC Charter.

Study sites will receive information about interim results ONLY if deemed necessary for the safety of their patients.

10.3.8.1. Interim Safety CV Analysis

This study is designed to contribute approximately 110 patients with MACE-4 endpoint towards the accrual of approximately 133 patients with MACE-4 endpoint demonstrating that LY3298176 treatment is not associated with excessive CV risk. Interim analysis of the CV safety meta-analysis is to be conducted when all the following conditions are met:

1. At least 100 patients have reached MACE-4 endpoint confirmed by the CEC across all trials included in the CV meta-analysis
2. All trials included in the CV meta-analysis SAP except for the current trial have achieved their database lock
3. All patients in the current trial who have not discontinued the study before 12 months complete the 12-month primary endpoint assessment
4. At least 300 patients in the current trial receive 18 months or longer of exposure to tirzepatide

An interim data extraction from the current trial will be conducted when all the conditions above are met to aid with the conduct of the interim safety CV meta-analysis. If the interim safety CV meta-analysis results in discharging excessive CV risk with tirzepatide, then close-out of the current trial will be initiated regardless of number of patients with MACE-4 in this study. If the interim safety CV meta-analysis does not result in discharging excessive CV risk with tirzepatide, then the current trial will continue until approximately 133 patients experience MACE-4 across all the trials included in the CV safety meta-analysis.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
AE	adverse event: Any untoward medical occurrence in a patient 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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APPADL	Ability to Perform Physical Activities of Daily Living
AST	aspartate aminotransferase
BG	blood glucose
BMI	body mass index
CEC	clinical endpoint committee
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSR	clinical study report
CT	computed tomography
CV	Cardiovascular
CVD	cardiovascular disease
DMC	data monitoring committee
DPP-4	dipeptidyl-peptidase-4
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EAS	efficacy analysis set
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	European Quality of Life
ERB	ethical review board
ESRD	end stage renal disease

ET	early termination
FAS	full analysis set
FBG	fasting blood glucose
FSH	follicle-stimulating hormone
FTV	final treatment visit
GCP	good clinical practice
GI	Gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP	glucagon-like peptide-1
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
INT	International normalized ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
IW-SP	Impact of Weight on Self-Perception
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
mITT	modified intention-to-treat
MMRM	mixed-model for repeated measures
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
OTC	over the counter
PK/PD	pharmacokinetics/pharmacodynamics
PRO	patient-reported outcome
QW	once weekly
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SC	subcutaneous
SD	standard deviation
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

SGLT-2	sodium-glucose co-transporter-2
SGLT-2i	sodium-glucose co-transporter-2 inhibitor
SMBG	self-monitored blood glucose
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE	treatment-emergent
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TTT	treat-to-target
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
	Bicarbonate
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, fasting
Urinalysis	Albumin
Albumin	Cholesterol
Creatinine	Creatine kinase (CK)
Nonpharmacogenetic Stored Samples	
Serum	**Pregnancy Test** (females only)[b]
EDTA plasma	
P800 plasma	
	eGFR (calculated by CKD-EPI equation)[c]
	Pancreas (exocrine)
	Serum pancreatic amylase
HbA1c	Serum lipase
Endocrine	**Immunogenicity**
Calcitonin	LY3298176 anti-drug antibody
Follicle-stimulating hormone	
	Lipid Panel (fasting)
Anti-GAD Antibodies	
	Total cholesterol
	LDL
	HDL
Samples for PK analysis	VLDL
Pharmacogentics Sample	
	Triglycerides

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; PK = pharmacokinetics; VLDL = very low-density lipoprotein cholesterol.

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

[b] Serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing potential; urine pregnancy tests may be performed at the investigator's discretion during the study. A local laboratory may be used for urine pregnancy tests.

[c] Estimated glomerular filtration rate will be calculated by the central laboratory at all visits and included in lab result reports.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for the following:

- ensuring that the patient 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 patient or 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 patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient'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.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional 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), and updates during the course of the study

- 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 following points:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences 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/endocrinology, cardiology, nephrology, internal medicine, family medicine, general medicine, or any other specialty physician who has experience treating Type 2 Diabetes with clinical research experience 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 clinical study report (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.

A qualified investigator 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
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, 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 verify data reported to detect potential errors

In addition, Lilly or its representatives will periodically check a sample of the patient 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 patient (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 I8F-MC-GPGM is described in Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

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

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

Appendix 5. World Health Organization Classification of Diabetes and Diagnostic Criteria

Type 1 Diabetes: Type 1 diabetes is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death.

Type 2 Diabetes: Type 2 diabetes, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in type 2 diabetes but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with type 2 diabetes later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

Appendix 6. Classification of Contraceptive Methods

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and 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 (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle). Note: periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception
- Vasectomy – for men in clinical trials

Effective Methods of Contraception (must use combination of 2 methods):

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

Appendix 7. Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period

Below are criteria for deciding when and how to intervene with patients who do not reach glycemic targets. An additional therapeutic intervention should be considered in patients who develop severe, persistent hyperglycemia after randomization at the discretion of the investigator in accordance with American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidance (Inzucchi et al. 2015). Rescue treatment with pramlintide, dipeptidyl peptidase-4 (DPP-IV) inhibitors, or glucagon-like peptide-1 (GLP-1) receptor agonists will not be allowed. Rescue medication will be prescribed as add-on to randomized treatment and patients will continue to follow the protocol-specified visit schedule.

Add-on glycemic rescue therapy will be allowed for patients based on the following criteria:

1) The patient is fully compliant with the assigned therapeutic regimen

AND

2) has no acute condition that raises blood glucose

AND

a) average daily blood glucose (BG) from the once-weekly 4-point self-monitored BG (SMBG) profile >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period any time during the first 8 weeks postrandomization;

OR

b) average daily blood glucose from the once-weekly 4-point SMBG profile >240 mg/dL (>13.3 mmol/L) over at least a consecutive 2-week period at any time 9-16 weeks postrandomization;

OR

c) average daily blood glucose from the once-weekly 4-point SMBG profile >200 mg/dL (>11.1 mmol/L) over at least a consecutive 2-week period at any time beyond the first 16 weeks postrandomization.

OR

d) HbA1c ≥8.5% (69 mmol/mol) on 2 consecutive measurements separated by at least 8 weeks at any time beyond the first 24 weeks post randomization

In the insulin glargine arm, the first step will be further titration of the insulin based on the corresponding Treat to-Target algorithm (until Week 16).

Appendix 8. Changes to Study Procedures due to the COVID-19 Pandemic

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes the novel COVID-19 pandemic, has caused numerous global restrictions to be enacted that may impact a patient's ability and/or willingness to attend their onsite study visit as originally scheduled. In such a situation, please follow the guidance below:

1) Patients should come for the primary endpoint visit (Visit 24) at the originally planned 52-week (±7 days) schedule whenever possible and safe to do so, at the investigator's discretion. However, in order to maximize the ability for onsite visits for Visit 24, minimize missing data, and preserve the intended conduct of the study, the visit window for Visit 24 may be brought forward no sooner than 14 days (Week 50) or extended up to 8 weeks (Week 60).

2) The sites will need to identify and document the details of how all patients and visits were affected by the COVID-19 pandemic restrictions.

3) Mobile (in home) healthcare visits may be performed at participants' homes when participants cannot travel to the site due to extenuating circumstances. These will be performed by a qualified home nursing service provider following sponsor approval, if permitted by local regulations. Procedures performed may include, but are not limited to, taking blood samples, conducting physical assessments, administering PROs, and collecting health information. Please note that requirements related to the reporting of SAEs remain unchanged. Every effort should be made for the participant to return to onsite visits as soon as reasonably possible, while ensuring the safety of the participant and investigational site staff.

4) Additional consent from the participant will be obtained for those who participate in home health services.

Appendix 9. Protocol Amendment I8F-MC-GPGM(b) Efficacy and Safety of LY3298176 Once Weekly versus Insulin Glargine in Patients with Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4)

Overview

Protocol I8F-MC-GPGM Efficacy and Safety of LY3298176 Once Weekly versus Insulin Glargine in Patients with Type 2 Diabetes and Increased Cardiovascular Risk (SURPASS-4) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table. Note that minor edits have been made throughout the protocol, which are not captured in the amendment summary table.

Amendment Summary for Protocol I8F-MC-GPGM Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Added a final treatment visit (FTV) and corresponding activities related to this visit	Addition of this visit will allow consistent collection of data as patients complete the treatment period.
Section 5.1 Overall Design	Changed visit numbers for the postrandomization period and Study Period III (variable treatment period)	Correction/clarification.
Section 5.1 Overall Design	Added language related to the FTV	Addition of this visit will allow consistent collection of data as patients complete the treatment period.
Section 10.3.8 Interim Analyses	Added language for a Safety Interim Analysis for the program wide MACE-4 Meta-Analysis	Based on regulatory interaction.
Appendix 8	Added language describing changes to the study procedures due to the COVID-19 pandemic	The added language provides guidance when a patient's ability and/or willingness to attend their onsite study visit is impacted by the global restrictions enacted in response to the COVID-19 pandemic.

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