Protocol I8F-JE-GPGC (a)

A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176

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LY3298176

Eli Lilly Japan K.K.
PPD

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Table of Contents

A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176

Section **Page**

Protocol I8F-JE-GPGC A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176 1
Table of Contents 2
1. Protocol Synopsis 8
2. Schedule of Activities 10
3. Introduction 19
3.1. Study Rationale 19
3.2. Background 19
3.3. Benefit/Risk Assessment 21
4. Objectives and Endpoints 22
5. Study Design 23
5.1. Overall Design 23
5.2. Number of Participants 25
5.3. End of Study Definition 25
5.4. Scientific Rationale for Study Design 25
5.5. Justification for Dose 25
6. Study Population 27
6.1. Inclusion Criteria 27
6.2. Exclusion Criteria 28
6.3. Lifestyle and/or Dietary Requirements 31
6.3.1. Meals and Dietary Restrictions 31
6.3.2. Caffeine, Alcohol, and Tobacco 31
6.3.3. Activity 31
6.4. Screen Failures 31
7. Treatment 32
7.1. Treatment Administered 32
7.1.1. Packaging and Labeling 32
7.2. Method of Treatment Assignment 33

7.2.1. Selection and Timing of Doses 33
7.3. Blinding 33
7.4. Dose Modification 34
7.4.1. Dose Escalation 34
7.5. Preparation/Handling/Storage/Accountability 35
7.6. Treatment Compliance 35
7.7. Concomitant Therapy 35
7.8. Treatment after the End of the Study 36
8. Discontinuation Criteria 37
8.1. Discontinuation from Study Treatment 37
8.1.1. Discontinuation of Inadvertently Enrolled Patients 37
8.2. Discontinuation from the Study 37
8.3. Patients Lost to Follow-up 38
9. Study Assessments and Procedures 39
9.1. Efficacy Assessments 39
9.2. Adverse Events 39
9.2.1. Serious Adverse Events 40
9.2.1.1. Suspected Unexpected Serious Adverse Reactions 40
9.2.2. Complaint Handling 41
9.3. Treatment of Overdose 41
9.4. Safety 41
9.4.1. Laboratory Tests 41
9.4.2. Vital Signs 41
9.4.2.1. Body Weight 41
9.4.3. Electrocardiograms 42
9.4.4. Safety Monitoring 43
9.4.4.1. Hepatic Safety 43
9.4.4.2. Pancreatic Safety 44
9.4.4.3. Hypersensitivity Reactions 44
9.4.4.3.1. Injection-Site Reactions 44
9.4.4.4. Glucose Monitoring 44
9.4.4.4.1. Hyperglycemia and Hypoglycemia Reporting 45
9.4.4.5. Nausea and Vomiting 47
9.5. Pharmacokinetics 47
9.5.1. Bioanalysis 47
9.6. Pharmacodynamics 47
9.6.1. Glucose Samples 48
9.6.1.1. Oral Glucose Tolerance Test 48

9.6.1.2. 7-Point Glucose Monitoring....48
9.6.2. Exploratory Sample Assessments and Storage....48
9.6.3. Meal Intake and Appetite....49
9.6.4. Immunogenicity Assessments....49
9.7. Genetics....50
9.8. Biomarkers....51
9.9. Health Economics....51
10. Statistical Considerations and Data Analysis....52
10.1. Sample Size Determination....52
10.2. Populations for Analyses....52
10.2.1. Study Participant Disposition....52
10.2.2. Study Participant Characteristics....52
10.3. Statistical Analyses....52
10.3.1. Safety Analyses....53
10.3.1.1. Clinical Evaluation of Safety....53
10.3.1.2. Statistical Evaluation of Safety....53
10.3.2. Pharmacokinetic Analyses....53
10.3.2.1. Pharmacokinetic Parameter Estimation....53
10.3.2.2. Pharmacokinetic Statistical Inference....54
10.3.3. Pharmacodynamic Analyses....54
10.3.3.1. Pharmacodynamic Parameter Estimation....54
10.3.3.2. Pharmacodynamic Statistical Inference....54
10.3.4. Pharmacokinetic/Pharmacodynamic Analyses....55
10.3.5. Evaluation of Immunogenicity....55
10.3.6. Data Review During the Study....55
10.3.7. Interim Analyses....55
11. References....56

List of Tables

Table **Page**

Table GPGC.1. Objectives and Endpoints 22
Table GPGC.2. Treatments Administered.....32
Table GPGC.3. Amendment Summary for Protocol I8F-JE-GPGC Amendment(a) 77

List of Figures

Figure **Page**

Figure GPGC 5.1. Illustration of study design for Protocol I8F-JE-GPGC. 23

List of Appendices

Appendix		Page
Appendix 1.	Abbreviations and Definitions	58
Appendix 2.	Clinical Laboratory Tests	62
Appendix 3.	Study Governance, Regulatory and Ethical Considerations	64
Appendix 4.	Clinically Significant Adverse Effects	67
Appendix 5.	Hepatic Monitoring Tests for Treatment-Emergent Abnormality	69
Appendix 6.	Pancreatic Monitoring	70
Appendix 7.	Blood Sampling Summary	73
Appendix 8.	Protocol I8F-JE-GPGC Blinding/Unblinding Plan	74

1. Protocol Synopsis

Title of Study:
A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176.

Rationale:
LY3298176 is a dual agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors being developed as a weekly treatment for type 2 diabetes mellitus (T2DM). This study of LY3298176, I8F-JE-GPGC (GPGC), will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3298176 administered once weekly for 8 weeks as subcutaneous (SC) injections to Japanese patients with T2DM.

Objectives/Endpoints:

Primary Objective	**Endpoints**
To investigate the safety and tolerability of LY3298176 following multiple SC doses administered to Japanese patients with T2DM	Adverse events
Secondary Objectives	**Endpoints**
To characterize the PK of LY3298176 following multiple SC doses in Japanese patients with T2DM	AUC and C_{max} of LY3298176
To investigate the PD effect of LY3298176 following multiple SC doses administered to Japanese patients with T2DM	Fasting plasma glucose

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum drug concentration; PD = pharmacodynamic; PK = pharmacokinetics; SC = subcutaneous; T2DM = type 2 diabetes mellitus.

Summary of Study Design:

Study GPGC is a Phase 1, multiple-site, patient- and investigator-blind, placebo-controlled, randomized, parallel dose–group, 8-week, multiple-ascending dose (MAD) study in Japanese patients with T2DM.

Treatment Arms and Planned Duration for an Individual Patient:
This study consists of 3 cohorts. Approximately 49 Japanese patients with T2DM will be randomized to 4 treatment groups, including 3 dose levels of LY3298176 and placebo. Patients will be administered 8 weekly SC doses of LY3298176 or placebo in a ratio of 12 LY3298176:3 placebo for Cohorts 1 and 3, and 16 LY3298176:3 placebo for Cohort 2. Patients in Cohort 1 will receive either LY3298176 with titration regimen starting from 2.5 mg for Days 1 and 8 followed by 5 mg for Days 15 and 22, and 10 mg for Days 29, 36, 43, and 50, or corresponding volume-matched placebo. Patients in Cohort 2 will be dosed after evaluation of safety data at the 10 mg-dose level in Cohort 1. The safety data up to Day 36 from at least 8 patients will be reviewed. Patients in Cohort 3 will be dosed after evaluation of safety data of the initial staggered group of Cohort 2. Patients in Cohort 2 will receive either LY3298176 with titration regimen starting from 5 mg for Days 1 and 8 followed by 10 mg for Days 15, 22, 29, and

36, and 15 mg for Days 43 and 50, or corresponding volume-matched placebo. Patients in Cohort 3 will receive either 5 mg LY3298176 or placebo for 8 weeks.

Number of Patients:
Approximately 49 Japanese patients with T2DM may be enrolled so that approximately 32 patients complete the study, in compliance with the defined dosing regimen.

Statistical Analysis:

Pharmacokinetic (PK) and PD analyses will be conducted on data from all patients who receive at least 1 dose of the investigational medicinal product (IMP) and have evaluable PK and PD data. Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

Safety: All IMP and protocol procedure–related adverse events (AEs) will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety parameters that will be assessed include safety laboratory parameters, vital signs, electrocardiogram parameters, injection-site reactions, and hypoglycemia.

Pharmacokinetics: PK parameter estimates for LY3298176 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration-time curve (AUC), and time to C_{max} (T_{max}) of LY3298176. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

PK dose proportionality may be assessed in an exploratory manner in model-based analysis.

The parameter T_{max} of LY3298176 will be analyzed using a nonparametric method.

PK parameters will be summarized using descriptive statistics.

Pharmacodynamics: The ability of LY3298176 to reduce fasting or dynamic glucose and the effects on insulin will be assessed. Such effects will be explored for different treatment regimens of LY3298176.

The AUC(0-2hr) for glucose and insulin during an oral glucose tolerance test will be calculated using the trapezoidal rule.

Absolute values, as well as change from baseline in each parameter, will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The model will include treatment as fixed effects and the patient as a random effect. For repeated measured parameters, day and treatment-by-day interaction terms will be included in the model. Baseline (Day -1) values, as well as other influencing variables, may be used as covariates. The main comparisons will be between each LY3298176-treated group and placebo group.

Pharmacokinetics/Pharmacodynamics: PK/PD modeling may be used to characterize the exposure-response relationships between LY3298176 concentrations and various PD endpoints, provided data are sufficient.

Immunogenicity: The frequency of antibody formation to LY3298176 may be determined. If any cross-reactive or neutralization assays are performed, the frequency of these antibodies will be determined.

The relationship between the presence of antibodies, antibody titers, and clinical parameters (eg, AEs) may be assessed. Likewise, the relationship between antibody titers, PK parameters, and PD response to LY3298176 may be assessed.

2. Schedule of Activities

Study Schedule Protocol I8F-JE-GPGC Cohorts 1, 2, and 3 except for Treatment Period

Procedure	Screening[a]	Prestudy[b]	Treatment Period	Follow-Up			ADA Follow-Up[c]
Days	**≤28 days**	**Before Day −1**		**64 ±2**	**85 ±2**	**ET2[d]**	**Every 3 months**
Outpatient visits to CRU	X	X		X	X	X	
Informed consent	X						
Distribution of glucose meters, test strips, and diaries/SMPG training	X[e]	X					
7-point SMPG		X[f]					
Medical history	X						
Physical examination	X						
Medical assessment	X			X	X	X	
AEs/concomitant medications	X			X	X	X	X
Chest x-ray[g]	X						
Height and weight	X						
Body temperature	X						
Vital signs (BP/PR)[h,i]	X			X	X	X	
12-Lead ECG[i,j]	X			X	X	X	
PK sampling[k,l]				X	X	X	X
Clinical safety lab (hematology, chemistry, urinalysis)[m,n]	X			X	X	X	
Clinical safety lab (serology)[n]	X						
Pregnancy test (serum, urine)[n,o,p]	X						
Follicle-stimulating hormone[n,o]	X						
Urine drug and alcohol screen[n,p]	X						
Hemoglobin A1c[l,m]	X						
Fasting glucose, insulin, glucagon[l,m]				X	X	X	
Immunogenicity[l]					X	X	X

Study Schedule Protocol I8F-JE-GPGC Cohort 1 for Treatment Period

Procedure	Treatment Period (Cohort 1)																					
Days	**−1**	**1**	**2**	**3**	**4**	**8**	**15**	**16**	**17**	**18**	**22 ±1**	**29**	**30**	**31**	**32**	**36 ±1**	**43 ±1**	**50**	**51**	**52**	**57**	**ET1[d]**
Inpatient stay at CRU[q]	X	X	X	X	X		X	X	X	X		X	X	X	X			X	X	X		
Outpatient visits to CRU						X					X					X	X				X	X
Remind Patients about 7-point SMPG						X					X					X				X		
7-point SMPG							X					X					X				X	
Randomization		X																				
IMP administration[r]		X				X	X up-titration				X	X up-titration				X	X	X					
Medical assessments[s]		Pre	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[t]		Pre				Pre	Pre				Pre	Pre				Pre	Pre	Pre			X	X
Body temperature	X	Pre																			X	
Vital signs (BP/PR)[h,i]	X	Pre, 1, 4, 8, 12	24	48	72	Pre	Pre	24	48	72	Pre	Pre	24	48	72	Pre	Pre	Pre			168	X
12-Lead ECG[i,j]		Pre, 8	24	48	72	Pre	Pre				Pre	Pre				Pre	Pre	Pre, 8	24		168	X
PK sampling[k,l]		Pre, 8	24	48	72	Pre	Pre				Pre	Pre				Pre	Pre	Pre, 8	24	48	168	X
Clinical safety lab (hematology, chemistry, urinalysis)[m,n]	X		24	48		Pre	Pre	24	48		Pre	Pre	24	48		Pre	Pre	Pre	24	48	168	X
OGTT[l,u]	X																		X			
Hemoglobin A1c[l,m]		Pre										Pre									168	X
Fasting glucose, insulin, glucagon[l,m]		Pre	24			Pre	Pre	24			Pre	Pre	24			Pre	Pre	Pre	24[v]		168	X
Meal intake and appetite[w]	L/D		L/D																L/D			
Lipid panel[l,m,x]		Pre										Pre							24			X

Study Schedule Protocol I8F-JE-GPGC Cohort 1 for Treatment Period

Procedure	**Treatment Period (Cohort 1)**																				
Days	**−1**	**1**	**2**	**3**	**4**	**8**	**15**	**16**	**17**	**18**	**22 ±1**	**29**	**30**	**31**	**32**	**36 ±1**	**43 ±1**	**50**	**51**	**52**	**57**	**ET1[d]**
Exploratory storage samples[l,m,y]		Pre				Pre													24			X
Pharmacogenetic sample[l]		Pre																				
Nonpharmacogenetic sample (storage)[l,m]		Pre					Pre					Pre					Pre	Pre			168	X
Immunogenicity[l]		Pre									Pre										168	X

Study Schedule Protocol I8F-JE-GPGC Cohort 2 for Treatment Period

Procedure	Treatment Period (Cohort 2)																				
Days	**−1**	**1**	**2**	**3**	**4**	**8**	**15**	**16**	**17**	**18**	**22 ±1**	**29 ±1**	**36 ±1**	**43**	**44**	**45**	**46**	**50**	**51**	**52**	**57**	**ET1[d]**
Inpatient stay at CRU[q]	X	X	X	X	X		X	X	X	X				X	X	X	X	X	X	X		
Outpatient visits to CRU						X	X				X	X	X	X							X	X
Remind Patients about 7-point SMPG						X					X		X							X		
7-point SMPG							X					X		X							X	
Randomization		X																				
IMP administration[r]		X				X	X up-titration				X	X	X	X up-titration				X				
Medical assessments[s]		Pre	X	X	X	Pre	Pre	X	X	X	Pre	Pre	Pre	Pre	X	X	X	Pre	X	X	X	X
AEs/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[t]		Pre				Pre	Pre				Pre	Pre	Pre	Pre				Pre			X	X
Body temperature	X	Pre																			X	
Vital signs (BP/PR)[h,i]	X	Pre, 1, 4, 8, 12	24	48	72	Pre	Pre	24	48	72	Pre	Pre	Pre	Pre	24	48	72	Pre			168	X
12-Lead ECG[i,j]		Pre, 8	24	48	72	Pre	Pre				Pre	Pre	Pre	Pre				Pre, 8	24		168	X
PK sampling[k,l]		Pre, 8	24	48	72	Pre	Pre				Pre	Pre	Pre	Pre				Pre, 8	24	48	168	X
Clinical safety lab (hematology, chemistry, urinalysis)[m,n]	X		24	48		Pre	Pre	24	48		Pre	Pre	Pre	Pre	24	48		Pre	24	48	168	X
OGTT[l,u]	X																		X			
Hemoglobin A1c[l,m]		Pre										Pre									168	X
Fasting glucose, insulin, glucagon[l,m]		Pre	24			Pre	Pre	24			Pre	Pre	Pre	Pre	24			Pre	24[v]		168	X
Meal intake and appetite[w]	L/D		L/D																L/D			
Lipid panel[l,m,x]		Pre										Pre							24			X

Study Schedule Protocol I8F-JE-GPGC Cohort 2 for Treatment Period

Procedure	**Treatment Period (Cohort 2)**																				
Days	**−1**	**1**	**2**	**3**	**4**	**8**	**15**	**16**	**17**	**18**	**22 ±1**	**29 ±1**	**36 ±1**	**43**	**44**	**45**	**46**	**50**	**51**	**52**	**57**	**ET1[d]**
Exploratory storage samples[l,m,y]		Pre				Pre													24			X
Pharmacogenetics sample[l]		Pre																				
Nonpharmacogenetic sample (storage)[l,m]		Pre					Pre					Pre		Pre				Pre			168	X
Immunogenicity[l]		Pre									Pre										168	X

Study Schedule Protocol I8F-JE-GPGC Cohort 3 for Treatment Period

Procedure	**Treatment Period (Cohort 3)**															
Days	**−1**	**1**	**2**	**3**	**4**	**8**	**15 ±1**	**22 ±1**	**29 ±1**	**36 ±1**	**43 ±1**	**50**	**51**	**52**	**57**	**ET1[d]**
Inpatient stay at CRU[q]	X	X	X	X	X							X	X	X		
Outpatient visits to CRU						X	X	X	X	X	X				X	X
Remind Patients about 7-point SMPG						X		X		X				X		
7-point SMPG							X		X		X				X	
Randomization		X														
IMP administration[r]		X				X	X	X	X	X	X	X				
Medical assessments[s]		Pre	X	X	X	Pre	Pre	Pre	Pre	Pre	Pre	Pre	X	X	X	X
AEs/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[t]		Pre				Pre	Pre	Pre	Pre	Pre	Pre	Pre			X	X
Body temperature	X	Pre													X	
Vital signs (BP/PR)[h,i]	X	Pre, 1, 4, 8, 12	24	48	72	Pre	Pre	Pre	Pre	Pre	Pre	Pre			168	X
12-Lead ECG[i,j]		Pre, 8	24	48	72	Pre	Pre	Pre	Pre	Pre	Pre	Pre, 8	24		168	X
PK sampling[k,l]		Pre, 8	24	48	72	Pre	Pre	Pre	Pre	Pre	Pre	Pre, 8	24	48	168	X
Clinical safety lab (hematology, chemistry, urinalysis)[m,n]	X		24	48		Pre	Pre	Pre	Pre	Pre	Pre	Pre	24	48	168	X
OGTT[l,u]	X												X			
Hemoglobin A1c[l,m]		Pre							Pre						168	X
Fasting glucose, insulin, glucagon[l,m]		Pre	24			Pre	Pre	Pre	Pre	Pre	Pre	Pre	24[v]		168	X
Meal intake and appetite[w]	L/D		L/D										L/D			
Lipid panel[l,m,x]		Pre							Pre				24			X
Exploratory storage samples[l,m,y]		Pre				Pre							24			X
Pharmacogenetics sample[l]		Pre														
Nonpharmacogenetic sample (storage)[l,m]		Pre					Pre		Pre		Pre	Pre			168	X
Immunogenicity[l]		Pre						Pre							168	X

Study Schedule Protocol I8F-JE-GPGC

Abbreviations: ADA = antidrug antibody; AE = adverse event; BP = blood pressure; CRU = clinical research unit; D = dinner; DPP = dipeptidyl peptidase; ECG = electrocardiogram; ET = early termination; IMP = investigational medicinal product; L = lunch; lab = laboratory tests; OGTT = oral glucose tolerance test; PK = pharmacokinetic; PR = pulse rate; SMPG = self-monitored plasma glucose.

Note: numbers are in hours in relation to dosing; Pre = predose.

[a] Screening shall be completed up to 28 days before treatment assignment. Patients treated with metformin or DPP-IV inhibitors (except for omarigliptin, trelagliptin, and linagliptin) will be required to withdraw their treatment and have at least a-28-day washout period before dosing with IMP.

[b] Patients who passed screening tests will visit the CRU to receive glucose meters, test strips, and diaries for 7-point SMPG before Day −1.

[c] Only for the patients who have clinically significant treatment-emergent antidrug antibodies. Refer to Section 9.6.4 for details.

[d] The patient who discontinues from the study between Day 1 to Day 57 inclusive will complete ET1 procedures as soon as possible. And then, the patient will be asked to complete ET2 procedures after a washout period of at least 28 days from the last IMP administration. The patient who discontinues from the study after the completion of Day 57 will complete ET2 procedures after a washout period of at least 28 days from the last IMP administration.

[e] Patients who were taking metformin or DPP-IV inhibitors (except for omarigliptin, trelagliptin, and linagliptin) at screening will be required to monitor their plasma glucose levels during the 28-day washout period.

[f] Patients will conduct the 7-point SMPG from the distribution of glucose meters until the day before Day −1.

[g] Patients who have completed chest x-ray within the past 12 months and whose x-ray and/or report are available for review are exempt from the chest x-ray examination.

[h] Refer to Section 9.4.2 for instructions on vital signs.

[i] Vital signs and ECGs should be scheduled before, but as close as possible to the PK sample times. Scheduled meals should occur after ECG/vital signs measurement.

[j] Refer to Section 9.4.3 for instructions on ECGs. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. A single local safety ECG will be measured at screening and Day 85 (follow-up) or ET visit. The Day 1 predose ECG will be taken in triplicate every 15 minutes for 1 hour (–60, –45, –30, and –15 min) to establish a baseline. At the other visits, ECGs will be collected in triplicate at the specified time points. ECGs must be recorded before collecting any blood for safety or PK samples and as close as possible to the time of the blood draw.

[k] PK sampling for LY3298176 on Day 1 at predose, 8 and 24 (Day 2), 48 (Day 3), 72 (Day 4), and 168 (Day 8) hours after the first dose (168-hour sample to be collected before the second dose of LY3298176). Additional PK samples to be collected at predose on Days 15, 22, 29, 36, and 43, and on Day 50 at predose, 8 and 24 (Day 51), 48 (Day 52), and 168 (Day 57) hours after the last dose, and at the follow-up visits on Day 64 and Day 85. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by both the investigator and sponsor.

[l] These tests will be performed or stored at the central laboratory or Lilly-designated laboratory.

[m] Patients will be required to fast for at least 8 hours before each blood sample is drawn.

[n] These tests will be performed at the local laboratory.

[o] These tests will be performed per investigator's discretion.

[p] Procedures may be repeated throughout the study as deemed necessary by the investigator.

[q] Patients may be required to remain at the CRU longer than the planned discharging day at the investigator's discretion to assure patients' safety or to provide additional safety monitoring.

[r] IMP will be administered after an overnight fast of at least 8 hours. IMP must be administered at least 6 days after the previous dose.

[s] Assessments of injection-site reactions will be included in the medical assessments.
[t] Weight will be measured in a consistent way per Section 9.4.2.1, always predose.
[u] OGTT (serum glucose and insulin) sampling schedule: Pre-glucose dose (75 g) and 0.5, 1, 1.5, and 2 hours post glucose dose. Patients should consume the glucose load within 5 minutes after an overnight fast of at least 10 hours.
[v] Only insulin and glucagon will be measured at 24 hours postdose on Day 51. All other time points include fasting glucose.
[w] Meal intake and subjective rating of appetite sensation will be evaluated before and 4 to 5 hours after standardized lunch and dinner meals on Days –1, 2, and 51. The standardized lunch and dinner meals will be provided at least 4 hours after the previous meal or the ingestion of glucose in the OGTT.
[x] Lipid panel includes high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglycerides. Triglyceride and total cholesterol concentrations in the safety panel will not be required on the days that the lipid panel is performed.
[y] Exploratory storage samples may be assayed for biomarkers like adiponectin, cortisol, and bone biomarkers. Refer to Section 9.6.2 for details.

3. Introduction

3.1. Study Rationale

LY3298176 is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors being developed for the treatment of type 2 diabetes mellitus (T2DM). This study of LY3298176, I8F-JE-GPGC (GPGC), will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3298176 administered once weekly for 8 weeks as subcutaneous (SC) injections to Japanese patients with T2DM.

3.2. Background

In normal physiology, the incretins GLP-1 and GIP are secreted from enteroendocrine cells in the gut after a meal to enhance the physiological responses to food intake, including sensation of satiety, insulin secretion, and nutrient disposal. It is now well known that patients with T2DM have impaired incretin responses (Nauck et al. 2004), and pharmacologic interventions providing either GLP-1 receptor agonistic peptides or dipeptidyl peptidase (DPP)-IV inhibitors (which delay degradation of endogenous GIP and GLP-1) are successfully used in the treatment of T2DM (Drucker and Nauck 2006; Amori et al. 2007; Baynes 2010).

Although GLP-1 is regarded as the incretin of therapeutic utility, published data demonstrate that overexpression of GIP may lead to improved body weight and glycemic control, and the combination of GLP-1 and GIP may result in improved glycemic efficacy and weight management compared with GLP-1 agonists alone in patients with T2DM (Kim et al. 2012; Finan et al. 2013).

LY3298176 is a long-acting, dual-incretin mimetic (dual agonist) based on a GIP peptide sequence that has been modified so that it binds to both GIP and GLP-1 receptors with similar affinity and shows selectivity over glucagon receptors. LY3298176 is conjugated to a fatty acid chain, which is expected to provide prolonged half-life and PD time action compared with native incretins because of its albumin-binding properties and allows for once-weekly SC dosing. By combining the 2 incretin pharmacology profiles, improved glycemic control may be expected on the basis of potential additive or synergistic effects on glycemic and weight benefits (Irwin et al. 2009).

LY3298176 is being investigated and intended for the treatment of T2DM as an adjunct to diet, exercise, and/or oral medications.

The safety, tolerability, and PK/PD of LY3298176 are being evaluated in an ongoing Phase 1 clinical pharmacology trial, Study I8F-MC-GPGA (GPGA). In Part A (single-ascending dose [SAD] portion) of Study GPGA, more than 50 healthy subjects received study drug with doses of LY3298176 ranging from 0.25 mg to 8 mg. Single doses of study drug were generally well tolerated. Gastrointestinal (GI) events (for example, loss of appetite, bloating, nausea, vomiting) were the most commonly reported adverse events (AEs). At the 8-mg dose level, the majority of subjects experienced drug-related GI events. Two of the subjects who received 8 mg reported AEs of nausea and vomiting that required treatment with antiemetics and intravenous fluids. Further dose escalation was therefore stopped. Following a single SC injection in healthy

subjects, the maximum drug concentration (C_{max}) increased with increasing dose and occurred between 8 and 96 hours (time to C_{max} [t_{max}]). The mean half-life ($t_{1/2}$) ranged from 109 to 123 hours (~5 days). In Part B (the multiple-ascending dose [MAD] portion) of Study GPGA, more than 30 healthy subjects have been dosed in cohorts of 4 weekly SC fixed doses of 0.5 mg, 1.5 mg, and 4.5 mg and an additional titration regimen cohort of 5 mg for 2 doses (Weeks 1 and 2), 8 mg (Week 3), and 10 mg (Week 4). Similar to Part A, the most commonly reported AEs have been GI events, including loss of appetite, nausea, bloating, heartburn, and vomiting. A majority of the AEs have been reported after the first week of dosing, with fewer AEs being reported after the third and fourth doses. The 8-mg dose was better tolerated in this titration approach compared with the single 8-mg dose evaluated in Part A. The limits of tolerability were not reached in the multiple-dose escalation in healthy subjects. Following multiple SC injections in healthy subjects, the C_{max} increased with increasing dose and occurred between 8 and 72 hours (t_{max}).

As of 30 June 2017, Part C of Study GPGA was currently ongoing; however, dosing had been completed. The first cohort of patients with T2DM received a fixed dose of 5 mg for 4 weeks. Gastrointestinal events were the most commonly reported AEs in these patients. LY3298176 appears to be better tolerated by patients with T2DM who received 5-mg doses compared to healthy subjects who received 4.5 mg in Part B of the study.

The second cohort of patients with T2DM received LY3298176 in a dose-titration scheme (5 mg LY3298176 for Weeks 1 and 2, and 10 mg for Weeks 3 and 4). Preliminary data have shown that more GI-related AEs occurred after the first 5- and 10-mg doses; however, patients with T2DM reported fewer and less severe GI-related AEs compared with those reported by the healthy subjects who received the weekly dose-titration schedule of 5 mg, 5 mg, 8 mg, and 10 mg.

The third cohort of patients with T2DM received LY3298176 via titration once weekly for 4 weeks, SC doses of 5 mg, 5 mg, 10 mg, and 15 mg. In this cohort, 15 patients with T2DM received the first dose of 5 mg, with 13 patients completing all 4-dose levels. Most of the AEs were mild and moderate, and 10 of 13 AEs were GI related, with symptoms of nausea and vomiting being the most frequently reported symptoms. Two patients discontinued the study. One patient was discontinued after the first dose of 5 mg because of increases in amylase and lipase without any clinical symptoms. This patient had a history of fatty liver, and an abdominal computed tomography showed fatty liver and no sign of pancreatitis. This patient also had increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The second patient was discontinued after receiving doses of 5 mg, 5 mg, and 10 mg because of an AE of colicky diarrhea. Diarrhea started after the second dose of 5 mg and lasted approximately 12 days. This patient required treatment with loperamide and hydration. The patient was early terminated (did not receive the last dose of 15 mg) because of prolonged diarrhea and resulting dehydration.

The last cohort of 12 patients with T2DM received 0.5 mg weekly for 4 weeks; all patients completed dosing. Four of 12 patients experienced AEs considered to be related to the study drug. Most common AEs were GI in nature with one subject reporting more AEs than the

others: 3 episodes of vomiting (one requiring treatment with Zofran), nausea, decreased appetite, and diarrhea; all these AEs occurred after the first dose. Two patients reported AEs related to pancreatic enzymes and 1 patient reported decreased appetite. At this time these events have been resolved.

These data in both healthy subjects and patients with T2DM support using dose titration to increase tolerability of higher doses of LY3298176.

Preliminary data have shown that there has been no apparent concentration-dependent increase in systolic or diastolic blood pressure (BP) after single or multiple doses; however, there was an increase in heart rate in the MAD portion of the study.

LY3298176 PK was studied across a range of doses administered as single doses or multiple doses (4 doses) via a once-weekly dosing regimen. Based on preliminary data, LY3298176 PK appeared linear and dose proportional during the dose range studied. Peak concentrations were observed at 1 to 2 days postdose, and the half-life was approximately 5 days.

In conclusion, based on preliminary data, PK profile of LY3298176 supports once-weekly SC dosing, and there were no safety concerns to preclude further clinical development.

3.3. Benefit/Risk Assessment

There is no anticipated therapeutic benefit for the patients.

To minimize the risk of hyperglycemia due to the washout of prestudy oral antidiabetic medication, patients will monitor their fasting glucose by SMPG, and the episodes of hyperglycemia will be reported and managed by the investigator or designated physician (Section 9.4.4.4.1).

Because LY3298176 is a long-acting, GIP and GLP-1 receptor dual agonist, the potential risks associated with LY3298176 may be similar to the risks associated with currently available long-acting GLP-1 receptor agonists. The known risks associated with increased GLP-1 receptor activity include but are not limited to: GI-related adverse reactions (particularly nausea, vomiting, and diarrhea), pancreatitis, cardiovascular risk (increased heart rate), hypoglycemia, systemic allergic reaction, injection-site reactions, antibody formation, and medullary thyroid carcinoma.

More information about the known risks, serious AEs (SAEs), and reasonably anticipated AEs of LY3298176 can be found in the Investigator's Brochure (IB).

More information about the known risks for the once-weekly GLP-1 receptor agonists can be found in the Bydureon® ([exenatide extended-release] for injectable suspension) package insert (AstraZeneca 2015, Japan) Trulicity® (dulaglutide injection, solution) package insert (Eli Lilly 2017, Japan).

4. Objectives and Endpoints

Table GPGC.1 shows the objectives and endpoints of the study.

Table GPGC.1. Objectives and Endpoints

Primary Objective	**Endpoints**
To investigate the safety and tolerability of LY3298176 after multiple SC doses administered to Japanese patients with T2DM	Adverse events
Secondary Objectives	**Endpoints**
To characterize the PK of LY3298176 after multiple SC doses in Japanese patients with T2DM	AUC and C_{max} of LY3298176
To investigate the PD effect of LY3298176 after multiple SC doses administered to Japanese patients with T2DM	Fasting plasma glucose levels
Exploratory Objectives	**Endpoints**
To investigate the exploratory PD effects of LY3298176 after multiple SC doses administered to Japanese patients with T2DM	Body weight, OGTT (serum glucose and insulin), 7p-SMPG, hemoglobin A1C, lipids, glucagon, subjective appetite sensation
To evaluate the formation of ADAs to LY3298176 after multiple SC doses administered to Japanese patients with T2DM	Presence of ADAs to LY3298176

Abbreviations: ADA = antidrug antibody; AUC = area under the concentration-time curve; C_{max} = maximum drug concentration; OGTT = oral glucose tolerance test; PD = pharmacodynamic; PK = pharmacokinetics; SC = subcutaneous; 7p-SMPG = 7-point self-monitored plasma glucose; T2DM = type 2 diabetes mellitus.

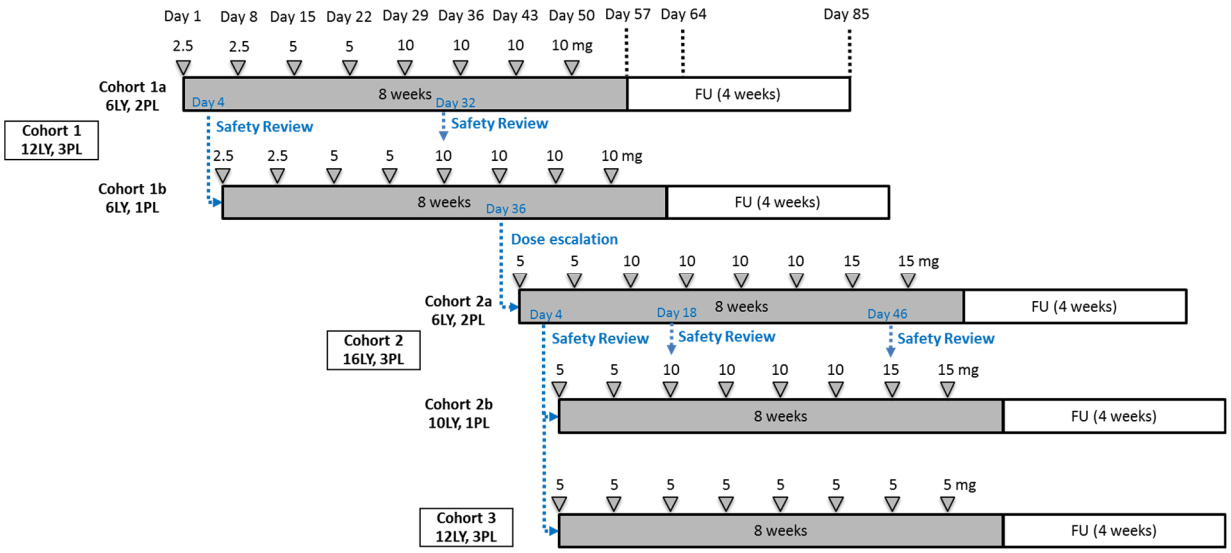
5. Study Design

5.1. Overall Design

Study GPGC is a Phase 1, multiple-site, patient- and investigator-blind, placebo-controlled, randomized, parallel dose–group, 8-week MAD study in Japanese patients with T2DM.

Study governance considerations are described in detail in Appendix 3.

Figure GPGC 5.1 illustrates the study design.



Abbreviations: LY = LY3298176; PL = placebo; FU = follow-up.

Figure GPGC 5.1. Illustration of study design for Protocol I8F-JE-GPGC.

This study consists of 3 cohorts. Patients will be randomized to 4 treatment groups, including 3 dose levels of LY3298176 and placebo as shown in Figure GPGC 5.1. Patients will be administered 8 weekly SC doses of LY3298176 or placebo. Study procedures and timing for prestudy, treatment, and follow-up phases are outlined in Section 2.

Screening to Prestudy

Patient eligibility for this study will be determined at a screening visit. Eligible patients will visit the clinical research unit (CRU) before Day -1 to receive training on the 7-point self-monitored plasma glucose (SMPG), glucose meters, test strips, and diaries. Patients will conduct the 7-point SMPG until the day before Day -1. In addition, patients treated with metformin or DPP-IV inhibitors (except for omarigliptin, trelagliptin, and linagliptin) will be required to withdraw their treatment and have at least a 28-day washout period before dosing with investigational medicinal product (IMP). These patients will be required to monitor their plasma glucose (PG) levels during the washout period.

Treatment Period

Patients will be admitted to the CRU on Day -1. If the investigator decides not to administer the first dose to a patient on a particular day based on the results of medical assessments, vital signs, or electrocardiograms (ECGs), the patient may be rescheduled to participate in the study, and any procedures performed up to that point may be repeated.

Patients will be given SC doses of LY3298176 (or placebo) on Days 1, 8, 15, 22, 29, 36, 43, and 50 after an overnight fast (at least 8 hours). Even if there are visit allowances of ±1 day, the interval of each IMP administration must be at least 6 days.

Patients in Cohort 1 will receive either LY3298176 with titration regimen starting from 2.5 mg for Days 1 and 8 followed by 5 mg for Days 15 and 22, and 10 mg for Days 29, 36, 43, and 50, or corresponding volume-matched placebo. Patients in Cohort 2 will receive either LY3298176 with titration regimen starting from 5 mg for Days 1 and 8 followed by 10 mg for Days 15, 22, 29, and 36, and 15 mg for Days 43 and 50, or corresponding volume-matched placebo. Patients in Cohort 3 will receive either 5 mg LY3298176 or placebo for 8 weeks (Section 5.5). The planned highest dose or dosing regimen of Cohort 2 may be changed for the reason of tolerability (Section 7.4).

If the investigator decides not to up-titrate the dose level of IMP for individual patients in the titration regimen in Cohorts 1 or 2 for the reason of safety and/or tolerability, patients may keep current dose level to the planned last dose at Day 50 and will no longer be allowed up-titration during the treatment period. Down-titration is not allowed during the treatment period for any patients in Cohorts 1, 2, or 3.

Safety, as assessed by AEs, vital signs, 12-lead ECGs, concomitant medications, safety laboratory measurements, and medical assessments from at least 8 patients (to include at least 5 on LY3298176) up to Day 36 predose procedure of Cohort 1, will be reviewed by the sponsor and investigator before dose-escalation decision to Cohort 2 (Section 7.4.1).

Dosing will be staggered in Cohorts 1 and 2 so that an initial group of up to 6 patients receiving LY3298176 and 2 patients receiving placebo will be dosed. On Days 4 and 32 of Cohort 1 and on Days 4, 18, and 46 of Cohort 2, the investigator and Lilly clinical pharmacologist, clinical research physician (CRP), or clinical research scientist (CRS) will review available safety data from these patients, and if no relevant safety signals are noted, the remaining patients will be dosed. Patients in Cohort 3 will be dosed after evaluation of safety data of the initial staggered group of Cohort 2.

PK sampling and safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, will be performed according to the Schedule of Activities (Section 2).

The investigator or qualified designee will review all available inpatient safety data before discharging patients from the CRU on the morning of each planned discharging day provided they are deemed medically fit by the investigator. Patients may be required to remain at the CRU longer than the planned discharging day at the investigator's discretion to assure patients'

safety or to provide additional safety monitoring. Patients will be discharged after the review of all final safety assessments from the last follow-up visit is completed by the investigator.

Follow-Up Period

Safety follow-up visits will occur approximately 2 and 5 weeks after the last dose of IMP. Patients who have treatment-emergent LY3298176 antidrug antibodies (ADAs) at the planned follow-up visit (Day 85) or early termination visit may be monitored until return to baseline (see Section 9.6.4).

5.2. Number of Participants

Approximately 49 Japanese patients with T2DM may be enrolled so that approximately 32 patients complete the study, in compliance with the defined dosing regimen. For purposes of this study, a patient completes the study when all scheduled procedures are completed in compliance with the defined dosing regimen, shown in the Schedule of Activities (Section 2) have been finished.

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) or the date of the last ADA follow-up visit for the last patient, if applicable.

5.4. Scientific Rationale for Study Design

Study GPGC is a Phase 1 study to investigate safety, tolerability, PK, and PD of LY3298176 subcutaneously administered once weekly to Japanese patients with T2DM. On the basis of the preliminary results of Study GPGA, patients with T2DM were selected over healthy subjects in this study to more accurately evaluate GI tolerability and the effects of glycemic control. The planned treatment duration of 8 weeks may allow patients to reach the planned 10-mg and 15-mg dose levels in Cohorts 1 and 2, respectively, by using an up-titration regimen from 2.5 mg and 5 mg, respectively, to reduce GI-related AEs. The staggered dosing design is used to minimize the safety risk because this is the first study to dose LY3298176 in Japanese subjects/patients.

The study is intended to evaluate whether doses used in this study are safe and tolerated in Japanese patients with T2DM. The data from this trial will support identification of an appropriate dose range for subsequent clinical studies in Japan.

5.5. Justification for Dose

The doses of LY3298176 in this study are selected to provide a full evaluation of the safety, tolerability, PK, and PD of LY3298176 in Japanese patients with T2DM to support dose selection in future clinical trials in patients with T2DM in Japan. The dose of LY3298176 for Cohort 1 is titrated from 2.5 mg to 10 mg—2.5 mg for Days 1 and 8; followed by 5 mg for Days 15 and 22; and then 10 mg for Days 29, 36, 43, and 50. The dose of LY3298176 for Cohort 2 is titrated from 5 mg to 15 mg—5 mg for Days 1 and 8; followed by 10 mg for Days 15, 22, 29, and 36; and then 15 mg for Days 43 and 50. The dose of LY3298176 for Cohort 3 is a fixed

5-mg weekly dose for 8 weeks. The anticipated dose-limiting safety and tolerability of LY3298176 are GI-related AEs, such as nausea and vomiting (Section 3.2), which have been consistently demonstrated with the GLP-1 drug class.

The planned dose levels of LY3298176 were selected on the basis of the following:

- Safety and tolerability of LY3298176 in healthy subjects and patients with T2DM in the Phase 1 Study GPGA through doses of up to 15 mg (Section 3.2). In Study GPGA, using a rapid titration scheme of 5 mg, 5 mg, 10 mg, and 15 mg, the dose of 15 mg was considered safe but not well tolerated. It is expected that a more gradual titration method is needed to reach 15 mg with better tolerability; hence, this study will explore getting to the highest dose of 15 mg via a longer titration during 8 weeks.
- The dose-titration regimen starting at 2.5 mg and 5 mg in Cohorts 1 and 2, respectively, are based on tolerability modelling and intended to reduce GI-related AEs.
- The 10-mg and 15-mg doses for Cohorts 1 and 2, respectively, will provide information on safety, tolerability, PK, and PD around expected maximum tolerated dose levels in the up-titration regimen.
- The fixed 5-mg dose in Cohort 3 is to compare safety, tolerability, PK, and PD profiles of LY3298176 in this study with that of Study GPGA (first cohort of Part C).

6. Study Population

Eligibility of patients for study enrollment will be based on the results of screening medical history, physical examination, medical assessment, vital signs, clinical laboratory tests, and ECG.

A chest x-ray will be completed at screening unless one has been obtained within the past 12 months, and the x-ray and/or report are available for review.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days before Day 1. Patients who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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 for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] Japanese males or females between the ages of 20 and 70 years inclusive at screening

[1a] male patients:

agree to use an effective method of contraception (barrier contraceptives, such as latex condoms, or complete abstinence from sexual intercourse with women) for the duration of the study and for 3 months after the last dose of IMP

[1b] female patients:

women not of childbearing potential because of surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) or menopause; women with an intact uterus are deemed postmenopausal if they are aged 45 years or older

AND

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

OR

who had at least 6 months of amenorrhea with follicle-stimulating hormone levels consistent with a postmenopausal state

[2] have T2DM diagnosed at least 1 year before enrollment

[3] have T2DM controlled with diet and exercise alone or are stable on a single oral antidiabetic medication (OAM), metformin or DPP-IV inhibitor only (other types of OAM [omarigliptin, trelagliptin, and linagliptin] are not allowed in this study), for at least 3 months; however, patients must withdraw the single OAM for at least 28 days before dosing with IMP

[4] have a hemoglobin A1c (HbA1c) ≥7.0% and ≤10.0% for patients treated with diet and exercise only, and for the patients who have washed out of antidiabetic medications, HbA1c ≥6.5% and ≤9.0%, at the screening visit

[5] have a body weight of at least 54.0 kg inclusive at screening

[6] have a body mass index of 20.0 kg/m^2 to 35.0 kg/m^2 inclusive at screening

[7] have clinical laboratory test results within normal reference range for the population or investigative site or results with acceptable deviations that are judged to be not clinically significant by the investigator; abnormalities of blood glucose, serum lipids, urinary glucose, and urinary protein consistent with T2DM are acceptable

[8] have blood pressure of <160/90 mm Hg and pulse rate of 50 to 100 bpm (supine) at screening, or with minor deviations judged to be acceptable by the investigator

[9] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[10] are able and willing to give signed informed consent

[11] have venous access sufficient to allow blood sampling as per the protocol

[12] are taking stable doses of over-the-counter or prescription medications (for example, antihypertensive agents, aspirin, lipid-lowering agents) for treatment of concurrent medical conditions providing the patients have been stable on their treatment regimen for at least 4 weeks before dosing with IMP

6.2. Exclusion Criteria

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

[13] are investigative site personnel directly affiliated with this study or their immediate families; immediate family is defined as a spouse, biological or legal guardian, child, or sibling

[14] are Lilly employees

[15] are currently enrolled in a clinical study involving an IMP or any other type of medical research judged not to be scientifically or medically compatible with this study

[16] have participated in a clinical study involving an IMP within the last 4 months; if the previous IMP has a long half-life, 5 half-lives or 4 months (whichever is longer) should have passed

[17] have previously completed or withdrawn from this study or any other study investigating LY3298176 and have previously received the IMP

[18] have received treatment with a drug that has not received regulatory approval for any indication within 30 days of screening

[19] have known allergies to LY3298176, GLP-1 analogues, or related compounds

[20] have had more than one episode of severe hypoglycemia, as defined by the American Diabetes Association criteria, within 6 months before entry into the study or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms; any patient who cannot communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia before to the first dose of IMP should also be excluded

[21] have an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 at screening

[22] have had a blood transfusion or severe blood loss or have known hemoglobinopathy (alpha-thalassemia), hemolytic anemia, sickle cell anemia, a hemoglobin value <11.0 g/dL (males) or <10.0 g/dL (females), or any other condition known to interfere with HbA1c methodology

[23] have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) in the past year or have received any glucocorticoid therapy within 30 days before screening

[24] have a significant history of or current cardiovascular (for example, myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism); respiratory; hepatic; renal; GI; endocrine; hematological (including history of thrombocytopenia); or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs or of constituting a risk when taking the study medication or interfering with the interpretation of data

[25] have a history of heart block or a pulse rate interval >220/msec or any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study

[26] intended use of over-the-counter or prescription medications within 14 days before planned dosing and for the duration of the study, apart from occasional intake of vitamin/mineral supplements, allowable antiemetics, and acetaminophen; if this situation arises, inclusion of an otherwise suitable patient may be at the discretion of the investigator (refer to Section 7.7)

[27] regularly use known drugs of abuse or show positive findings on drug screening

[28] show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies and/or HIV antigen at screening

[29] show evidence of hepatitis B or positive hepatitis B surface antigen and/or evidence of hepatitis C or positive hepatitis C antibody at screening

[30] are women who are lactating

[31] have donated 400 mL or more of blood in the last 12 weeks (males) or in the last 16 weeks (females), any blood donation (including apheresis) within the last 4 weeks, or total volume of blood donation in the past year is 1200 mL (males) or 800 mL (females) or more at screening

[32] have an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females) (1 unit = 12 oz or 360 mL of beer, 5 oz or 150 mL of wine, 1.5 oz or 45 mL of distilled spirits) or are unwilling to stop alcohol consumption during the 24 hours before and 72 hours postdose, and 24 hours before each CRU admission and each outpatient visit, and throughout the duration of each CRU visit

[33] smoke >10 cigarettes per day or the equivalent or are unable or unwilling to refrain from nicotine during CRU admission

[34] have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis) or GI disorder (for example, relevant esophageal reflux or gall bladder disease) or any GI disease that impacts gastric emptying (for example, gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogues or DPP-IV inhibitors; patients with dyslipidemia and patients who have had cholecystolithiasis (removal of gall stones) and/or cholecystectomy (removal of gall bladder) in the past, with no further sequelae, may be included in the study at the discretion of the investigator

[35] have a history of atopy or clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe postdose hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

[36] have evidence of significant active neuropsychiatric disease as determined by the investigator

[37] have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2

[38] have serum AST or ALT >2× the upper limit of normal (ULN) or total bilirubin (TBL) >1.5× ULN (with the exception of Gilbert's syndrome)

[39] have a history of malignancy within 5 years before screening

[40] have any skin conditions (including, but not limited to, tattoos or scars) that may interfere with the interpretation of assessment or administration of IMP

[41] are unsuitable for inclusion in the study in the opinion of the investigator or sponsor

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Patients will be required to fast overnight for at least 8 hours before taking an SC dose of LY3298176 (or placebo) on Days 1, 8, 15, 22, 29, 36, 43, and 50 and before each blood sample is drawn as described in the Schedule of Activities (Section 2). Water may be consumed freely. Standard meals will be provided after approximately 15 minutes from IMP administration in the CRU. Standardized lunch and dinner meals will be provided in the CRU to assess meal intake and subjective rating of appetite sensation (Section 9.6.3).

When not resident in the CRU, patients should, as much as possible, maintain their routine prestudy dietary patterns.

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine: Patients should refrain from caffeine-containing food/beverages (for example, cola, chocolate drinks, tea, and coffee) during the CRU stay. Patients will be allowed to maintain their regular caffeine consumption outside the CRU throughout the study period.

Alcohol: No alcohol will be allowed during the 24 hours before and 72 hours postdose, and 24 hours before each CRU admission and each outpatient visit, and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 3 units for males and 2 units for females (a unit is defined in Exclusion Criterion [32], Section 6.2).

Tobacco: No nicotine use will be permitted while at the CRU. While not resident in the CRU, patients may smoke no more than 10 cigarettes or consume the equivalent amount of nicotine per day.

6.3.3. Activity

Patients will be advised to maintain their regular levels of physical activity/exercise during the study. When certain study procedures are in progress at the site, patients may be required to remain supine, recumbent, or sitting.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened once. The interval between rescreenings should be at least 2 weeks. If rescreening is performed, the individual must sign a new informed consent form and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of once-weekly SC dose levels of LY3298176 (2.5 mg to 10 mg titration regimen for Cohort 1, 5 mg to 15 mg titration regimen for Cohort 2, and 5 mg fixed dose for Cohort 3) with corresponding volume-matched placebo. Table GPGC.2 shows the treatment regimens.

Each vial of the IMP will contain 5 mg of LY3298176, will be reconstituted in sterile water for injection (Japan Pharmacopeia), and will be administered subcutaneously. Doses will be dispensed in accordance with the randomization scheme provided by the sponsor. Patients assigned to placebo treatment will receive SC injections of normal saline with the volume matching the LY3298176 at each dose level. Please refer to the IMP Operation/Handling Procedure for detailed instructions.

All injections will be administered into the SC tissue of the abdominal wall. Injection sites will be alternated weekly between 4 sites on the abdominal wall (ie, right and left upper quadrants and right and left lower quadrants).

Whenever possible, IMP administration should be carried out by the same personnel. Dosing will commence at approximately the same time of day in all dose cohorts. The actual time of dosing will be recorded in the patient's electronic case report form (eCRF).

Table GPGC.2. Treatments Administered

Dose level	Number of vial	Volume per injection (mL)	Number of injection	Total volume of injection (mL)
LY 2.5 mg/PL	1	0.5	1	0.5
LY 5 mg/PL	1	1.0	1	1.0
LY 10 mg/PL	2	1.0	2	2.0
LY 15 mg/PL	3	1.0	3	3.0

Abbreviations: LY = LY3298176; PL= placebo.

The investigator or designee is responsible for:

- explaining the correct use of the IMP to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of IMP dispensing and collection,
- returning all unused medication to Lilly or its designee at the end of the study.

7.1.1. Packaging and Labeling

Investigational medicinal products for this study are as follows:

- LY3298176 will be provided in a vial, which will be provided in a carton.
- Placebo will be provided as sodium chloride (saline) in a vial.

The IMP will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Randomization tables for allocation of LY3298176 or placebo will be prepared by the statistician for the study and provided to the site pharmacists involved in dose preparation. The allocation and dispensing of the IMP will be fully documented and verified by a second person. Detailed records of the amounts of the IMP received, dispensed, and remaining at the end of the study will be maintained by the site pharmacist.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the patient's eCRF.

7.3. Blinding

The dosing regimen is patient- and investigator-blind. To preserve the blinding of the study, all study site personnel, except pharmacy staff who prepare and dispense study medication, will be blinded to treatment allocation.

Blinding will be maintained until the database is locked with data up to Day 85 (blinded period) as described in the separate Blinding Plan (Appendix 8).

The site pharmacist who prepares and dispenses study medication will receive a randomization table with treatment codes to enable preparation of blinded placebo doses. The pharmacist will assign treatment.

Emergency codes will be available to the investigator. A code, which reveals the treatment group for a specific study patient, may be opened during the study only if the patient's well-being requires knowledge of the patient's treatment assignment.

If a patient's study treatment assignment is unblinded during the blinded period, the patient must be discontinued from the study unless the investigator obtains specific approval from a Lilly clinical pharmacologist, CRP, or CRS for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study patient's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding during the blinded period is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

For the blinded items in the clinical laboratory tests, please refer to Appendix 2.

7.4. Dose Modification

If the investigator decides not to up-titrate the dose level of IMP at Days 15, 29, or 43 in the titration regimen for individual patients in Cohorts 1 or 2 for the reason of safety and/or tolerability, patients may keep current dose level to the planned last dose at Day 50 and will no longer be allowed up-titration during the treatment period. Down-titration is not allowed during the treatment period for any patients in Cohorts 1, 2, or 3.

The planned highest dose of Cohort 2, 15 mg LY3298176, may be reduced to 12.5 mg before to the first patient visit of Study GPGC if the first interim analysis of the ongoing Phase 2 Study I8F-MC-GPGB indicates that the 15 mg dose is not well tolerated.

7.4.1. Dose Escalation

The dose escalation decision will be made on the basis of the safety data at the 10-mg dose level of Cohort 1 to proceed to Cohort 2. The safety data up to Day 36 (predose procedure) of Cohort 1 from at least 8 patients (to include at least 5 on LY3298176) will be reviewed.

Safety data will be the primary criteria for the dose escalation. In addition, if available at the time of dose-escalation decision, PK results may be used as supporting data for dose escalation. No dose decision can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist, CRP, or CRS.

Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator and will be considered related to the IMP unless there is clear evidence that the event is not related.

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for Cohort 2.

The planned dosing regimen of Cohort 2 may be changed to 2.5 mg for Days 1 and 8; followed by 5 mg for Days 15 and 22; and 8 mg for Days 29, 36, 43, and 50, or the corresponding volume-matched placebo before the first dose of Cohort 2 if the safety assessment for the dose-escalation decision indicates that the 10-mg dose of Cohort 1 is not well tolerated.

If any of the following scenarios occur, dosing at the current level and dose-escalation from Cohort 1 to Cohort 2 will be discontinued:

1) if a single patient experiences an SAE other than anticipated pharmacology of LY3298176 (for example, GI-related AEs [particularly nausea, vomiting, and diarrhea] or hypoglycemia)
2) two clinically significant events (CSEs) in each cohort that are related to LY3298176 administration, with the exception of anticipated pharmacology of LY3298176
3) if 50% or more of patients in a cohort experience a symptomatic hypoglycemic episode with plasma/serum glucose levels of ≤3.0 mmol/L [54 mg/dL])

4) if more than 4 patients in 1 cohort experience moderate treatment-related AEs that impair normal activities

5) if 2 or more patients experience an acute pancreatitis event (Appendix 6)

Examples of unrelated events could include but are not limited to: events occurring before LY3298176 dosing; events experienced after receiving placebo; personal injury accidents that were not a result of hemodynamic changes or neurological symptoms (dizziness, visual disturbance, numbness, loss of muscle control); events resulting from viral or bacterial infections; or changes in clinical chemistry or liver enzymes as a result of documented acute viral hepatitis, alcohol, or other hepatotoxic drug use.

A CSE will be determined by the investigator or suitable designee (Appendix 4) and may include findings that do not fulfill the criteria for SAEs. Patients experiencing CSEs thought to be related to the IMP will be encouraged to complete a 28-day follow-up period before study discharge.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions (2°C to 8°C) have been maintained, as communicated by sponsor, during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only participants enrolled in the study may receive IMP or study materials, and only authorized site staff may supply or administer IMP. All IMP should be stored in an 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 IMP accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

The IMP will be administered at the clinical site, and documentation of treatment administration will occur at the CRU.

7.7. Concomitant Therapy

Treatment with drugs that are excluded in the entry criteria (Section 6) is not permitted.

Patients on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study.

In general, concomitant medication should be avoided; however, acetaminophen (1g/dose, maximum 2g/day) may be administered at the discretion of the investigator for treatment of headaches, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the patient may be at the discretion of the investigator, preferably after consultation with a Lilly clinical pharmacologist, CRP, or CRS. Stable doses (refer to

Section 6) of over-the-counter or prescription medications (for example, antihypertensive agents, aspirin, lipid-lowering agents) for treatment of concurrent medical conditions are allowed.

All concomitant medications used during the course of study will be recorded in the eCRF.

7.8. Treatment after the End of the Study

Not applicable for this study.

8. Discontinuation Criteria

Patients discontinuing from the treatment prematurely for any reason should complete AE and other follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the IMP for abnormal pancreatic tests **should be considered** by the investigator when a patient meets the following condition:

- lipase and/or amylase are confirmed to be ≥3× ULN. Please refer to algorithm for the monitoring of pancreatic events in Appendix 6.

Discontinuation of the IMP for abnormal liver tests **should be considered** by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- ALT or AST >8× ULN
- ALT or AST >5× ULN sustained for more than 2 weeks
- ALT or AST >3× ULN and TBL >2× ULN or international normalized ratio >1.5
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3× ULN
- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist, CRP, or CRS and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist, CRP, or CRS to allow the inadvertently enrolled patient to continue in the study with or without continued treatment with IMP.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an IMP 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
- investigator decision

  - the investigator decides that the patient should be discontinued from the study
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, then discontinuation from the study occurs before introduction of the new agent
- patient decision
  - the patient or legal representative requests to be withdrawn from the study

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

9. Study Assessments and Procedures

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

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

Appendix 7 provides a summary of the maximum number and volume of invasive blood samples, for all sampling, during the study.

Unless otherwise stated in 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

This section is not applicable for this study.

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 IMP or the study, or that caused the patient to discontinue the IMP before completing the study. The patient should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form is signed, study site personnel will record, via 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. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

If a patient's IMP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF.

9.2.1. Serious Adverse Events

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

- 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

Study site personnel must alert the Lilly clinical pharmacologist, CRP, CRS, or its designee of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety 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 up 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.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received IMP. However, if an SAE occurs after signing informed consent, but before receiving IMP, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

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

Pregnancy (maternal or paternal exposure to IMP) 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.

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 reports as related to IMP or procedure. Lilly has procedures

that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on IMPs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3298176 is considered any dose higher than the dose assigned through randomization.

Refer to the IB for LY3298176.

9.4. Safety

9.4.1. Laboratory Tests

For each patient, clinical laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Blood pressure (BP) and pulse rate (PR) should be measured after approximately 5 minutes in the supine position.

If orthostatic measurements are required, patients should be supine for approximately 5 minutes and stand for at least 2 minutes. If the patient feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

Body temperature will be measured as specified in the Schedule of Activities and as clinically indicated (Section 2).

9.4.2.1. Body Weight

Weight will be measured in a consistent manner using a calibrated scale according to the Schedule of Activities (Section 2). Patients will be weighed in light clothing at approximately the same time in the morning before dosing and after an overnight fast and evacuation of bowel and the bladder, if possible. During the treatment period, weight will be measured twice on each

scheduled occasion, with the patient stepping off the scale between measurements. Both weight measurements will be recorded in the source document and the eCRF. Wherever possible, the same scale will be used for all weight measurements throughout the study.

9.4.3. Electrocardiograms

For each patient, 12-lead digital ECGs should be collected according to the Schedule of Activities (Section 2).

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

For each patient, a single 12-lead ECG will be collected locally at screening and follow-up or early termination visit according to the Schedule of Activities (Section 2). At all other time points, ECGs will be collected and stored using an ECG machine provided by the central ECG vendor. The Day 1 predose ECG will be taken in triplicate every 15 minutes for 1 hour to establish a baseline. At all other scheduled times, consecutive triplicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed to ensure high-quality records. All ECGs recorded should be stored at the investigational site.

Electrocardiograms must be recorded before collecting any blood for safety or PK tests. Patients must be supine for approximately 5 to10 minutes before ECG collection and remain supine but awake during ECG collection.

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

If a clinically significant quantitative or qualitative change from baseline is identified (including, but not limited to, changes in QT interval/QT interval corrected for heart rate [QTc] using Fridericia's formula [QTcF] from baseline) after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his or her review of the ECG printed at the time of evaluation from at least one of the replicate ECGs from each time point. Any new clinically relevant finding should be reported as an AE.

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

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

9.4.4. Safety Monitoring

The Lilly clinical pharmacologist, CRP, or CRS will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist, CRP, or CRS will periodically review the following data:

- trends in safety data
- laboratory analytes
- serious and nonserious AEs, including AEs of special interest (for example, GI events, hypoglycemia, injection-site reactions, and hypersensitivity reactions) and reported and adjudicated pancreatitis

When appropriate, the Lilly clinical pharmacologist, CRP, or CRS will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the Blinding/Unblinding Plan (Appendix 8).

9.4.4.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 5) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, γ-glutamyl transferase, and creatinine 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 on the basis of consultation with the Lilly clinical pharmacologist, CRP, or CRS. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.4.4.2. Pancreatic Safety

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing at time points specified in the Schedule of Activities (Section 2). Additional measurements may be performed at the investigator's discretion. Further diagnostic assessments will be recommended as per the algorithm (refer to Appendix 6) for the monitoring of pancreatic events whenever lipase and/or amylase is confirmed to be ≥3× ULN at any visit postdose, even if the patient is asymptomatic. If pancreatitis is suspected, the case will be further defined during an adjudication process. Any patient who develops symptoms of pancreatitis must not receive further administration of LY3298176.

9.4.4.3. Hypersensitivity Reactions

All hypersensitivity reactions will be reported by the investigator either as AEs or, if any serious criterion is met, as SAEs. Dosing should be temporarily discontinued in any individual suspected of having a severe or serious allergic/hypersensitivity reaction to IMP. Investigational medicinal product may be restarted if, in the opinion of the investigator, the event was not related to IMP and if/when it is safe to do so. If dosing is permanently discontinued, the patient should remain in the study as needed per medical judgement.

The report of a clinically significant AE of drug reaction or injection-site reaction may prompt notification of the sponsor, clinical photography, and referral for dermatologic evaluation and consideration of a skin biopsy and laboratory evaluations (ALT, AST, complete blood count with percent eosinophils, and additional immunogenicity testing).

9.4.4.3.1. Injection-Site Reactions

If an injection-site reaction is present, it will be fully characterized (including erythema, induration, pain, itching, and swelling) and will be closely monitored until resolution.

Investigational site staff will be provided with separate instructions/training on how to consistently evaluate injection-site reactions and their severity. Photographs of injection-site reactions may be taken in a standardized fashion for record-keeping purposes; however, the photographs will not be used to evaluate injection-site reaction severity.

9.4.4.4. Glucose Monitoring

Patients will be instructed on how to use the glucose meter provided by the site and conduct SMPG tests. In addition to the PG monitoring, patients will be educated on the symptoms of hypoglycemia. Throughout their participation in the study, patients will monitor PG levels. Patients will be provided diaries and instructed to record PG results whenever the patient experiences symptoms of hypoglycemia, while not in the CRU. The investigator or designee will review PG results clinically indicative of hypoglycemia or hyperglycemia.

Additionally, patients who were taking metformin or a DPP-IV inhibitor (except for omarigliptin, trelagliptin, and linagliptin) at screening will be required to monitor their PG in the morning before breakfast during the 28-day washout period.

9.4.4.4.1. Hyperglycemia and Hypoglycemia Reporting

Episodes of hyperglycemia (fasting plasma/serum glucose >270 mg/dL [15 mmol/L]) or hypoglycemia (plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]) will be reported by the investigator or designated physician who will be responsible for advising the patient on what further actions to take. Additional monitoring may be requested at the investigator's discretion.

If the fasting plasma/serum glucose during the dosing period exceeds the acceptable level, defined as hyperglycemia on 3 or more separate days during any 2-week period between screening and the end of the dosing period, the patient will be evaluated further at the study site. If fasting plasma/serum glucose continues to exceed the acceptable level, IMP will be discontinued, and treatment with an appropriate antidiabetic agent may be initiated by the investigator. The patient will continue to be followed up in the study (for safety, PK, and immunogenicity assessment) for at least 28 days after his or her last dose. If hyperglycemia occurs during the follow-up period, the patient will remain in the study until completion of the planned follow-up.

Hypoglycemia episodes will be recorded on specific eCRF pages. Hypoglycemia will be treated appropriately by the investigator and additional monitoring of plasma/serum glucose levels may be performed. The following categories of the 2017 American Diabetes Association position statement on glycemic targets (American Diabetes Association 2017) on the basis of recommendations of the International Hypoglycaemia Study Group (International Hypoglycaemia Study Group 2017) should be applied for reporting in the eCRF and evaluating hypoglycemic events.

The main categories of hypoglycemia are outlined below:

Documented Glucose Alert Level (Level 1): plasma/serum glucose ≤70 mg/dL (3.9 mmol/L)

- **Documented symptomatic hypoglycemia:** with typical symptoms of hypoglycemia.
- **Documented asymptomatic hypoglycemia:** without typical symptoms of hypoglycemia.
- **Documented unspecified hypoglycemia:** with no information about symptoms of hypoglycemia available. (This has also been called unclassifiable hypoglycemia.)

Documented Clinically Significant Hypoglycemia (Level 2): with similar criterion as above except for threshold plasma/serum glucose <54 mg/dL (3.0 mmol/L)

- **Level 2 documented symptomatic hypoglycemia**
- **Level 2 documented asymptomatic hypoglycemia**
- **Level 2 documented unspecified hypoglycemia**

Severe Hypoglycemia (Level 3)

- **Severe hypoglycemia (in adults):** Patients had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma/serum glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma/serum glucose concentration to normal is considered sufficient evidence that the event was induced by a low plasma/serum concentration (plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]).
- **Severe hypoglycemia requiring medical attention:** Severe hypoglycemic events when patients require therapy by Health Care Providers (Emergency Medical Technicians, emergency room personnel, etc) are of particular interest to payers. Therefore, some clinical trials may collect data on this subset of severe hypoglycemia episodes, especially if economic outcomes analyses may be based on trial results.

Other Hypoglycemia

- **Nocturnal hypoglycemia:** Any documented hypoglycemic event (including severe hypoglycemia) that occurs at night and presumably during sleep. At Lilly, this is captured as hypoglycemia that occurs between bedtime and waking. This definition is more useful than the commonly used ~midnight to ~6 AM definition, which does not take patients' individual sleep times into consideration and is consistent with the American Diabetes Association recommendations for reporting events that occur during sleep (American Diabetes Association 2005). It is also important to collect the actual time when a hypoglycemic event occurred to allow further characterization of hypoglycemia timing (eg, to allow analysis of frequency of events occurring during a 24-hr time period). Nocturnal hypoglycemia may occur at severity Levels 1, 2, or 3.
- **Relative hypoglycemia (also referred to as pseudohypoglycemia [Seaquist et al. 2013]):** An event during which typical symptoms of hypoglycemia occur, that does not require the assistance of another person, and is accompanied by plasma/serum glucose >70 mg/dL (3.9 mmol/L). The plasma/serum glucose value for patients with chronically poor glycemic control can decrease so rapidly that patients may report symptoms of hypoglycemia before their plasma/serum glucose concentration falls below 70 mg/dL (3.9 mmol/L). Events with plasma/serum glucose ≤70 mg/dL should not be categorized as relative hypoglycemia. Evaluation and statistical analysis of this category is optional. However, if a patient reports a relative hypoglycemia event where assistance from another person was received or the patient experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycemia event and report it appropriately.
- **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia were present, but plasma/serum glucose measurement was not reported.

- **Overall (or total) hypoglycemia:** This optional category combines most cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). It does not include relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in the category of overall (or total) hypoglycemia.

If a hypoglycemic event meets the criteria of severe, it needs to be recorded as serious in the eCRF (that is, recorded as an SAE). In the case of a hypoglycemic event (other than severe), the actual glucose value, if measured, should be recorded in the eCRF, with any treatments administered, and not be recorded as an AE. Cases of hypoglycemia may be treated with foods rich in carbohydrate such as fruit, juice, skimmed milk, or energy bars. All episodes of hypoglycemia that are determined by the investigator to constitute severe hypoglycemia according to the definition above should be reported as SAEs.

9.4.4.5. Nausea and Vomiting

Nausea and vomiting events are considered AEs of interest and will be recorded as AEs in the eCRF. For each event assessment of severity, duration, and investigator's opinion of relatedness to IMP and protocol procedure will be captured.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of LY3298176. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour time period) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of LY3298176 will be assayed using a validated liquid chromatography mass spectrometry method. Analyses of samples collected from patients treated with placebo are not planned.

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

9.6. Pharmacodynamics

Assessment of LY3298176 pharmacology may include fasting PG levels; insulin; lipid profile (total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides); HbA1C; body weight; 7-point SMPG test; glucagon; and oral glucose tolerance test (OGTT;

AUC for glucose and insulin). Additional exploratory PD analysis may be analyzed as deemed appropriate.

Blood samples will be obtained for the measurement of PD. The scheduled times for the collection of these samples are as listed in the Schedule of Activities (Section 2). The timing of PD samples is intended to assess pharmacologic effects of LY3298176. The sampling times may be modified at the discretion of the sponsor, but the total number of the samples or total blood volume will not increase.

The sample(s) will be stored for up to a maximum of 1 year after the last patient visit for the study at a facility selected by the sponsor.

9.6.1. Glucose Samples

Plasma/serum concentrations of glucose, as indicated in the Schedule of Activities (Section 2), will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

9.6.1.1. Oral Glucose Tolerance Test

Glucose and insulin will be measured by an OGTT to assess effects of LY3298176 on glycemic control, disposition index, and insulin sensitivity. The schedule for OGTTs is indicated in the Schedule of Activities (Section 2).

Patients shall maintain adequate carbohydrate intake 3 days before the scheduled OGTT. Patients shall fast for at least 10 hours overnight before administration of the glucose. A 75-g glucose dose will be given orally. Patients should consume the glucose load within 5 minutes. Blood samples will be drawn for assessment of glucose and insulin at pretest, 0.5, 1, 1.5, and 2 hours after the initiation of the glucose load.

9.6.1.2. 7-Point Glucose Monitoring

Patients will be asked to perform a 7-point PG profile according to the Schedule of Activities (Section 2). Patients will be asked to test their self-monitored PG levels before each meal, approximately 2 hours after each meal, and at bedtime. Patients will be asked to record their self-monitored PG levels in their diaries according to instructions. The complete 7-point PG profile must be completed in a single day. If a patient does not complete the entire profile in a single day, all 7 points must be collected on a subsequent day. In the event that the baseline 7-point SMPG is conducted on the day before Day -1, all 7 points must be completed on that day to avoid interference with the OGTT that will be administered on the subsequent day (Day -1).

9.6.2. Exploratory Sample Assessments and Storage

Samples will be collected and retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ethical review boards (ERBs)/IRBs impose shorter time limits for the study, at a facility selected by the sponsor. The duration allows the sponsor to explore the effects of LY3298176 on potential biomarkers such as adiponectin, cortisol, and bone biomarkers. Blood samples will be collected as specified in the Schedule of Activities (Section 2).

9.6.3. Meal Intake and Appetite

To explore the effects of LY3298176 on meal intake and appetite sensation, patients will be provided standardized lunch and dinner meals with an approximate total energy and macronutrient contents of 700 kCal and 20% protein, 25% fat, and 55% carbohydrate according to the Schedule of Activities (Section 2). The meal intake will be recorded in the source document. The subjective rating of appetite sensations is measured by a 100-mm visual analogue scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption before and 4 to 5 hours after the standardized lunch and dinner meals. The standardized lunch and dinner meals will be provided at least 4 hours after the previous meal or the ingestion of glucose in the OGTT. The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000). The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "extremely" and "not at all." Patients are required to rate their subjective sensations on four 100-mm scales combined with the questions: "How hungry do you feel right now?", "How satisfied do you feel right now?", "How full do you feel right now?", and "How much food do you think you could eat right now?" A staff member will use a caliper to measure the distance from 0 to the mark that the patient placed on the VAS and record the measurement in the source document. Overall appetite score is calculated as the average of the 4 individual scores—satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4 (van Can et al. 2014). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

9.6.4. Immunogenicity Assessments

Samples from patients in each cohort will be tested for the development of treatment-emergent antidrug antibodies (TE-ADAs) against LY3298176. A blood sample will be collected at specific study visits according to the Schedule of Activities (Section 2). All samples for immunogenicity should be taken predose when applicable. To interpret the results of immunogenicity, a PK sample should be collected at the same time point as the immunogenicity sample. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days after the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour time period of each sampling will

All patients will have an ADA sample measured at early discontinuation or at the follow-up visit (Day 85) approximately 5 weeks after the last dose of LY3298176. A risk-based approach will be used to monitor patients who have clinically significant TE-ADAs at the last visit. 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 or those with a 4-fold (2 dilutions) increase in titer from baseline if ADAs were detected at baseline. Clinically significant TE-ADAs will be defined as any TE-ADA at the follow-up visit (Day 85) with:

- a high titer (≥1280) or an increasing titer from last measured value
- an association of the TE-ADA with a moderate to severe injection-site reaction or infusion-related reaction
- cross-reactive and/or neutralizing binding of an ADA with endogenous GLP-1 or GIP

Patients who have clinically significant TE-ADAs should be followed up with ADA testing every 3 months for up to approximately 1 year or until the ADA titers have returned to baseline ADA titer (defined as ADA titer within 2-fold of baseline), whichever occurs earlier. A PK sample may be collected at the follow-up immunogenicity assessment(s) if warranted and agreed upon between both the investigator and sponsor.

Every attempt should be made to contact patients for the follow-up immunogenicity assessment; however, if patients are unwilling or unable to return for the visit, this is not considered a protocol violation.

Patients followed up for at least 1 year since last dose who have not returned to baseline, as defined above, will be assessed for safety concerns and, if no clinical sequelae are recognized by the clinical team, no further follow-up will be required.

Patients who have clinical sequelae that are considered potentially related to the presence of TE-ADAs may also be asked to return for additional follow-up testing.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and 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.

9.7. Genetics

A 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 exposure or response to LY3298176 and to investigate genetic variants thought to play a role in T2DM and related complications. 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 investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3298176 or after LY3298176 is 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, multiplex assays, and candidate gene studies. Regardless of technology utilized, 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 DNA, RNA, 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 for 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 investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3298176 or after LY3298176 or is commercially available.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size for the study was chosen to provide sufficient data to evaluate the primary objective of this study and is not intended to achieve any a priori statistical requirements.

Approximately 49 Japanese patients with T2DM may be enrolled so that approximately 32 patients complete the study with compliant defined dosing regimen. The estimated drop-out rates are 30% for Cohorts 1 and 3 and 50% for Cohort 2. Patients will be administered 8 weekly SC doses of LY3298176 or placebo in a ratio of 12 LY3298176:3 placebo for Cohorts 1 and 3, and 16 LY3298176:3 placebo for Cohort 2. Considering the possibility of higher drop-out rate when administered the highest dose level of LY3298176, the number of patients to be enrolled in Cohort 2 is higher than those for the other 2 cohorts.

Replacement of discontinued patients is not planned because the sample size is determined considering the expected drop-out rate.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

All patients who discontinue from the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.2.2. Study Participant Characteristics

The patient's age, sex, weight, height, or other demographic characteristics will be recorded and may be used in the PK, PD, and safety analyses as quantitative or classification variables.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

PK and PD analyses will be conducted on data from all patients who receive at least 1 dose of the IMP and have evaluable PK and PD data.

Patients treated with placebo within each cohort of the study will be pooled for PD and safety analyses.

Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements. Primary safety analyses will be conducted by treatment group defined by intended titration regimen group. Additional analyses will be conducted on the basis of the treatment groups defined by titration regimen as actually treated, if deemed necessary after data review.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Statistical analyses will be fully detailed in the statistical analysis plan.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IMP and protocol procedure–related AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment group will be presented by severity and by association with IMP as perceived by the investigator. Symptoms reported to occur before the first IMP dosing will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of IMP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, ECG parameters, injection-site reactions, and hypoglycemia. The parameters will be listed and summarized using standard descriptive statistics.

Laboratory measurements will be summarized with respect to observed values and change from baseline by treatment group at each time point using descriptive statistics. In addition, all clinical chemistry, hematology, and urinalysis data outside the reference ranges will be tabulated by parameter and treatment group.

Vital signs will be summarized with respect to observed values and change from baseline (Day 1, Predose) by treatment at each time point using descriptive statistics. For change from baseline values, a mixed-model repeated-measure model with treatment, time (of measurement), and treatment-by-time interaction as fixed effects, patient as random effect, and baseline as covariate will be used to determine the effects of LY3298176.

Electrocardiogram parameters, including the pulse rate, QT interval, RR interval, and QTc using Fridericia's formula (QTcF), QRS interval duration, and heart rate, will be summarized. The number and percentage of patients with a maximum increase from baseline in QTcF will be summarized for each treatment group according to the following categories: >30 milliseconds and >60 milliseconds. In addition, the number and percentage of patients with QTcF postdose values according to the following categories: >450 milliseconds, >480 milliseconds, and >500 milliseconds, will be summarized by treatment group. Exploratory analyses may be performed to determine the effects of LY3298176 concentration-response analysis of QTcF.

Additional analysis will be performed, if warranted, upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3298176 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, AUC, and T_{max} of LY3298176. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

Model-based analysis will be performed combined with data from other studies. LY3298176 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software (NONMEM, Dublin, Ireland). Additionally, the effect of intrinsic and extrinsic patient factors such as age, weight, sex, and renal function on PK may be examined as needed.

10.3.2.2. Pharmacokinetic Statistical Inference

PK dose proportionality may be assessed in an exploratory manner in model-based analysis.

The parameter T_{max} of LY3298176 will be analyzed using a nonparametric method.

PK parameters will be summarized using descriptive statistics by dosing regimen.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

The ability of LY3298176 to reduce fasting or dynamic glucose and the effects on insulin will be assessed. Such effects will be explored for different treatment regimens of LY3298176.

The AUC(0-2h) for glucose and insulin during an OGTT will be calculated using the trapezoidal rule. The AUC(0-2h) as well as other derived parameters or observed concentration at specific time points for each patient on the study day will also be baseline-adjusted. The concentrations on Day -1 will be used as baseline.

10.3.3.2. Pharmacodynamic Statistical Inference

Statistical inference on PD parameters will be based on the patients who are compliant to each treatment regimen. Pharmacodynamic parameters may be transformed before statistical analyses, if deemed necessary.

Absolute values, as well as change from baseline in each parameter, will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The model will include treatment, or treatment regimen actually received, as fixed effects and the patient as a random effect. For repeated measured parameters, day and treatment-by-day interaction terms will be included in the model. Baseline (Day -1) values, as well as other influencing variables, may be used as covariates. The main comparisons will be between each LY3298176-treated group and placebo group.

The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic modeling may be used to characterize the exposure-response relationships between LY3298176 concentrations and various PD endpoints, provided data are sufficient.

10.3.5. Evaluation of Immunogenicity

The frequency of antibody formation (presence and titers) to LY3298176 will be determined. If any cross-reactive or neutralization assays are performed, the frequency of antibodies will be determined. If there are a sufficient number of patients with positive antibodies to LY3298176, the change of antibodies (negative to positive) will be summarized using shift tables.

The relationship between the presence of antibodies, antibody titers, and clinical parameters (eg, AEs) may be assessed. Likewise, the relationship between antibody titers, PK parameters, and PD response to LY3298176 may be assessed.

10.3.6. Data Review During the Study

Access to safety data is scheduled to occur at least once to review the safety data up to Day 36 (predose procedure) of Cohort 1 from at least 8 patients to proceed to Cohort 2. The available PK data may be accessed at the review. Pharmacokinetic data is not mandatory for the dose escalation or for moving to the next cohort. The purpose of this review is to guide dose selection for the next dosing session, and/or to inform the design of subsequent studies. The investigator and the Lilly sponsor team will make the determination regarding dose escalation based upon their review of the data. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

10.3.7. Interim Analyses

Interim analysis may be conducted when all data through Day 85 become available from all cohorts. Additional interim analysis may be conducted to proceed to the subsequent Japan studies. For this purpose, at least safety and PK data may be analyzed.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
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 AE 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
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
C_{max}	maximum drug concentration
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 the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
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.
CRU	clinical research unit
CSE	clinically significant event
DPP	dipeptidyl peptidase

ECG	electrocardiogram
eCRF	electronic case report form
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.
ERB	ethical review board
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	investigator's brochure
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.
investigational medicinal product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
MAD	multiple-ascending dose
OGTT	oral glucose tolerance test
PG	plasma glucose
PK/PD	pharmacokinetic/pharmacodynamic
QTc	QT corrected for heart rate
QTcF	QTc using Fridericia's formula

randomize	the process of assigning patients to an experimental group on a random basis
SAE	serious adverse event
SMPG	self-monitored plasma glucose
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
TBL	total bilirubin level
TE-ADA	treatment-emergent antidrug antibody
T2DM	type 2 diabetes mellitus
T_{max}	time to maximum drug concentration
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets
- Differential WBC Absolute counts of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Leukocytes
- Microscopy[b]

Lipid Panel[c,d]
- HDL-C
- LDL-C (calculated)
- Total cholesterol
- Triglycerides

Serology[a,e]
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody and/or HIV antigen

Clinical Chemistry (fasting)[a]
- Sodium
- Potassium
- Chloride
- Serum creatinine
- Calcium
- Phosphorus
- Glucose
- Blood urea nitrogen
- Uric acid
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Lipase
- Amylase
- Total cholesterol[f]
- Triglyceride[f]
- eGFR[e]

Biomarkers[d]
- Fasting plasma glucose, insulin, glucagon[c]
- OGTT serum glucose and insulin[c]
- Exploratory storage sample[c]

Other Tests
- Pregnancy test (urine, serum)[a,b]
- Follicle-stimulating hormone [a,b,e]
- Drug and alcohol screen[a]
- Hemoglobin A1c[c,d]
- Pharmacogenetic sample (storage)[c,d]
- Nonpharmacogenetic sampling (storage)[c,d]
- LY3298176 Plasma levels[d,g]
- Immunogenicity[d,g]

Abbreviations: eGFR = estimated glomerular filtrating ratio; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; OGTT = oral glucose tolerance test; RBC = red blood cells, WBC = white blood cells.

[a] Performed at local laboratories.

[b] If clinically indicated, per investigator's discretion.

[c] Performed or stored at a central laboratory.

[d] These results will not be reported to investigator sites except for the screening hemoglobin A1c.
[e] Performed at screening only.
[f] Total cholesterol and triglyceride concentrations in the safety panel will not be required on the days that the lipid panel is performed.
[g] Assayed at Lilly-designated laboratory.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- 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) before the performance of any protocol procedures and before the administration of investigational medicinal 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.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator 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 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 current investigator's brochure and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

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

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.

Final Report Signature

The investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

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 training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (CRFs), and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly 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 the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of patient personal information collected will be provided in a written document to the patient by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, 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.

Discontinuation of the Study

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

Appendix 4. Clinically Significant Adverse Effects

The table below summarizes the type and severity of symptoms, clinical signs, and clinical laboratory findings that may qualify as a clinically significant event. These are intended as a guideline to the investigator(s), not as a set of absolute criteria. The underlying principle is to define a level of moderate to severe abnormality in safety findings that could cause harm to health and would preclude further dosing of a patient/subject who experiences this effect. Safety parameters not included in this table may be interpreted in a similar fashion according to investigator judgment.

Clinically Significant Adverse Effects

Parameter	CSE level
Symptoms	
Severe hypoglycemia	One episode of severe hypoglycemia defined as low blood glucose with mental status impairment severe enough to require third-party assistance
Dizziness/hypotension	Orthostatic CNS symptoms (dizziness, confusion) that are not vasovagal responses to provocative stimuli (for example, phlebotomy, nausea, bowel or bladder function), and are associated with orthostatic SBP decrease >20 mm Hg or DBP decrease >10 mm Hg or heart rate >105 bpm, for >3 hours
Sensorium	Disorientation to time, place, or identity. Any abnormal ideation
Mood	Feelings of grief or loss that interfere with study procedures or activities of daily living; any suicidal ideation
Headache/pain	Any focal or generalized head pain that disrupts normal activities and is not responsive to medical therapies
Pruritus	Generalized itching for more than 24 hours that is unresponsive to oral antihistamine
Signs	
Systolic blood pressure	>30 mm Hg increase from baseline values and an absolute level >190 mm Hg
Diastolic blood pressure	>20 mm Hg increase from baseline values and an absolute level >115 mm Hg
Heart rate	Resting (sitting or recumbent) HR >120 bpm
Cardiac rhythm	Any rhythm other than sinus rhythm, mild sinus bradycardia, or mild sinus tachycardia
QTc	>500 milliseconds or >60 milliseconds increase from baseline value
QRS morphology	Significant prolongation of QRS interval or new onset of bundle branch block
Tremor	Readily visible tremor during normal movement deemed unrelated to hypoglycemia
Reflexes	New onset of clonic reflexes
Clinical Laboratory	Confirmed by repeat measurements within 48 hours
Hemoglobin	Absolute value <10 g/dL and >2 g/dL reduction from baseline
Neutropenia	Absolute neutrophils <1,500/μL and >1,000 μL decrease from baseline
Lymphopenia	Absolute lymphocyte count <800/μL and >500/μL decrease from baseline
Platelet count	<75,000/μL and >50,000/μL decrease from baseline
Creatinine	>2 mg/dL and >0.5 mg/dL increase from baseline value
Urea	>8 mmol/L and >3 mmol/L increase from baseline values
Alanine aminotransferase	>5-fold above laboratory reference upper limit value
Aspartate aminotransferase	>5-fold above laboratory reference upper limit value
Bilirubin (total)	>1.5-fold above laboratory reference upper limit value
Potassium	<2.5 or >5.5 mEq/L and >0.5 mEq/L change from baseline value
Sodium	<130 or >150 mEq/L and >10 mEq/L change from baseline value

Abbreviations: BPM = beats per minute; CNS = central nervous system; CSE = clinically significant event; DBP = diastolic blood pressure; HR = heart rate; QTc = QT interval corrected for heart rate; SBP = systolic blood pressure.

Appendix 5. 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 Lilly clinical pharmacologist, clinical research physician, or clinical research scientist.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
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
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Antinuclear Antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti–Smooth Muscle Antibody (or Antiactin**
CPK	**Antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = γ-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 6. Pancreatic Monitoring

Glucagon-like peptide-1 agonists have been associated with a possible risk of acute pancreatitis. In 2006, the US prescribing information for exenatide was revised to include the event of pancreatitis. In 2007, the US prescribing information for this medication was amended to include pancreatitis under precautions. Epidemiologic studies have indicated that there is an increased incidence and prevalence of pancreatitis in persons with type 2 diabetes mellitus (T2DM).

To enhance understanding of the natural variability of pancreatic enzymes in the T2DM population and to assess for any potential effects of LY3298176 on the exocrine pancreas, amylase and lipase values will be monitored in all current and future clinical trials with LY3298176.

Additional monitoring will be requested for amylase or lipase values ≥3× the upper limit of normal (ULN) at any visit after randomization, even in asymptomatic patients (see figure below). Lipase and amylase may also be obtained at any time, at the investigator's discretion, during the clinical trials for any patient suspected of having symptoms suggestive of pancreatitis (eg, severe gastrointestinal signs and/or symptoms).

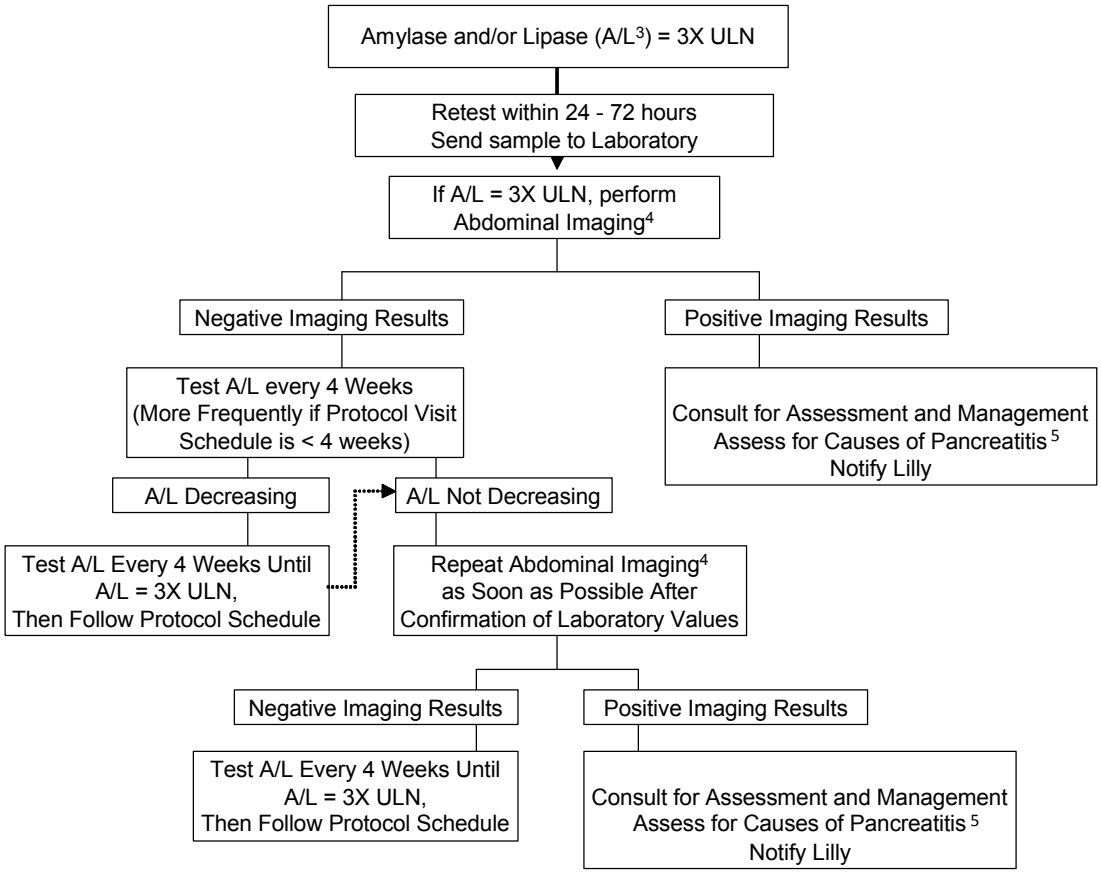
Acute pancreatitis is an adverse event (AE) defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3× ULN
- characteristic findings of acute pancreatitis on computed tomography scan or magnetic resonance imaging

Most patients with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back in approximately half of cases. The pain is often associated with nausea and vomiting. However, experience with glucagon-like peptide-1 agonists has demonstrated that some patients/subjects asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase. For patients considered by investigators to be asymptomatic for pancreatitis, but whose value(s) for lipase and/or amylase are ≥3× ULN, an algorithm is in place to follow up with these patients safely and to quickly reach or not reach a diagnosis of pancreatitis.

Pancreatic Enzymes: Safety Monitoring Algorithm In Patients without Symptoms of Pancreatitis[1,2]

Follow this algorithm when the value(s) for serum amylase and/or lipase are = 3x upper limit of normal (ULN)



1. Symptomatic – related primarily to abdominal pain consistent with pancreatitis; however, in the opinion of the investigator severe nausea and vomiting plus other symptoms consistent with pancreatitis may be considered symptomatic as well.

2. If in the opinion of the investigator, the patient has symptoms of acute pancreatitis:
   (a) Stop injectable study drug
   (b) Consult for assessment and management
   (c) Assess for causes of pancreatitis
   (d) Notify Lilly

3. A/L = amylase and/or lipase. Either or both enzymes can be used to meet the algorithm criteria.

4. Abdominal imaging is most valuable when performed at the time of elevated enzyme values. If in the opinion of the radiologist or investigator, it is safe for the patient/subject to receive contrast, an enhanced abdominal CT is preferred. MRI is also an acceptable imaging modality.

5. At a minimum, order a CBC and a pancreatic panel (which includes LFTs, calcium and triglycerides). Record all concomitant medications.

Abbreviations: A/L = amylase and/or lipase; CBC = complete blood count; CT = computed topography; LFTs = liver function tests; LY = LY3298176; MRI = magnetic resonance imaging; ULN = upper limit of normal.

Patients diagnosed with pancreatitis will be discontinued from the study. Investigators will be responsible for following up, through an appropriate health care option, these pancreatitis AEs until the events resolve or are explained. AEs that meet the diagnostic criteria of acute pancreatitis will be captured as serious AEs. For all other pancreatic AEs (eg, idiopathic or asymptomatic pancreatic enzyme abnormalities), the investigator will be responsible for determining the seriousness of the event (AE or serious AE) and the relatedness of the event to investigational medicinal product.

Appendix 7. Blood Sampling Summary

This table summarizes the approximate number of samples and blood volumes for all blood sampling (screening, safety laboratories, bioanalytical assays, and the other tests) during the study.

Protocol I8F-JE-GPGC Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples		Total Volume (mL)	
		Cohort 1 or 2	Cohort 3	Cohort 1 or 2	Cohort 3
Screening serology and Serum pregnancy tests[a]	9[b]	1	1	9	9
Clinical safety laboratory tests[a]	10[b]	20	16	200	160
Lipid panel	2.5	3	3	7.5	7.5
LY3298176 pharmacokinetics	3	18	18	54	54
Potential additional LY3298176 pharmacokinetic samples	3	3	3	9	9
Glucagon	2	15	13	30	26
Fasting plasma glucose and insulin	4.5	15	13	67.5	58.5
Oral glucose tolerance test (serum glucose and insulin)	2.5	10	10	25	25
HbA1c	2	4	4	8	8
Immunogenicity	6	4	4	24	24
Exploratory storage sample[d]					
Adiponectin	2	2	2	4	4
Cortisol	2.5	3	3	7.5	7.5
Bone biomarkers	3.5	2	2	7	7
Pharmacogenetics	6	1	1	6	6
Nonpharmacogenetics Storage sample	4.5	6	6	27	27
Total				485.5[c]	432.5[c]

Abbreviation: HbA1c = hemoglobin A1c.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Because screening and safety (chemistry and hematology) tests are performed at local laboratories at each site, this volume is an estimate and will vary depending on the local laboratory's testing requirements.

[c] The maximum blood volume will increase if follow-up visits for antidrug antibody testing are needed.

[d] Blood volumes for this storage sample is calculated based on the assumption that the following biomarkers will be assayed for.

Appendix 8. Protocol I8F-JE-GPGC Blinding/Unblinding Plan

Levels of unblinding are indicated in the table below. This table provides general guidance as to who will be allowed access to randomization codes at various steps of the trial. The information in the protocol will always take precedence over this table.

Randomization data are kept strictly confidential and are accessible only by authorized personnel until unblinding of the trial as described below. All measures possible must be taken to maintain the blinded portion of the study, which means that access to the randomization code must be restricted to authorized personnel as described in the protocol and summarized in the table below.

If there is a need for unblinding of select people from Lilly and/or the third-party organization who are not dealing with the site, the detailed process, including formation of the unblinded team, creating restricted access electronic folders, and measures taken to guard against inappropriate dissemination of treatment codes (for example, by maintaining no contact with the study team until team is unblinded), will be described in the Unblinding Plan or another appropriate document, and approval will be sought from Lilly and Covance team statisticians.

Study I8F-JE-GPGC Blinding and Unblinding Plan

	Study Timelines				
Study Team Member	**Screening**	**Randomization**	**Treatment Phase**	**Follow-Up**	**Database Lock (up to Day 85)**
General					
Drug supply	NA	U	U	U	U
Randomization statisticians	NA	U	U	U	U
ECG reader	NA	B	B	B	U
Bioanalysis lab/sample analysis	NA	U	U	U	U
Clinical Site					
Pharmacist	NA	U	U	U	U
Dosing staff	NA	B	B	B	U
Patient	NA	B	B	B	U
Investigator	NA	B	B	B	U
Study monitor	NA	U	U	U	U
Covance					
Project integration	NA	U	U	U	U
Data management	NA	U	U	U	U
Programming	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical writing	NA	U	U	U	U
Pharmacokinetic scientist/associate	NA	U	U	U	U
Lilly					
CPM	NA	U	U	U	U
CPA	NA	U	U	U	U
DSA	NA	U	U	U	U
SDTM core team	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical writing	NA	U	U	U	U
Clinical pharmacologist	NA	U	U	U	U
Pharmacokinetic scientist/associate	NA	U	U	U	U

Abbreviations: B = blinded; CPA = clinical pharmacology associate; CPM=clinical project management; DSA = data sciences associate; ECG = electrocardiogram; lab = laboratory; NA = not applicable; SDTM = study data tabulation model; U = unblinded.

Appendix 9. Protocol Amendment I8F-JE-GPGC(a) Summary
A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176

Overview

Protocol I8F-JE-GPGC, A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176, has been amended. The new protocol is indicated by Amendment (a) 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 as follows:

- The study will be unblinded triggered by the database lock with data up to Day 85 to initiate the subsequent Japan clinical studies.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Table GPGC.3. Amendment Summary for Protocol I8F-JE-GPGC Amendment(a)

Section # and Name	Description of Change	Brief Rationale
7.3. Blinding and Appendix 8. Protocol I8F-JE-GPGC Blinding/Unblinding Plan	Blinded period ends when the database is locked with data up to Day 85.	To initiate the subsequent clinical studies, the unblinded data of GPGC study up to Day 85 will be provided to ERBs and investigators for better understanding the profile of LY3298176 in Japanese patients with T2DM.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

7.3. Blinding

Blinding will be maintained until the database is locked with data up to Day 85 (blinded period) ~~throughout the conduct of the study~~ as described in the separate Blinding Plan (Appendix 8).

If a patient's study treatment assignment is unblinded during the blinded period, the patient must be discontinued from the study unless the investigator obtains specific approval from a Lilly clinical pharmacologist, CRP, or CRS for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study patient's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding during the blinded period is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Appendix 8. Protocol I8F-JE-GPGC Blinding/Unblinding Plan

	Study Timelines				
Study Team Member	**Screening**	**Randomization**	**Treatment Phase**	**Follow-Up**	**Database Lock (up to Day 85)**
General					
Drug supply	NA	U	U	U	U
Randomization statisticians	NA	U	U	U	U
ECG reader	NA	B	B	B	U~~B~~
Bioanalysis lab/sample analysis	NA	U	U	U	U
Clinical Site					
Pharmacist	NA	U	U	U	U
Dosing staff	NA	B	B	B	U~~B~~
Patient	NA	B	B	B	U~~B~~
Investigator	NA	B	B	B	U~~B~~
Study monitor	NA	U	U	U	U

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