Protocol I8F-MC-GPGB (a)

A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus

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Approval Date: 28-Nov-2017

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A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus

Confidential Information

LY3298176

This is a randomized, double-blind, parallel, placebo- and active comparator-controlled, Phase 2, multicenter, multi-country study in patients with type 2 diabetes.

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

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1. Synopsis

Title of Study:

A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus

Rationale:

Study I8F-MC-GPGB is a 26-week Phase 2 study designed to examine the safety, efficacy, and pharmacokinetics (PK)/pharmacodynamics (PD) of 4 dose levels of once weekly (QW) LY3298176 compared with QW dulaglutide 1.5 mg and QW placebo in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control with diet and exercise with or without a stable dose of metformin. The primary endpoint will be the effect on hemoglobin A1c (HbA1c). These data will support dose selection for Phase 3.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To demonstrate a dose–response relationship of QW subcutaneous injections of LY3298176 on HbA1c change from baseline relative to placebo, in patients with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.	The change in HbA1c from baseline to 26 weeks
Secondary To determine the effect of LY3298176 versus dulaglutide (and to compare the effect of each versus placebo) on: • The mean body weight change from baseline to 12 and 26 weeks • The percentage of patients with 5% or greater body weight loss at 26 weeks • The change from baseline of HbA1c at 12 weeks • The percentage of patients with 10% or greater body weight loss at 26 weeks • The percentage of patients reaching the HbA1c target of ≤6.5% and of ≤7.0% • The change from baseline of fasting blood glucose (FBG) at 12 and 26 weeks • The change from baseline to 26 weeks in high-density lipoprotein cholesterol, total cholesterol, triglycerides, and low-density lipoprotein cholesterol • The waist circumference	• The change in mean body weight from baseline to 12 and 26 weeks • The percentage of patients with 5% or greater body weight loss from baseline to 26 weeks • The change in HbA1c from baseline to 12 weeks • The percentage of patients with 10% or greater body weight loss from baseline to 26 weeks • The percentage of patients reaching the HbA1c target of ≤6.5% and of ≤7.0% • The change in FBG from baseline to 12 and 26 weeks • The change in lipids from baseline to 26 weeks • The change from baseline to 12 and 26 weeks

Objectives	Endpoints
Secondary (continued) Safety and tolerability, including gastrointestinal tolerability, incidence and rate of hypoglycemia, hypersensitivity reactions, and pancreatic safety	• Adverse events and glucose data
To evaluate the development of treatment-emergent anti-drug antibodies to LY3298176	• Number of patients testing positive for anti-LY3298176 antibodies
To assess the PK and PD of LY3298176 and potential patient factors that may influence its PK and PD	• PK and PD
To assess the relationship between LY3298176 dose and/or exposure and key efficacy and safety measures, where applicable	• Dose-exposure–response analyses

Summary of Study Design:

Study GPGB is a multicenter, randomized, double-blind, parallel, placebo- and active comparator-controlled Phase 2 trial in patients with T2DM who failed to achieve adequate glycemic control on diet and exercise alone or on a stable dose of metformin (≥1000 mg/day for at least 3 months prior to Visit 1).

Treatment Arms and Duration:

There are 6 treatment arms, including placebo, 4 dose levels of LY3298176, and dulaglutide 1.5 mg.

Number of Patients:

There will be 540 patients screened with the goal of randomizing 300 patients and having 45 patients per treatment arm who complete the study.

Statistical Analysis:

Efficacy: The primary efficacy outcome of HbA1c change from baseline to the 26-week endpoint will be analyzed using a Bayesian dose–response model. Analyses will be performed on the modified intent-to-treat (mITT) analysis set. Supportive analysis of the primary efficacy outcome for the mITT dataset will be the mixed model for repeated measures (MMRM) with body mass index (<30, ≥30), metformin use, treatment, visit, and treatment-by-visit interaction as fixed effects, baseline HbA1c as a covariate, and patient as a random effect. Additional covariates may be added and will be detailed in the statistical analysis plan.

The mean weight change from baseline at 12 and 26 weeks along with the mean change from baseline of HbA1c at 12 weeks will be analyzed using similar dose–response models as the primary analysis. The percentage of patients with ≥5% (and with ≥10%) body weight loss, the percentage of patients reaching the HbA1c target of ≤6.5% (and of ≤7.0%) at 26 weeks, and the proportion of patients requiring rescue therapy will be analyzed using a logistic regression analysis with fixed effects of treatment and strata, and baseline as a covariate. The change from baseline of FBG, self-monitoring of blood glucose levels, waist circumference, mean percentage change in lipids and change from baseline to 12 and 26 weeks for fibroblast growth factor-21, adiponectin, β-hydroxy butyrate, free fatty acids, glycerol, monocyte chemoattractant protein-1 (MCP-1), glucagon, C-peptide, and insulin levels will be calculated

using a similar MMRM-based model to the one used for the supporting primary analysis. Summaries will include descriptive statistics for continuous measures (sample size, mean, standard deviation [SD], median, minimum, and maximum) and for categorical measures (sample size, frequency, and percentage).

Pharmacokinetics/Pharmacodynamics: LY3298176 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. The relationships between LY3298176 dose and/or concentration and efficacy, tolerability, and safety, as well as biomarkers, will be characterized if exploratory analyses of the PD data warrant further PK/PD analyses upon review. Such analyses may include, but are not necessarily limited to, QTc interval, blood pressure, heart rate, glucose, HbA1c, insulin, nausea/vomiting, etc. In addition, the relationship between biomarkers and LY3298176 efficacy will be analyzed, if deemed appropriate. If positive antibody titers to LY3298176 are observed, the relationship between LY3298176 PK or any relevant PD parameters and antibody titer will be performed.

Safety: The summary statistics for continuous variables will be sample size, mean, SD, median, minimum, and maximum. The summary statistics for categorical variables will be sample size, frequency, and percentage. Exposure to each therapy during the treatment period of the study will be calculated for each patient and summarized by treatment group. Additional analyses, such as concentration–safety lab plots, may be performed if warranted upon review of the data.

2. Schedule of Activities

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study Day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		112/(17)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Administrative																		
Informed consent	X																	
Diabetes/medical history/therapy	X																	
Inclusion/Exclusion	X		X															
Preexisting conditions	X		X															
Randomization			X															
IWRS			X	X		X		X		X	X		X	X	X	X	X	X
Drug accountability				X		X		X		X	X		X	X	X	X		X
BG meter/supplies, if needed		X						X		X	X		X	X	X	X		
BG meter, instructions		X	X															
Diet, exercise, BG counseling		X																
Study diary, dispense		X	X	X		X		X		X	X		X	X	X	X		
Review patient diaries for BG values, AEs, hypoglycemic or hyperglycemic events		X	X	X		X		X		X	X		X	X	X	X	X	X
Subcutaneous injection training		X	X															

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		112/(17)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Study drug and injection supplies, dispense			X	X		X		X		X	X		X	X	X	X		
Health habits (alcohol use yes/no, tobacco use current/past)	X																	
Patient returns unused study drug supplies								X		X	X		X	X	X	X		X
Study drug, assess compliance								X		X	X		X	X	X	X		X
Patient Demographics																		
Age	X																	
Gender	X																	
Race/Ethnicity	X																	
Clinical Variables																		
Physical examination	X															X		X
Symptom-driven physical exam			X					X		X	X		X	X	X	X	X	X
Height	X																	
Weight	X		X	X		X		X		X	X		X	X		X	X	X
Waist circumference	X		X					X		X	X		X	X		X	X	X
Vital signs (BP and PR)	X		X	X		X		X		X	X		X	X		X	X	X
Antidiabetic medication	X	X	X	X		X		X		X	X		X	X	X	X	X	X
Concomitant medication	X	X	X	X		X		X		X	X		X	X	X	X	X	X

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		112/(17)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Other																		
ECGs[b]	X		X							X[c]	X[c]	X[c]				X[c]	X	X
Evaluation of Injection Site Reactions			X	X		X		X		X	X		X	X	X	X		X
APPADL and IW-SP questionnaires		X									X					X		X
Diagnostics (Safety)																		
Screening Laboratory Tests[d]	X																	
Pregnancy test[e]	X		X															
Estradiol, FSH, LH[f]	X																	
Chemistry panel	X		X					X			X					X	X	X
Lipase and amylase	X		X	X		X		X		X	X		X	X	X	X	X	X
Lipid panel	X		X					X			X					X		X
eGFR	X		X					X			X					X	X	X
Hematology	X							X			X					X	X	X
Urinalysis	X										X					X	X	X
Urine albumin, creatinine, UACR	X										X					X	X	X

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	−3	−2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		112/(17)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Diagnostics (Efficacy)																		
Calcitonin	X		X								X					X		X
HbA1c	X		X	X		X		X		X	X		X	X	X	X	X	X
Fasting glucose	X		X			X		X			X					X	X	X
Fasting insulin and c-peptide			X					X			X					X		X
Fasting glucagon			X					X			X					X		X
Total and active GLP-1/GIP			X					X			X					X	X	X
Remind Patients about 7-point SMBG		X				X				X					X	X		
7-point SMBG		X[g]						X			X					X	X	
Osteopontin, FGF-21 (active), Adiponectin, β-hydroxy butyrate, glycerol, free fatty acids, MCP-1, CTX-1, P1NP, osteocalcin			X								X					X		X

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		112/(17)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						
Pharmacogenetic stored samples			X															
Nonpharmacogenetic stored samples			X			X		X			X					X		
Immunogenicity testing			X	X		X		X			X					X	X	X
PK sample for Immunogenicity[h]						X[h]		X[h]									X[h]	
Pharmacokinetics (see PK schedule)[a]				X[a*]	X[a]		X[a]		X[a]	X[a*]	X[a*]	X[ac]				X[a*]		X[a]

Abbreviations: AE = adverse event; APPADL = Ability to Perform Physical Activities of Daily Living; BG = blood glucose; BP = blood pressure; d = day; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; FGF-21 = fibroblast growth factor-21; FSH = follicle-stimulating hormone; GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic peptide; HbA1c = hemoglobin A1c; IWRS = Interactive Web Response System; IW-SP = Impact of Weight on Self-Perception; LH = luteinizing hormone; PK = pharmacokinetics; PR = pulse rate; SMBG = self-monitoring of blood glucose; UACR = urine albumin-to-creatinine ratio.

* Indicates PK samples to be collected predose.

a See Pharmacokinetics Schedule of Events, Appendix 6.

b ECGs should be collected centrally at Visits 3, 10, 11, 12, 16, and 801, and locally at screening and early termination.

c ECG should be collected immediately prior to PK sample collection.

d Screening laboratory tests include serum hepatitis B surface Ag, hepatitis C antibody (Ab), and human immunodeficiency virus Ab tests for all patients.

e Serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing potential. For the remainder of the study, a urine pregnancy test may be performed at the investigator's discretion if pregnancy is suspected during the study (local laboratory).

f Collect serum estradiol, FSH, and LH in women whose menopausal status needs to be determined.

g Two baseline collections during the lead-in period.

h PK samples specifically for immunogenicity.

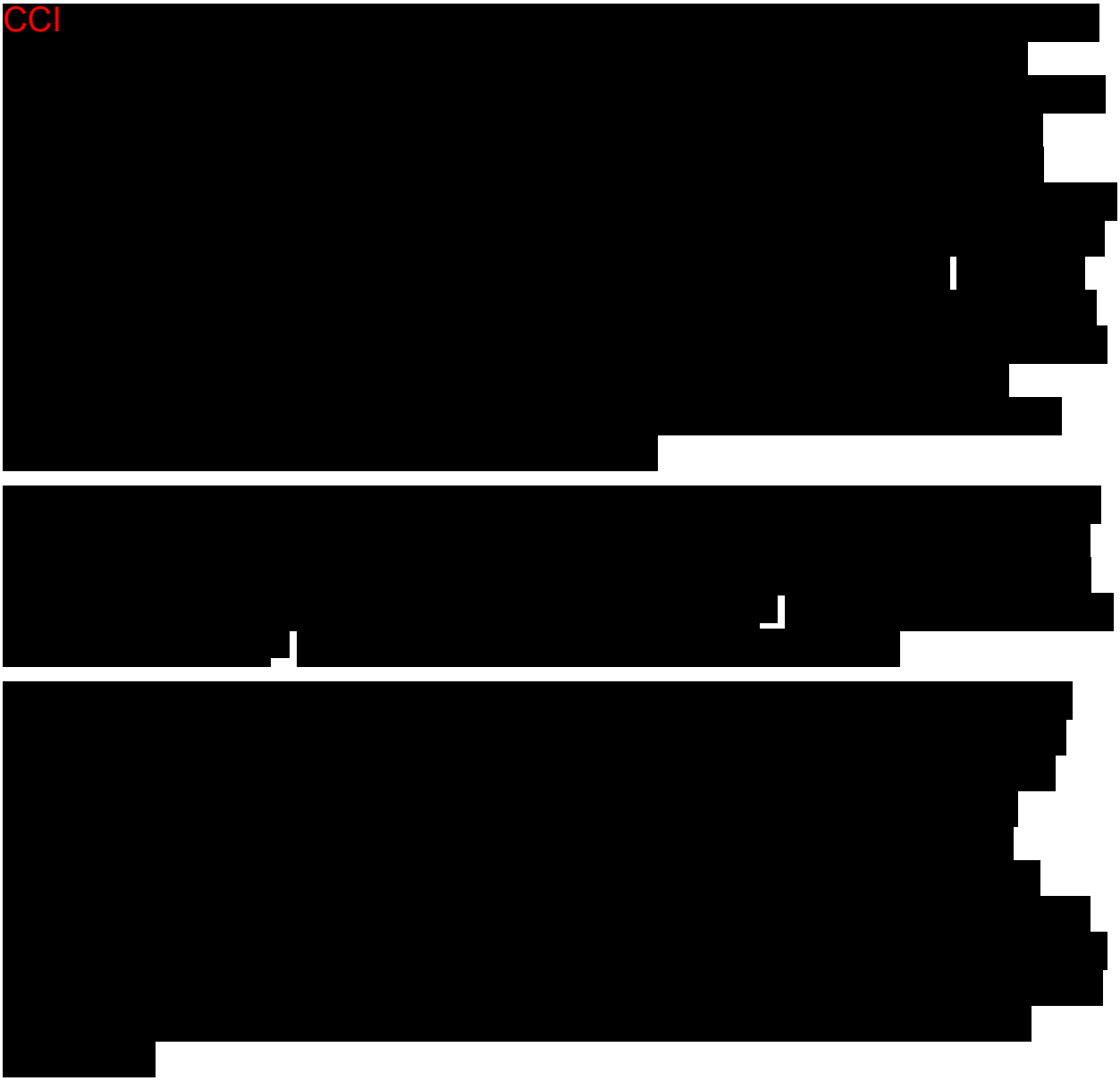
3. Introduction

3.1. Study Rationale

Study I8F-MC-GPGB is a 26-week Phase 2 study designed to examine the safety, efficacy, and pharmacokinetics (PK)/pharmacodynamics (PD) of 4 dose levels of once weekly (QW) subcutaneously administered LY3298176 compared with QW subcutaneously administered dulaglutide 1.5 mg and QW placebo in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control with diet and exercise with or without a stable dose of metformin. The primary objective will be the effect on hemoglobin A1c (HbA1c). These data will support dose selection for Phase 3.

3.2. Background

CCI



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3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of LY3298176 may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs that are expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate, periodically during the course of the study, and may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of dulaglutide may be found in the USPI or SmPC (Trulicity® USPI, 2015; Trulicity® SmPC, 2016).

4. Objectives and Endpoints

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

Table GPGB.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective of this study is to demonstrate a dose–response relationship of QW SC injections of LY3298176 on HbA1c change from baseline relative to placebo, in patients with T2DM inadequately controlled with diet and exercise alone or treated with a stable dose of metformin.	The change in HbA1c from baseline to 26 weeks
Secondary To determine the effect of LY3298176 versus dulaglutide (and to compare the effect of each versus placebo) on:	
• The mean body weight change from baseline to 12 and 26 weeks	• The change in mean body weight from baseline to 12 and 26 weeks
• The percentage of patients with 5% or greater body weight loss at 26 weeks	• The percentage of patients with 5% or greater body weight loss from baseline to 26 weeks
• The change from baseline of HbA1c at 12 weeks	• The change in HbA1c from baseline to 12 weeks
• The percentage of patients with 10% or greater body weight loss at 26 weeks	• The percentage of patients with10% or greater body weight loss from baseline to 26 weeks
• The percentage of patients reaching the HbA1c target of ≤6.5% and of ≤7.0%.	• The percentage of patients reaching the HbA1c target of ≤6.5% and of ≤7.0%
• The change from baseline of fasting blood glucose (FBG) at 12 and 26 weeks	• The change in FBG from baseline to 12 and 26 weeks
• The change from baseline to 26 weeks in high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C)	• The change in lipid laboratory data from baseline to 26 weeks
• The waist circumference	• Change from baseline to 12 and 26 weeks
Safety and tolerability, including GI tolerability, incidence and rate of hypoglycemia, hypersensitivity reactions, and pancreatic safety	• AE reports and evaluation of laboratory data
To evaluate the development of treatment-emergent anti-drug antibodies to LY3298176	• Number of patients testing positive for anti-LY3298176 antibodies
To assess the PK and PD of LY3298176 and potential patient factors that may influence its PK and PD	• PK and PD
To assess the relationship between LY3298176 dose and/or exposure and key efficacy and safety measures, where applicable	Dose-exposure–response analyses

Tertiary/Exploratory Evaluate the effect of LY3298176 compared with placebo and dulaglutide on:	
• Change from baseline of 7-point self-monitoring of blood glucose (SMBG) profiles at 4, 12, 26, and 30 weeks	• The change in SMBG profile from baseline to 4, 12, 26, and 30 weeks
• Biomarkers	• The change from baseline to 12 and 26 weeks
• Patient-reported outcomes (PRO)	• The change from baseline to 12 and 26 weeks
• Pharmacogenetic objectives are a. To evaluate genetic variants in genes in the glucagon signaling pathway and GIP/GLP-1-associated genes for association with efficacy responses to LY3298176 such as change from baseline in HbA1c, fasting glucose, body weight, and body mass index (BMI). b. To evaluate the association of genetic variants in the glucagon signaling pathway and GIP/GLP-1-associated genes with other PD and clinical endpoints of interest (including circulating glucagon levels, BP, serum amylase and lipase, GI tolerance, lipid metabolism, bone metabolism, etc.). c. To investigate the genetic variants associated with dulaglutide treatment response (identified from dulaglutide clinical trials) on the efficacy and safety endpoints in response to LY3298176.	

5. Study Design

5.1. Overall Design

Study GPGB is a multicenter, randomized, double-blind, parallel, placebo-controlled trial with 3 study periods in patients who have type 2 diabetes.

Figure GPGB.1 illustrates the study design, including recommended dose titration scheme (see Section 7.1 for details on dose titration).

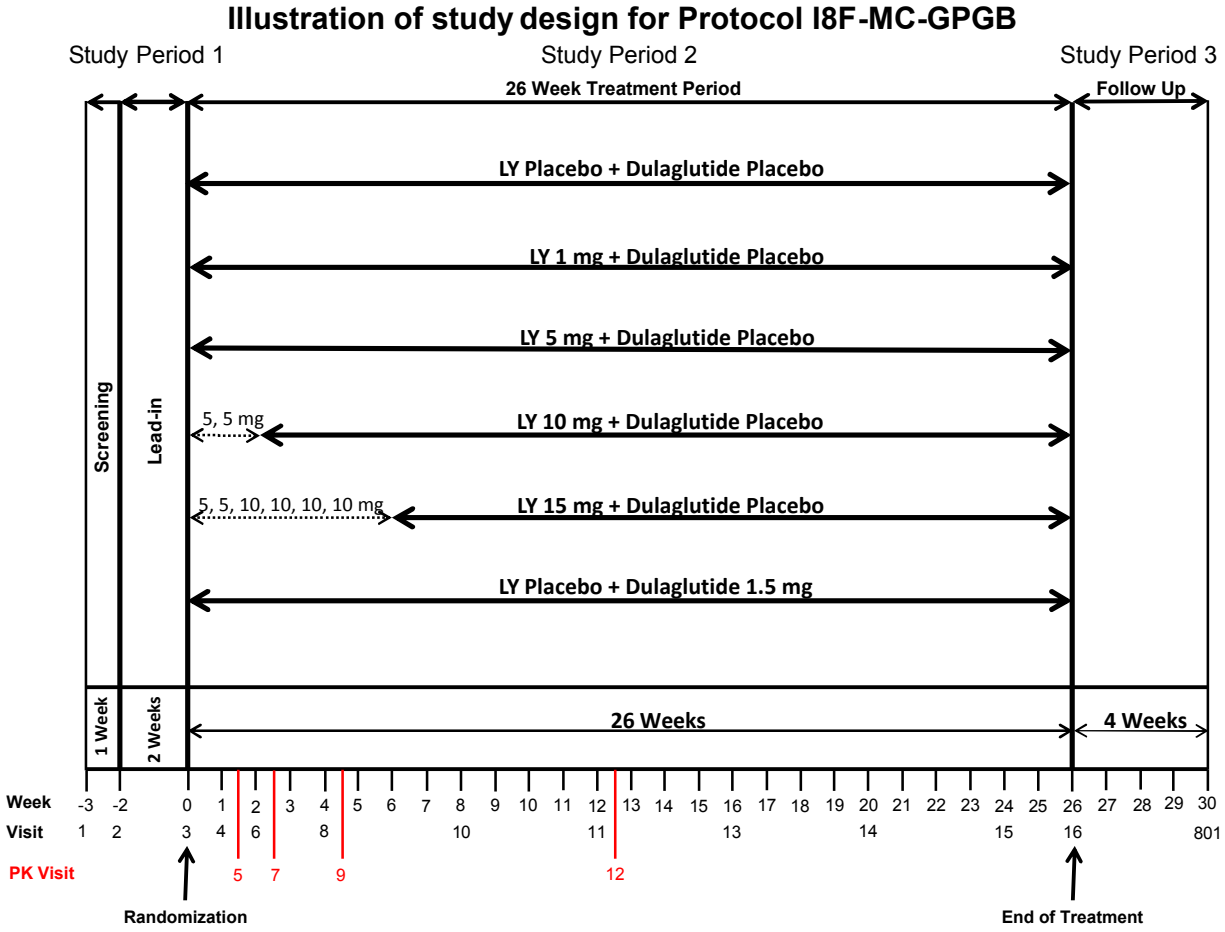

Figure GPGB.1. Illustration of study design for Clinical Protocol I8F-MC-GPGB.

All LY3298176 dose levels above 5 mg will be reached through dose titration (see Section 7.1).

Study procedures and timing for the lead-in, blinded treatment, and follow-up phases are outlined in Section 2. Eligibility for this study will be determined at a screening visit (Visit 1). Screening procedures will be performed on approximately Day –21 according to the Schedule of Activities. Patients will receive training on the routine blood glucose monitoring and paper diary completion required during the study. Patients should follow the investigator's instructions related to frequency of SMBG but should test their glucose a minimum of 3 times per week and

as specified for determination of 7-point glucose profiles (see Section 9.1.2.1). Eligible patients will return to the site for some baseline procedures during the lead-in phase (Visit 2) and again for randomization to treatment and to receive their first dose of study drug at Visit 3.

After randomization and the first dose (Visit 3), patients will return to the site for PK collection just prior to the second dose (Visit 4). Patients will also have a predose PK collection prior to Week 8 (Visit 10), Week 12 dose (Visit 11), and Week 26 (Visit 16) dose. There will be postdose PK collections after the second dose (PK-specific Visit 5), third dose (PK-specific Visit 7), fifth dose (PK-specific Visit 9, and 12-week dose (PK-specific Visit 12) (see Appendix 6, Pharmacokinetics Schedule of Events).

A safety follow-up visit will occur approximately 4 weeks following the last dose of the study drug. Patients randomized to LY3298176 who develop treatment-emergent anti-LY3298176 antibodies will be monitored after the last visit (see Section 9.8.1).

Throughout the study, patients treated with metformin will remain on the same dose they were receiving at Visit 1 unless changes need to be made for safety reasons. All patients will be encouraged to maintain their prestudy diet and exercise levels through the course of the study.

In the treatment phase, a double-dummy dose administration scheme will be employed to ensure patients and investigators (as well as sponsor study team and monitors) remain blind to the LY3298176, dulaglutide 1.5 mg, and placebo treatment assignments within each treatment group. At each dosing occasion, the study drug will be administered as 1 to 3 SC injections of LY3298176 or matched placebo and 1 SC injection of dulaglutide 1.5 mg or its placebo. Therefore, each patient will self-administer 2 to 4 injections per week.

5.2. Number of Participants

Approximately 540 participants will be screened to achieve 300 randomized and 270 evaluable participants for an estimated total of 45 evaluable participants per treatment group.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

Study GPGB is a Phase 2 study designed to examine the efficacy and safety of QW LY3298176 compared with dulaglutide 1.5 mg and placebo in patients with T2DM who have inadequate glycemic control with diet and exercise alone or on a stable dose of metformin.

Inclusion of an active comparator (dulaglutide 1.5 mg) in Study GPGB will allow for a direct comparison of the safety and efficacy of QW LY3298176 to an injectable GLP-1 RA (as well as to placebo) over a 6-month time period. In addition, effects of the medication on other parameters such as circulating biomarkers, other measures of glycemic control, lipids, and various safety-related assessments will also be determined. The planned duration of 6 months will allow for a more optimal comparison of the body weight effects of the 2 drugs, as the

putative mechanism of action of LY3298176 suggests that treatment with LY3298176 will result in continued weight loss over a 6-month period. The data from this trial will form the primary basis to assess dose/exposure–response of LY3298176 efficacy for selection of doses to be included in Phase 3 testing. In addition, safety and tolerability over a wide dose range of LY3298176 versus placebo and dulaglutide 1.5 mg will be assessed to enable robust benefit–risk characterizations in T2DM.

The placebo arm was included in order to determine whether any efficacy or safety effects of LY3298176 that are different in magnitude from those of dulaglutide 1.5 mg are in fact equivalent to or are also different from no treatment (i.e., placebo).

The current study will enroll patients with inadequate glycemic control based on HbA1c values ranging from 7.0% to 10.5%, inclusive. Similar ranges of screening HbA1c have been used in numerous studies of T2DM treatments.

Patients treated with diet and exercise alone, or in combination with stable metformin monotherapy (≥1000 mg/day), will be enrolled. Patients on a second oral antihyperglycemic medication (OAM) may be also be eligible if the second OAM was discontinued 3 months or more prior to Visit 1 (refer to Section 6.2, Exclusion Criterion 23). Stable metformin treatment for at least 3 months is required to minimize glucose variability prior to study entry.

5.5. Justification for Dose

LY3298176 doses of 1 mg, 5 mg, 10 mg (titrated), and 15 mg (titrated), administered subcutaneously QW, were selected based on the following:

- Safety and tolerability of LY3298176 in healthy subjects and T2DM patients in the Phase 1 study GPGA through doses of 10 mg.
- The margin of safety for the 15-mg maximum dose in this study has an exposure multiple of approximately 1 to the no-observed-adverse-effect level in rats and monkeys in the 6-month toxicology studies.
- The 1 mg was selected using PK/PD modeling and is predicted to achieve LY3298176 concentration levels that will demonstrate HbA1c lowering compared with placebo.
- The selected dose levels and dose range support a robust dose-exposure–response analysis of multiple safety and efficacy measures to support selection of dose(s) of LY3298176 with optimal benefit/risk ratio for further clinical development.

6. Study Population

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

6.1. Inclusion Criteria

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

Type of Patient and Disease Characteristics

[1] Have T2DM for at least 6 months before screening based on the disease diagnostic criteria (Appendix 5, World Health Organization [WHO] Classification for Diabetes).

[2] Have an HbA1c value at screening of ≥7.0% and ≤10.5% and treated with diet and exercise alone or a stable dose of metformin (either immediate release or extended release, ≥1000 mg/day and not more than the locally approved dose) for at least 3 months prior to screening/Visit 1. Note: patients from some countries may be required to be on metformin in order to enroll in the protocol.

Patient Characteristics

[3] Male or female patients 18 to 75 years of age, inclusive

[3a] Male patients:

Male patients should be willing to use reliable contraceptive methods throughout the study and for at least 3 months after last injection (see Appendix 7).

[3b] Female patients:

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

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

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

  OR

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

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

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

AND

- if sexually active, agree to use two forms of effective contraception, where at least one form is highly effective for the duration of the trial and for 30 days thereafter (see Appendix 7).
- not be breastfeeding.

[4] Have a BMI between 23 and 50 kg/m^2 (inclusive) at screening.

Informed Consent

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

- perform SMBG
- prepare (with assistance if necessary) study medication
- self-inject (with assistance if necessary) up to 4 injections each week
- complete study diary(ies), as required for this protocol
- are receptive to continuing their prestudy diet, activity levels, and follow simple dietary advice as appropriate

[6] Be willing to maintain metformin dose during the trial, if taking a stable dose of metformin at study entry. Patients experiencing hypoglycemia during the study may have their metformin dose reduced.

[7] Are reliable and willing to make themselves available for the duration of the study, and who will comply with the required study and dosing visits and abide by the Clinical Research Site policy and procedure and study restrictions.

[8] Are able and willing to give signed informed consent and have given written informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing their site.

6.2. Exclusion Criteria

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

Medical Conditions

[9] Have type 1 diabetes mellitus.

[10] Have uncontrolled diabetes defined as more than 2 episodes of ketoacidosis or hyperosmolar state requiring hospitalization in the 6 months prior to Visit 1.

[11] Have had more than 1 episode of severe hypoglycemia, as defined by the occurrence of neuroglycopenic symptoms requiring the assistance of another person for recovery, within 6 months prior to Visit 1, or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any patient that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded.

[12] Have a history of acute or chronic pancreatitis or elevation in serum lipase/amylase (greater than 2 times the upper limit of normal [ULN]) or fasting serum triglyceride level of >500 mg/dL at screening.

[13] Have a diagnosis of gastroparesis or history of bariatric surgery or a clinically significant gastric emptying abnormality, in the opinion of the investigator.

[14] Have active proliferative diabetic retinopathy.

[15] Have known liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or alanine aminotransferase (ALT) levels >2.5 times the ULN at Visit 1, as determined by the central laboratory at screening.

[16] Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.

[17] Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to patient safety. Subjects on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.

[18] Have a screening calcitonin ≥20 pg/mL as determined by the central laboratory at Visit 1.

[19] Have had any of the following within the last 6 months prior to screening: myocardial infarction (MI), unstable angina, coronary artery bypass graft, percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischemic attack (TIA), cerebrovascular accident or decompensated congestive heart failure, or currently have New York Health Association Class III or IV heart failure.

[20] Have an electrocardiogram (ECG) considered by the investigator indicative of active cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at screening. A QTc (Fridericia) interval greater than 450 ms in men and greater than 470 ms in women is specifically excluded.

[21] Known significant autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea.

[22] Have a personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, sibling, or children) before the age of 40 years, or a personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at screening.

[23] Have poorly controlled hypertension (i.e., mean seated systolic BP ≥160 mm Hg or mean seated diastolic BP ≥95 mm Hg) at screening, or a change in antihypertensive medications within 30 days of screening, renal artery stenosis, or evidence of labile BP including symptomatic postural hypotension.

[24] Random triglycerides >500 mg/dL (5.7 mmol/L). If the patient is on lipid-lowering therapies, doses must be stable for 30 days prior to screening.

[25] Have an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, as determined by the central laboratory at Visit 1, or a level of eGFR that would contraindicate the use of metformin per the label in the respective country. Patients on metformin must meet local label requirements.

[26] Have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).

[27] Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years prior to screening.

[28] Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies historically or at screening.

[29] Evidence of hepatitis B and/or positive hepatitis B surface antigen or evidence of hepatitis C.

[30] Have a history of a transplanted organ (corneal transplants [keratoplasty] allowed).

[31] Have evidence of a significant active, uncontrolled medical condition or a history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the screening investigator at screening.

[32] Have had a significant change in weight, defined as a gain or loss of at least 4 kg (9 lb) in the 3 months prior to screening.

[33] Have had a blood donation of 450 mL or more in the prior 3 months of screening or any blood donation within the prior month, or a blood transfusion or severe blood loss within the prior 3 months, or have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females), or any other condition known to interfere with HbA1c methodology.

[34] Have any other condition (including known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol.

Prior/Concomitant Therapy

[35] With the exception of stable doses of metformin, patients on another OAM (including, but not limited to, sulfonylureas, DPP-4i, sodium–glucose cotransport 2 inhibitors, alpha-glucosidase inhibitors, meglitinides) in addition to metformin therapy may be randomized if the additional OAM treatment was discontinued at least 3 months prior to screening.

[36] Have used insulin for diabetic control within the prior year. However, short-term use of insulin for acute conditions is allowed (≤14 days) in certain situations, such as during a hospitalization or perioperatively (see Section 7.7).

[37] Have had any exposure to dulaglutide, other GLP-1 analogs, or other related compounds within the prior 3 months or any history ever of allergies to these medications. Patients who previously took GLP-1 analogs or related compounds and who discontinued those medications >3 months prior to Visit 1 for intolerability or lack of efficacy should not be randomized.

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

[39] Are receiving chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have received such therapy within 4 weeks immediately prior to screening.

[40] Are currently taking a central nervous system stimulant (e.g., Ritalin-SR®) with the exception of caffeinated beverages at screening.

[41] Within 30 days of the initial dose of study drug, have received treatment with a drug that has not received regulatory approval for any indication. If the previous study drug has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[42] Have an average weekly alcohol intake that exceeds 21 units per week (males) and 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].

[43] Evidence of regular use of known drugs of abuse in the opinion of the investigator.

Prior/Concurrent Clinical Trial Experience

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

[45] Previous exposure or known allergies to LY3298176.

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

Other Exclusions

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

[48] Are Eli Lilly and Company employees or are employees of any third party involved in study who require exclusion of their employees.

[49] Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study or for 8 weeks following the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened only once at the discretion of the investigator. Before rescreening is performed, the patient must sign a new informed consent form (ICF) and receive a new identification number. If, in the opinion of the investigator, an ineligible lab test result is the result of an error or extenuating circumstance, then that parameter can be retested once (if feasible within the time constraints of the screening period) without the patient having to be rescreened. However, screen failures for HbA1c may not be retested or rescreened.

7. Treatments

7.1. Treatments Administered

This study will evaluate 4 parallel dose groups of LY3298176 at SC dose levels of 1 mg, 5 mg, 10 mg, and 15 mg QW for up to 26 weeks and the results will be compared with those for dulaglutide 1.5 mg and placebo. The study design is composed of 6 parallel treatment groups (approximately 45 patients per group). One treatment group will receive LY3298176 placebo and placebo for dulaglutide. One treatment group will receive active dulaglutide 1.5 mg and LY3298176 placebo. In the 4 remaining treatment groups, patients randomized to the 1-mg and 5-mg doses of LY3298176 will receive 1 injection of active LY3298176 and 1 injection of dulaglutide placebo. Patients randomized to the 10-mg dose of LY3298176 will receive 2 injections of active LY3298176 and 1 injection of dulaglutide placebo after the titration period, and patients randomized to the 15-mg dose of LY3298176 will receive 3 injections of active LY3298176 and 1 injection of dulaglutide placebo after the titration period (Table GPGB.2). All SC dose administrations of LY3298176 and dulaglutide should be in different quadrants of the abdomen.

This study involves dose titration in 5-mg increments for doses above 5 mg (Table GPGB.3). Although the investigator and patients will know dose group assignment (LY3298176 1 mg, 5 mg, 10 mg, or 15 mg) due to the study drug dose volume and titration scheme, they will not know whether they are actually receiving placebo, LY3298176, or dulaglutide. Thus, patients may be titrating placebo. In the description of the titration below, please note patients may receive LY3298176 or a complementary dose volume of placebo.

Patients assigned to the 1-mg and 5-mg treatment groups will receive that dose level throughout the study and will not have dose titration. All patients in the 10-mg and 15-mg groups will receive 5 mg as the first and second doses (Visits 3 and 4). Patients assigned to the 10-mg and 15-mg groups will receive 10 mg as the third dose (Visit 6), and the patients assigned 10 mg will continue that dose for the duration of the study. The patients assigned to the 15-mg dose will continue to receive 10 mg through dose 6 and will begin 15 mg as dose 7 and will continue that dose for the duration of the study. Patients in every dose group except the 1-mg and 5-mg groups who have reached their target dose and have received the target dose for 2 weeks but still are unable to tolerate that dose level (have vomiting or moderate to severe nausea), may have the dose reduced by 5 mg (10-mg patients would receive 5 mg and 15-mg patients would receive 10 mg) and may remain on the reduced dose for the remainder of the study. The dose the patient administers each week should be recorded on the case report form (CRF) during titration and throughout the study.

Table GPGB.2. Investigational Product Administration and Treatment Regimens

	Total Number of Injections			
Randomization	**LY3298176**	**PBO LY3298176**	**Dulaglutide 1.5 mg SDP**	**PBO Dulaglutide SDP**
LY 1 mg	1	0	0	1
LY 5 mg	1	0	0	1
LY 10 mg	2	0	0	1
LY 15 mg	3	0	0	1
Dulaglutide 1.5 mg	0	Up to 3	1	0
PBO	0	Up to 3	0	1

Abbreviations: LY = LY3298176; PBO= placebo; SDP = single-dose pen.

Table GPGB.3. Recommended Dose Titration Schedule[a]

Study Phase	**Randomization**	**Treatment Phase**							
Visit	3	4	6	N/S	8	N/S	N/S	N/S	10–16
Day	0	7	14	21	28	35	42	49	56–182
Week of Treatment[b]	0	1	2	3	4	5	6	7	8–26
Dose Number	1	2	3	4	5	6	7	8	9–27
LY 1-mg Group	1	1	1	1	1	1	1	1	1
LY 5-mg Group	5	5	5	5	5	5	5	5	5
LY 10-mg Group	5	5	10	10	10	10	10	10	10
LY 15-mg Group	5	5	10	10	10	10	15	15	15

Abbreviations: LY = LY3298176; N/S = none scheduled.

[a] This is the recommended titration time course. The dose utilized should be captured on the study drug CRF.

[b] There are no scheduled visits for Weeks 3, 5, 6,and 7 dosing. The investigator should give the patient the expected titration dose for Week 3 at the Week 2 visit (Visit 6) and for Weeks 5- 7 at the Week 4 visit (Visit 8). However, for any titration week, the investigator may have the patient come to the site for an unscheduled visit to dilute the vials and self-administer the study drug under study site supervision. If a patient does not tolerate a target dose level for 2 weeks due to vomiting or moderate to severe nausea and the investigator believes that the patient will not tolerate the dose with further exposure, the investigator may decrease the dose by 5 mg and the patient should remain at that dose level for the duration of the study (see Section 7.4 for additional discussion on dose modification).

Patients will be required to dilute study drug vials and administer injections of the study drug by syringe and to administer 1 single-dose pen (SDP) injection of dulaglutide or matching placebo themselves. Patients should inject study drug and SDP injections on the same date and at approximately the same time. The study site will send vials, diluent, syringes, needles, and SDPs home with patients. Patients will be diluting the vials and self-injecting at home during weeks without a clinical site visit and instructions will be provided. For all clinical site visits other than PK-specific visits, the patient should dilute the vials and administer the study drug (including dulaglutide SDP or matching placebo) at the clinical research site under the supervision of study personnel in order to reinforce patient understanding and confidence. The investigator or site staff may assist patients with vial reconstitution and study drug injection any other time they deem necessary.

Patients taking background metformin (either immediate release or extended release) are strongly encouraged to remain on the same type of metformin during the trial, if possible. Changing formulations or manufacturers of metformin during the study participation should be minimized. If a dose change (i.e., conversion of extended release to immediate release or vice versa) is required, the investigator should determine the most appropriate clinically equivalent metformin dose. The metformin dose should be at least 1000 mg/day and not more than the highest dose allowed per local label.

The patient receiving metformin should continue the baseline dose of metformin, unless the patient experiences documented hypoglycemia, in which case the dose may be reduced.

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

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

Patients will be instructed to contact the investigator as soon as possible if he/she has a complaint or problem with the study drug or drug delivery system so that the situation can be assessed.

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. LY3298176, dulaglutide 1.5 mg, and their matched placebos will be supplied by Lilly. CCI

[redacted] Patients will inject the dose volume appropriate for their

treatment group, including placebo patients within a group. Dulaglutide or matching placebo will be provided as SDPs. LY3298176 vials and dulaglutide 1.5 mg SDPs must always be stored in a secure location with access limited to designated study staff members.

Instructions for the reconstitution of study drug will be provided separately to each patient and the investigator. CCI [redacted] The reconstituted LY3298176 or placebo solution should be used immediately after reconstitution.

Study drug (including dulaglutide 1.5 mg) must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). Temperature logs must be maintained to verify correct storage conditions at the investigator site, throughout the study. Patients should be instructed to store the study drug in their refrigerator but are not required to maintain temperature logs.

Dulaglutide 1.5 mg or its placebo should be injected in a different quadrant of the abdomen from the concomitant LY3298176 or LY3298176 placebo injections.

7.1.2. Medical Devices

The manufactured medical devices provided for patient use in the study are dulaglutide and matching placebo SDPs, glucose meters, and lancet devices.

7.2. Method of Treatment Assignment

A unique 4-digit patient number will be assigned to each patient when the patient signs the ICF.

Patients will be assigned to dulaglutide 1.5 mg, placebo, or 1 of 4 LY3298176 dose levels. Patients who meet all criteria for enrollment will be randomized at Visit 3 and assigned to their respective treatment arms via IWRS using the following stratification variables: baseline HbA1c (<8.5%, ≥8.5%), metformin use (Yes, No), and BMI (<30, ≥30). There will be equal randomization to the treatment arms (1:1:1:1:1:1). However, LY3298176 placebo patients will be randomized such that a portion will be randomized to each cohort in order to receive the same dose volume as that cohort in order to maintain the study blind. For the active dulaglutide 1.5 mg group, LY3298176 placebo patients should also be distributed through the treatment groups in order to maintain the blind.

The randomization scheme will be performed using IWRS that will ensure balance between treatment arms.

7.2.1. Selection and Timing of Doses

Assignment to 1 of the 4 LY3298176 doses, dulaglutide 1.5 mg, or placebo will occur at randomization. There are no restrictions on the time of day each weekly dose is given, but it is advisable to administer SC injections on the same day and same time each week. The actual date and time of all dose administrations will be recorded in the subject's CRF. If a dose of study drug, including dulaglutide or its placebo, is missed, the patient should take it as soon as possible unless it is within 72 hours of the next dose, in which case that dose should be skipped and the next dose taken at the appropriate time.

7.2.2. Specific Restrictions/Requirements

Prior to beginning the study, patients will complete informed consent and baseline tests.

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

Patients will report to the clinical research site for safety assessments and will remain in the clinic until all procedures for that visit are complete and the investigator has deemed it safe to release the patient from the clinic. There will be no inpatient stays. In addition, patients will report to the clinical research site for PK-specific visits (Visits 5, 7, 9, and 12).

Meals/Diet – Patients shall fast for at least 8 hours overnight prior to each outpatient visit where fasting samples are drawn or weight measurements taken.

Alcohol – Alcohol will not be permitted 8 hours prior to the dosing day, until the patient has been discharged from the clinical research site.

Exercise – 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 recumbent or sitting.

Blood donation – Study participants should be instructed not to donate blood or blood products during the study or for 8 weeks following the study.

Contraception – Male patients or their female partners of child-bearing potential must use reliable contraception during intercourse throughout the treatment period and for 3 months after the last dose of study drug (as the risk of LY3298176 to the unborn fetus is unknown). Female patients of childbearing potential, if sexually active, should use two forms of effective contraception, where at least one form is highly effective for the duration of the trial and for 30 days thereafter. Please see Appendix 7 for further details regarding contraception.

7.3. Blinding

This is a double-blind study. Although the patient and the investigator will know which dose group (1 mg, 5 mg, 10 mg, or 15 mg LY3298176) the patient is assigned to, they will not know whether the patient is receiving LY3298176, dulaglutide 1.5 mg, or placebo.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency codes, generated by a computer drug-labeling system, will be available to the investigator. These codes, which reveal the patient's treatment group when opened, may be opened during the study ONLY if the patient's well-being requires knowledge of the patient's treatment assignment.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a decision. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

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

7.4. Dosage Modification

Adjustment in study drug dose level will be allowed for patients assigned to the LY3298176 10-mg and 15-mg groups. If a patient in a LY3298176 treatment group of 10 mg or 15 mg does not tolerate the target titrated dose for 2 weeks once the assigned dose is reached, in other words if the patient is still vomiting or has moderate to severe nausea and the investigator does not believe that the patient will tolerate the dose with further exposure, then the investigator may drop the dose back to the next lower dose. Thus, if a patient has reached the target dose of 10 mg and has vomiting or moderate to severe nausea for 2 weeks, then the patient's dose level may be dropped back to 5 mg and the patient may remain on 5 mg for the duration of the study. Similarly, the 15-mg dose would be dropped to 10 mg. The actual dose received should be recorded on the CRF each week. Dosing of concomitant metformin is discussed in Section 7.7.

7.5. Preparation/Handling/Storage/Accountability

The study site must store the study drug in a locked and secure environment. The study drug must be refrigerated (not frozen) at 2°C to 8°C. Dry ice should not be used for cooling. Patients will be provided with double-blinded vials containing lyophilized LY3298176 or LY3298176 placebo and Sterile Water for Injection (along with syringes) and SDPs containing dulaglutide or dulaglutide placebo, at clinic visits according to the Study Schedule. The patients will also receive insulated bags with cooling gel packs for use in transporting the study drug from the site to the home. Study drug in each participating country will be labeled according to the country's regulatory requirements.

Commercial metformin may be made available during the treatment period to patients who entered the trial on this agent. Appropriate use and storage information will be available by referring to the package insert.

7.6. Treatment Compliance

During the study, patients will be asked to return their unused study drug materials and completed diaries to the site so that their compliance may be assessed.

Patients who are significantly noncompliant will be permanently discontinued from study medication. A patient will be considered significantly noncompliant if he/she intentionally misses 4 or more doses of study medication. Similarly, a patient will be considered significantly noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

7.7. Concomitant Therapy

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

The only concomitant antihyperglycemic medication permitted during this study is metformin, unless glycemic criteria for rescue therapy are met (see Section 7.8.1). Metformin treatment must be stable for at least 3 months prior to screening at a daily dose of ≥1000 mg/day. Patients who enter the study on diet and exercise alone will not be allowed to initiate metformin therapy after study entry unless criteria for rescue therapy are met.

Patients who are being treated with metformin upon entering this study should remain on the same (or equivalent if switching to sustained release) metformin dose throughout the course of the study unless a change in dose is required to protect patient safety.

If a patient switches from the immediate-release formulation of metformin to the sustained-release formulation, the change will be on a milligram-per-milligram basis.

In certain situations (such as during a hospitalization or perioperatively), it may be necessary for a patient to be treated with insulin(s). Treatment with insulin will be allowed for up to 14 consecutive days prior to or during the trial. If a patient requires treatment with insulin for more than 14 consecutive days, that patient will be considered a "rescue" patient and may remain in the study but will not receive additional study drug.

Doses of antihypertensive and lipid-lowering therapies must be stable for 30 days prior to screening. Doses of antihypertensive and lipid-lowering agents should not be changed during this study unless necessary to protect patient safety on an emergency basis (e.g., hypertensive crisis).

Doses of other prescription medications (e.g., thyroxine, estrogen or progesterone replacement, or selective estrogen receptor modulators) for treatment of concurrent medical conditions should remain constant during the study whenever possible.

If the need for additional concomitant medication arises, the patient may be continued in the study on study medication if, in the investigator's opinion, the addition of the new medication does not pose a safety risk. If an additional concomitant medication is started, the sponsor should be informed as soon as possible. Nausea and/or vomiting during this study may be treated with antiemetics that do not increase QTc (e.g., cyclizine or meclizine) but should not be used prophylactically. Nonsteroidal anti-inflammatory medications (including ibuprofen, aspirin), acetaminophen, cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis without notifying the sponsor and are not restricted by the stable dosing requirements listed above. Any additional

medication used during the course of the study (including those not requiring sponsor notifications) must be documented on the appropriate electronic case report form (eCRF).

Specifically excluded concomitant medications include the following:

- Chronic use of drugs that directly reduce GI motility including but not limited to anticholinergics, antiemetics, and opiates (e.g., metoclopramide, phenergan, dicyclomine, and morphine)
- Chronic use of medications that directly promote motility (e.g., bethanechol and cisapride)
- Prescription or over-the-counter medications to promote weight loss
- Systemic glucocorticoid therapy of greater than 14 consecutive days' duration (with the exception of topical, intranasal, intraocular, intra-articular, and inhaled preparations)
- Central nervous system stimulants (e.g., Ritalin-SR)
- Any drug, other than those provided in this study, that has not received regulatory approval.

7.8. Treatment after the End of the Study

7.8.1. Special Treatment Considerations (Rescue Therapy)

Investigators will be trained on how to apply decision criteria for the timing and method of intervention in patients who do not reach glycemic targets during the 26-week treatment period. An additional therapeutic intervention should be considered in patients who meet the following criteria:

- The patients are fully compliant with assigned therapeutic regimen.

  AND

- In the absence of any acute condition that raises blood glucose either of the following occurs:
  - During the first 6 weeks post-randomization: An average fasting glucose level above 270 mg/dL (15.0 mmol/L) occurs over at least a 2-week period (at least 4 values/week must be available).

    OR

  - Any time after the first 6 weeks to 26 weeks post-randomization: An average fasting glucose level above 240 mg/dL (13.3 mmol/L) occurs over at least a 2-week period (at least 4 values/week must be available).

If these conditions are met, then patients may begin treatment with another antihyperglycemic agent as determined by their physician. If treatment with another antihyperglycemic agent is instituted, then study drug should be permanently discontinued. Patients may remain in the study for safety follow-up, but the date at which they begin rescue therapy will be the last date for collection of efficacy measures.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

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

- Abnormal liver tests or when a patient meets one of the following conditions:
  - ALT or aspartate aminotransferase (AST) >8× ULN
  - ALT or AST >5× ULN for more than 2 weeks
  - ALT or AST >3× ULN and total bilirubin level >2× ULN or prothrombin time >1.5× ULN
  - 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 total bilirubin >2x ULN
  - ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Investigator Decision
  - the investigator decides that the patient should be discontinued from the study medication
- Any medication for weight loss is given for more than 1 week
- Adverse Event
- When any one of the following events occur, Lilly or its designee is to be alerted immediately:
  - Pancreatitis or pancreatic cancer (refer to Section 9.2.1.2.5 for details)
  - Estimated glomerular filtration <30 mL/min
  - Any severe injection site reaction or 2 or more moderate injection site reactions occurring a week or more apart
  - Any significant study drug-related hypersensitivity reaction
  - Any nonfatal major cardiovascular (CV) events (refer to Section 9.2.1.2.6 for details)
  - Any other treatment-emergent adverse event (TEAE), SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken.
- If the patient, for any reason (including protocol-mandated institution of rescue therapy; see Section 7.8.1), requires treatment for greater than 1 week with another therapeutic agent that has been demonstrated to be effective for treatment of diabetes. Also, a change in dose of metformin is not allowed (except for incidences of hypoglycemia; see Section 7.1). However, a change to an equivalent dose strength from immediate-release to extended-release (or vice versa) formulation is allowed.

- If the patient intentionally misses 4 or more doses (consecutive or not) of study medication or intentionally or repeatedly takes more than the prescribed dose of study medication (see Section 9.3).
- If the patient develops any exclusion criteria, such as pregnancy or nursing.

If study drug is permanently discontinued, the patient should remain in the study if possible.

8.1.2. Temporary Discontinuation from Study Treatment

After randomization, the investigator may temporarily discontinue study drug, for example, due to an AE (e.g., nausea and vomiting), a clinically significant laboratory value, or a natural disaster. If study drug discontinuation is due to an AE, the event is to be followed and documented. Every effort should be made by the investigator to maintain patients in the study and to restart study drug promptly after any temporary discontinuation, as soon as it is safe to do so. The dates of study drug discontinuation and restart will be documented. Patient noncompliance should not be recorded as temporary discontinuation of study drug on the eCRF.

In the event that the patient requires the discontinuation of the study drug, he/she may continue participation in the study, attend all visits, and undergo all protocol procedures, and patient data from the time of discontinuation of study drug will not be included in the primary analyses.

After study drug discontinuation, patients may commence any standard diabetes therapy in line with local or regional standards of care, and as considered appropriate by the investigator.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, notified discussion must occur between the sponsor CRP/ clinical research scientist (CRS) and the investigator to determine if the patient may continue in the study. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without treatment with the investigational product.

8.2. Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include the following:

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Sponsor decision
    - Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

- Investigator decision
    - The investigator decides that the patient should be discontinued from the study
- Subject decision
    - The patient requests to be withdrawn from the study.

Patients who discontinue the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he/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.

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

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

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

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

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy measure is HbA1c, as determined by the central laboratory. Blood samples for HbA1c measurements will be collected at specific clinic visits as summarized in Section 2.

9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be collected at the times shown in Section 2.

- Body weight: Patients will be weighed on an electronic scale in a light hospital gown at approximately the same time in the morning after an overnight fast and evacuation of any bowel and bladder contents (See Appendix 8). The scale's performance will be monitored at least monthly using standard weights, and records of these assessments will be kept in the study binder.
- HbA1c
- FBG
- Serum lipids, circulating biomarkers (including fasting insulin, glucagon, lipids, free fatty acids, glycerol, β-hydroxy butyrate, fibroblast growth factor-21 [FGF-21], and adiponectin).
- Waist circumference: Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. The patient should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing. The patient should be relaxed, and the measurements should be taken at the end of a normal expiration. The measurement should be repeated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

9.1.2.1. Exploratory Efficacy Assessments

- Seven-point SMBG profiles consisting of measurements obtained before each meal, approximately 2 hours after each meal, and at bedtime on a day during the week before the scheduled clinic visit. Patients will record their SMBG levels in their diaries, according to instructions. The complete 7-point profile must be collected on a single day.

If a patient does not complete the entire profile on a single day, all 7 points must be collected on a subsequent day.

9.1.3. Appropriateness of Assessments

All efficacy measures are widely used and generally recognized as reliable, accurate, and relevant with respect to the management of T2DM.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

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

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

The investigator answers yes/no when making this assessment.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

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

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

If the AE or SAE is believed to have been caused by a device issue, in addition to recording the relatedness in the CRF, a product complaint must also be reported.

9.2.1. Serious Adverse Events

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

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (i.e., immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason: important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.
- When a condition related to the investigational device necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Although all AEs occurring after signing the ICF are recorded in the CRF, SAE reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.1.2. Adverse Events of Special Interest

The following Adverse Events of Special Interest (AESIs) of varying clinical significance will be used to determine the tolerability of LY3298176 over the range of doses selected for this clinical trial. All AESIs should be captured and reported to Lilly on the AE eCRF or on a specific eCRF, if applicable (see below). Any AESI that meets the definition of an SAE (see Section 9.2.1) must be reported as an SAE.

When any one of the following events occur, Lilly or its designee must be alerted immediately, whether it is assessed as an SAE or not:

- Confirmed pancreatitis or pancreatic cancer
- Any severe injection site reaction or 2 or more moderate injection site reactions occurring a week or more apart
- Any study drug-related hypersensitivity reaction
- Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken.

9.2.1.2.1. Injection Site Reactions

All injection site reactions and information regarding their time of day, time relative to injection, size, amount of erythema, induration, and pruritus, as well as severity, will be recorded on specific CRFs. In addition, if the reaction is clinically significant, the site should attempt to contact the sponsor for potential follow-up procedures. Injection site reactions do not need to be recorded as AEs as well unless they meet SAE criteria.

9.2.1.2.2. Hypersensitivity Reactions

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

9.2.1.2.3. Hypoglycemia

Hypoglycemia episodes will be recorded on a specific eCRF. Information regarding severity, time of day, and investigator's opinion of relatedness to study drug and procedure will be

recorded. Hypoglycemia episodes should not be recorded as AEs unless the event meets serious criteria. Hypoglycemia will be classified as follows (American Diabetes Association 2005):

- Documented Symptomatic Hypoglycemia: Any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia and has a plasma glucose level of ≤3.9 mmol/L (≤70 mg/dL)
- Asymptomatic Hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia, but with ≤3.9 mmol/L (≤70 mg/dL) plasma glucose.
- Severe Hypoglycemia: An episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Nocturnal Hypoglycemia: Any hypoglycemic event that occurs between bedtime and waking
- Probable Symptomatic Hypoglycemia: An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤3.9 mmol/L [≤70 mg/dL]).

9.2.1.2.4. Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea events will be recorded on a specific eCRF. They should not be recorded as AEs unless the event meets an SAE criterion. For each event, assessment of severity, duration, and Investigator's opinion of relatedness to study drug and protocol procedure will be captured.

9.2.1.2.5. Acute Pancreatitis

Acute pancreatitis is defined as an AE of interest for this study. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems(Banks et al. 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

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

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with investigational product,

but will continue in the study on another glucose-lowering regimen (see Section 7.8.1 for details on rescue intervention). The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

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

In addition to the diagnostic assessment in patients who develop symptoms of acute pancreatitis, each patient will have measurements of pancreatic amylase and lipase at screening, baseline, and at each non-PK-specific visit to assess any potential effects of LY3298176 on the exocrine pancreas (refer to Section 2, Schedule of Activities). Further diagnostic assessment per Lilly algorithm for assessment of asymptomatic pancreatic hyperenzymemia will be required whenever lipase and/or pancreatic amylase are ≥3× ULN at any time during the study. If this situation occurs at Visit 801 (Week 30), the patient will be required to undergo this additional workup, and the data will be collected in the clinical trial database.

All suspected cases of acute or chronic pancreatitis, as well as cases of confirmed lipase or pancreatic amylase values ≥3× ULN, will be adjudicated by an independent committee of expert physicians. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis, those with severe or serious abdominal pain, and those that undergo additional assessments due to confirmed hyperenzymemia will be entered into a specifically designed eCRF page by study site or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

9.2.1.2.6. Major Adverse Cardiovascular Events

Deaths (CV and non-CV), nonfatal MIs, supraventricular arrhythmias, and nonfatal strokes that occur during the treatment period or follow-up period will be adjudicated by an independent adjudication committee in compliance with a study-specific adjudication charter. Investigative sites will also be asked to submit any cases of TIA or hospitalization for unstable angina for adjudication as well to ensure that all true stroke and MI events are captured. Hospitalizations for heart failure and coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention) will also be submitted for adjudication.

Cardiovascular event definitions will be based on the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials (Hicks et al. 2015) and the ESC/ACCF/AHA/WHF Expert Consensus Document Third Universal Definition of Myocardial Infarction (Thygesen et al. 2012). An adjudication committee will enter the results of adjudication in the corresponding eCRF page.

9.2.1.2.7. Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Individuals with personal or family history of certain thyroid or nonthyroid endocrine abnormalities or certain preexisting laboratory and genetic characteristics will be excluded from the study (see Section 6.2). The assessment of thyroid safety during the trial will include reporting of thyroid TEAEs and measurements of calcitonin according to Section 2 at screening, baseline, and Visits 11 and 16 (Months 3 and 6) or ET visit. The purpose of calcitonin measurements is to assess the potential of LY3298176 to affect thyroid C-cell function, which includes development of C-cell hyperplasia and neoplasms.

Patients who develop serum calcitonin increases ≥50% of the mean of the baseline and screening values AND an absolute value ≥20 pg/mL and <35 pg/mL at Visits 11 and 16 (Months 3 and 6) will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be encouraged to undergo additional endocrine assessment and longer term follow-up by an endocrinologist to exclude a serious adverse effect on the gland.

Patients with an increase in serum calcitonin ≥50% of the mean of the baseline and screening values AND an absolute value ≥35 pg/mL at Visits 9 and 12 (Months 3 and 6) will be recommended to immediately undergo additional endocrine assessments and longer term follow-up by an endocrinologist.

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

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

For patients with suspected or confirmed overdose with LY3298176 or dulaglutide, there is no specific antidote. The patient should be watched for GI symptoms and hypoglycemia. Treatment is supportive, depending on the patient's symptoms.

Refer to the IB for LY3298176 and to the Product Label for dulaglutide.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, 12-lead ECGs should be collected according to Section 2. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

Electrocardiograms should be recorded in triplicate according to study-specific recommendations included in the Manual of Operations for the study, using standardized equipment provided by the sponsor.

Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the subject meets entry criteria and for immediate subject management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE. The investigator (or qualified designee) is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of evaluation.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the patient will be assessed by the investigator for symptoms (e.g., palpitations, near syncope, and syncope) and 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/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

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

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

In addition, for each patient, a single ECG will be recorded at screening and if the patient discontinues from the study prematurely (Section 2) for immediate patient management. These ECGs will be stored at the investigation site.

Any treatment-emergent clinically significant ECG finding resulting in a diagnosis should be reported as an AE in the eCRF.

9.4.2. Vital Signs

Sitting BP and PR will be measured using standardized equipment provided by the sponsor according to Section 2. Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required (see Section 2). The participant should be required to sit quietly for 5 minutes before vital sign measurements are taken. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of BP measurements. The arm used for the BP measurement should be supported at heart level. At Visit 1 (screening), to determine which arm should be used to collect BP and PR throughout the study, BP and PR will be measured once in each arm, and the arm that had the higher systolic BP should be used to collect all 3 measurements of both BP and PR at all study visits. For each parameter (PR, systolic BP, and diastolic BP), 3 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart, and each measurement of sitting PR and BP will be recorded in the eCRF. Any AE related to changes in BP and PR should be reported.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to Section 2.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE.

9.4.4. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. In addition, the study team will review safety reports in a blinded fashion according to the schedule provided in the Trial-Level Safety Review plan. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly CRP/CRS will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

In addition, specific safety measures are included in the protocol to ensure appropriate monitoring of pancreatic, thyroid, and liver safety. Laboratory findings that trigger pancreatic and thyroid safety monitoring per Lilly standards are provided in Sections 9.2.1.2.5 and 9.2.1.2.7, respectively. Details of liver safety monitoring are provided in Section 8.1.1. If a study patient experiences elevated ALT ≥3× ULN or elevated total bilirubin ≥2× ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Appendix 4).

9.5. Pharmacokinetics

Blood samples for PK analyses will be collected from all randomized patients in accordance with Section 2 and Appendix 6 and at early termination. However, only samples from patients assigned to treatment with LY3298176 will be analyzed for drug concentration.

- Predose PK samples will be collected only at Weeks 1, 8, 12, and 26.
- Following dose at Weeks 1, 2, 4, and 12, a postdose PK sample will be collected. Patients may have their PK sample collected any time within the pre-specified collection window at their convenience.
    - At Weeks 1 and 2 all patients will have a PK sample collected within a time window of 1 to 48 hours (within 2 days of dose).
    - At Week 4 all patients will have a PK sample collected within a time window of 48 to 72 hours (2 to 3 days postdose).
    - At Week 12 all patients will have a PK sample collected within a time window of 96 to 168 hours (i.e., any time between 4 days after study drug administration up to just prior to the next dose of study drug administration).
- The patient will be required to come to the site for additional PK-specific visits dependent on the time window of PK sampling.

Date and time of each sample and the most recent LY3298176 dose prior to PK blood draw must be recorded.

Drug concentration information that would unblind the study will not be reported to study sites or blinded personnel while the study is blinded.

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

9.6. Pharmacodynamics

Samples to evaluate the PD properties of LY3298176 are included in the efficacy measures and not applicable here.

9.7. Pharmacogenetics

9.7.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analyses as specified in Section 2 where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3298176 and dulaglutide, 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 investigator site personnel.

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

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

9.8. Biomarkers

Collection of samples for other biomarker research is part of this study. Blood samples will be collected as specified in Section 2.

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 measurements of biomolecules, including DNA, RNA, proteins, lipids, and other cellular elements.

Serum and plasma ethylenediaminetetraacetic acid (EDTA) and P800 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 diabetes, mechanism of action of LY3298176, and/or research method or in validating diagnostic tools or assay(s) related to diabetes.

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

9.8.1. Samples for Immunogenicity Research

Samples from patients in each treatment arm will be tested for the development of treatment-emergent LY3298176 antidrug antibodies (ADA), defined as 4-fold increase in titer from baseline. A blood sample will be collected at specific study visits according to the Schedule of Activities (Section 2).

Treatment-emergent positive LY3298176 ADA samples will be evaluated for their ability to neutralize the activity of assigned treatment (LY3298176-neutralizing antibodies). Positive

LY3298176 ADA samples may also be tested for cross-reactivity with native GLP-1 and GIP, and if positive, then for neutralizing antibodies against native GLP-1 and GIP.

All patients will have an ADA sample measured at the follow-up visit (Visit 801) approximately 1 month after the last dose of LY3298176. A risk-based approach will be used to monitor patients who develop treatment-emergent antidrug antibodies (TE-ADA) (defined as >4-fold titer increase over baseline) after treatment with LY3298176. Clinically significant TE-ADA will be defined as any TE-ADA at the follow-up visit (Visit 801) with:

- A high (≥1280) or increasing titer
- An association of TE-ADA with a moderate to severe injection site reaction or infusion-related reaction
- Cross-reactive and neutralizing binding of an ADA with endogenous GLP-1 or GIP.

Patients who have clinically significant TE-ADA will be followed with ADA testing every 3 months for approximately 1 year or until the ADA titers have returned to baseline ADA titer (defined as ADA titer within 2-fold of baseline).

Patients followed 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 is 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-ADA 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 for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by Lilly. The duration allows the sponsor to respond to future regulatory requests related to LY3298176.

9.9. Health Economics

Health-related quality of life will be assessed using the Ability to Perform Physical Activities of Daily Living (APPADL) and Impact of Weight on Self-Perception (IW-SP) questionnaires, which are self-rated questionnaires that provide standardized measures of patients' perceived current health status. Patients will complete the questionnaires at the specific clinic visits summarized in Section 2. At these visits, the questionnaires should be completed before any other study procedures (if the patient is not adversely affected by their fasted state) or completed after the patient has sufficiently recovered from the preceding visit procedures.

- The APPADL questionnaire has demonstrated test–retest reliability, validity, and responsiveness to weight loss in individuals with T2DM, thereby making it useful in evaluating weight loss interventions (Hayes et al. 2011, 2012). The APPADL contains 7 items that assess how difficult it is for patients to engage in certain activities considered to be integral to normal daily life, such as walking, standing, and climbing stairs. Items are scored on a 5-point numeric rating scale where 5 = "not at all difficult" and 1 = "unable to do." A raw overall score is calculated by summing the scores of the 7 items. A transformed overall score is obtained by linearly transforming the raw overall

score to a 0 to 100 scale. Higher raw overall scores and lower transformed overall scores indicate better ability to perform activities of daily living.

- The IW-SP questionnaire contains 3 items that assess how often the patient's body weight affects how happy they are with their appearance and how often they feel self-conscious when out in public (Hayes and DeLozier 2015). Items are scored on a 5-point numeric rating scale where 5 = never and 1 = always. A raw overall score is calculated by summing the scores of the 3 items. A transformed total score is obtained by linearly transforming the raw total score to a 0 to 100 scale. Higher raw overall score and lower transformed overall score indicate better self-perception.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 300 patients will be randomized to placebo, dulaglutide, or 1 of 4 LY3298176 treatment arms assuming a 10% dropout rate resulting in approximately 45 completers per arm.

The Bayesian approach using a dose–response model with respect to an HbA1c change from baseline to 26 weeks will provide approximately 98% probability to show with 90% confidence that at least 1 LY3298176 dose has superior glycemic control over placebo with a superiority bound of –0.8%. The sample size also provides more than 95% probability to show with 80% confidence that at least 1 LY3298176 dose has noninferior glycemic control compared with dulaglutide from baseline to 26 weeks with a 0.3% noninferiority bound. This assumes a change from baseline glycemic effect profile shown in Table GPGB.4, and a standard deviation (SD) of 1.0%.

In addition, this sample size also provides approximately 89% probability to show with 60% confidence that at least 1 LY3298176 dose has superior weight loss compared with dulaglutide from baseline to 26 weeks with a superiority bound of –2 kg. This assumes a change from baseline weight loss profile shown in Table GPGB.4, and a SD of 6 kg.

Table GPGB.4. Dose–Response Assumption Used in Sample Size Determination

	Placebo	LY 1 mg	LY 5 mg	LY 10 mg	LY 15 mg	Dulaglutide
CFBL HbA1c (%)	0%	–0.74%	–1.17%	–1.29%	–1.44%	–1.28%
CFBL body weight (kg)	0	–2.0	–3.0	–5.0	–6.0	–2.5

Abbreviations: CFBL = change from baseline; kg = kilogram; LY = LY3298176.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined in Table GPGB.5.

Table GPGB.5. Definitions of Populations to Be Analyzed in Study GPGB

Population	Description
Enrolled	All participants who sign informed consent.
ITT (intention-to-treat)	All randomized patients.
mITT (modified ITT)	All randomized patients with at least 1 post-baseline measurement according to the treatment the patients were assigned.
PP (per protocol)	All randomized patients who were compliant with study drug and completed the protocol.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be included in the treatment group to which they were randomized. In the event of a treatment error, participants will be analyzed according to the treatment they actually received.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

The intention-to-treat (ITT) population is defined as all randomized patients. Statistical analyses (including the primary analysis) will be conducted on the modified ITT (mITT) population. The mITT population is defined as all randomized patients with at least 1 post-baseline measurement according to the treatment the patients were assigned. The per-protocol (PP) population is defined as all randomized patients who were compliant with study drug and completed the protocol and is a subset of the mITT population. The safety population is defined as all randomized patients who have received at least 1 dose of study drug. Safety analyses will be performed on the safety population.

Some efficacy measures will also be analyzed on the PP dataset. The PP analysis will include patients who meet the following additional criteria:

- Have been appropriately randomized
- Have not discontinued from the study for any of the early discontinuation criteria
- Have not missed 4 or more doses during the treatment period
- Have not been rescued or taken a concomitant antihyperglycemic medication besides metformin for more than 7 cumulative days during the treatment period

Patients who have had rescue therapy will be included in the mITT population, but not the PP population. The efficacy measures will be censored at the time of rescue for analyses using mITT population.

No adjustments for multiplicity will be performed.

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

The baseline value used for the analyses will be the last scheduled baseline value obtained for each patient prior to randomization.

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

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

All patients who discontinue the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment. The percentage of patients discontinuing from each treatment will be compared using the Fisher's exact test.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized by treatment group. Categorical variables will be summarized by frequencies and percentages. For categorical variables, comparisons between treatment groups will be assessed using a Pearson Chi-Square test. Continuous variables will be summarized by means and SDs. For continuous variables, comparisons between the treatment groups will be performed using a 1-way analysis of variance with treatment as the fixed effect.

10.3.2.3. Concomitant Therapy

Listings and summary of concomitant therapies will be provided by treatment group.

10.3.2.4. Treatment Compliance

Treatment compliance will be listed using all randomized patients and summarized using the mITT population. For a given patient, overall compliance for treatment period is defined as not missing 2 or more consecutive doses of the assigned treatment or missing 4 or more at any point in the study. Patients who miss 4 or more doses at any point during the study will be considered significantly noncompliant and will be permanently discontinued from study medication. These patients will not be included in the PP analysis.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy outcome is HbA1c changes from baseline to the 26-week endpoints.

The primary analyses will be performed on the mITT analysis set using a Bayesian dose–response model. The model will include LY3298176 doses and placebo.

The Hierarchical Logistic Model will be used as the dose–response model for HbA1c change from baseline to the 26-week endpoint. Priors for modeled dose–response will follow a normal distribution. Priors for variance will follow inverse gamma distributions. The placebo group will be modeled with the LY3298176 doses, whereas dulaglutide will be modeled separately. Details of these prior distributions will be provided in the SAP.

The primary analysis will consist of this dose–response model and examining the probability each LY3298176 dose has demonstrated superiority relative to placebo using a superiority margin of –0.8%. Analyses will also consist of the 90% one-sided credible interval for the difference in mean response for each LY3298176 dose versus placebo at 26 weeks. No adjustment for multiplicity will be performed. Probabilities based on posterior distributions of

each dose group's mean response exceeding the placebo group's mean response by clinical thresholds of interest (e.g., by –0.6%) will also be provided.

The longitudinal model will be the linear regression longitudinal model. The observed 26-week endpoint will be modeled using a linear regression model from previous time points. Priors for terms in the mean dose–response function will follow a normal distribution. Priors for variance will follow an inverse gamma distribution. All the doses will be modeled separately using this longitudinal model. Details of these prior distributions will be provided in the SAP.

Descriptive statistics by treatment for HbA1c and HbA1c change from baseline at the 26-week endpoint will be presented using all observed data with no imputations and no elimination of patients with protocol violations. The descriptive statistics will be presented by visit and will include sample size, mean, SD, median, minimum, and maximum.

10.3.3.2. Supporting Analyses of Primary Outcome

Supportive analyses of the primary efficacy outcome for the mITT dataset will be MMRM using restricted maximum likelihood with metformin use (yes/no), treatment, visit, and treatment-by-visit interaction as fixed effects, HbA1c baseline as a covariate, and patient as a random effect. The dependent variable will be the post-baseline change from baseline values. The unstructured covariance matrix will be selected initially. If the unstructured covariance structure leads to nonconvergence, Akaike's information criterion will be used to select the best covariance structure. The treatment p-value will be used as evidence of difference between active drug and placebo, whereas the comparison of least-square (LS) means versus placebo (unadjusted for multiple comparisons) will provide magnitude and significance of this difference.

A further robustness check will be made using the PP dataset and applying the same MMRM procedure as described in the above paragraph. Any differences in conclusions will be further investigated by examining differences in the mITT and the PP datasets.

The MMRM analysis will be examined for robustness by checking for treatment-by-strata and treatment-by-baseline HbA1c interactions in the MMRM model using the mITT dataset. If any of these checks give positive indications, supportive analyses accounting for the identified issues will be compared along with the primary analysis.

An analysis of covariance (ANCOVA) model will be used for the primary efficacy outcome for the mITT dataset with fixed effects of metformin use, treatment, and baseline HbA1c as covariates. Missing endpoints will be imputed using last observation carried forward (LOCF). For this model, the endpoint is defined as latest HbA1c measurement obtained for a patient in the time interval between randomization and 26 weeks after randomization.

10.3.3.3. Secondary Analyses

10.3.3.3.1. Secondary Analysis on Primary Efficacy Endpoint

The secondary analysis of the primary endpoint will consist of the dose–response model, which will also be used to examine the probability that any LY3298176 dose has exhibited noninferiority in comparison to the dulaglutide dose using a noninferiority margin of 0.3%. This analysis will be used for internal business decisions.

10.3.3.3.2. Analyses on Secondary Efficacy Endpoints

In addition to the primary efficacy analysis of HbA1c, the following secondary efficacy outcomes will be analyzed on the mITT population:

- Body weight change from baseline to 12 and 26 weeks
- Percentage of patient with 5% or greater body weight loss at 26 weeks
- Change from baseline of HbA1c at 12 weeks
- Percentage of patients with 10% or greater body weight loss at 26 weeks
- Percentage of patients reaching the HbA1c target of ≤6.5% and of ≤7.0%
- Change from baseline of FBG at 12 and 26 weeks
- Change from baseline of waist circumference at 12 and 26 weeks

The mean weight change at 12 and 26 weeks as well as the 12-week HbA1c endpoint will be analyzed using a similar dose–response model as the primary endpoint. HbA1c will continue to be analyzed using a superiority bound of –0.8% to placebo as well as a noninferiority bound of 0.3% relative to dulaglutide. The weight change from baseline at both 12 and 26 weeks will use a superiority bound of 2.0 kg. In addition, supportive analyses of the mean weight change for the mITT dataset will be the MMRM similar to that of the primary efficacy outcome.

The percentage of patients with ≥5% (and with ≥10%) body weight loss, the percentage of patients reaching the HbA1c target of ≤6.5% (and of ≤7.0%) at 26 weeks, and the proportion of patients requiring rescue therapy will be analyzed using a logistic regression analysis with fixed effects of treatment and stratification factors, and baseline as a covariate.

The change from baseline of FBG and waist circumference profiles will be calculated using a similar MMRM-based model to the one used for the primary analysis. The corresponding baseline will be used in the model instead of the baseline HbA1c levels. The MMRM model will also include a term for the HbA1c stratification group.

Patients who initiated rescue therapy will be analyzed. The proportion of such patients in each group will be analyzed using a logistic regression analysis with fixed effects of treatment and strata. Time to start of rescue therapy will also be analyzed between the groups using a log-rank test.

In addition to change from baseline in weight and waist circumference, change from baseline in BMI will be listed and summarized.

Descriptive statistics for each outcome will be presented by treatment group. For continuous variables, the descriptive statistics will include sample size, LS means, LS means standard error, mean, SD, median, minimum, and maximum. For categorical variables, the descriptive statistics will include sample size, frequency, and percentage.

10.3.4. Safety Analyses

10.3.4.1. Clinical Evaluation of Safety

The safety population will be used for safety analyses. Both the overall and the pairwise comparisons of each LY3298176 dose versus placebo and dulaglutide will be reported for these safety analyses.

Safety measures will include vital signs, body weight, TEAEs (including SAEs and AEs of special interest), laboratory measures (including anti-LY3298176 antibodies), and ECGs. Summary statistics will be presented by treatment for the safety measures.

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

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

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

In addition, the following safety outcomes will be analyzed on the mITT population:

- Change from baseline to 26 weeks in HDL-C, total cholesterol, triglycerides, and LDL-C
- Change from baseline to 12 and 26 weeks in fasting FGF-21, adiponectin, β-hydroxy butyrate, glucagon, and insulin levels
- Percentage of patients requiring rescue therapy

The change from baseline of HDL-C, total cholesterol, triglycerides, LDL-C, fasting FGF-21, adiponectin, β-hydroxy butyrate, glucagon, and insulin levels will be calculated using a similar MMRM-based model to the one used for the primary analysis. The corresponding baseline will be used in the model instead of the baseline HbA1c levels. The MMRM model will also include a term for the HbA1c stratification group.

Additional analysis, such as concentration–safety lab plots, may be performed if warranted upon review of the data.

10.3.4.2. Adverse Events

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

Reported and adjudicated CV, pancreatic, and thyroid-related AEs will be listed by patient, and if there are a sufficient number of cases they may be summarized by treatment group.

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

Discontinuations due to TEAEs will be listed by patient and summarized by treatment group.

In addition, exposure–response analyses of TEAEs may be performed if necessary.

10.3.4.3. Vital Signs

All vital signs will be listed using all randomized patients.

Descriptive statistics for the actual measurements and changes from baseline for systolic and diastolic BP and PR will be presented by treatment arm and visit. Corresponding figures may be presented.

Vital signs will be analyzed using a similar MMRM-based model as for the secondary analysis on the primary endpoint.

In addition, exposure–response analysis of vital signs may be performed if deemed necessary.

10.3.4.4. Laboratory Measures

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

A listing of laboratory measurements for individual patients will be presented by visit. An additional listing will be presented for all laboratory measurements that are outside the normal range.

Descriptive statistics for the laboratory analyses will be presented by treatment group and visit, including safety off-treatment visits.

Laboratory analyses with categorical responses will be summarized by visit and treatment group using frequency and percentage.

Shift tables will be evaluated at endpoint (LOCF); the maximum/minimum post-baseline observation (as applicable for a lab) will be compared to the baseline observation by examining the proportion of patients whose test values are within and outside the reference ranges.

10.3.4.5. Evaluation of Immunogenicity

The frequency of antibody formation to LY3298176 will be determined. If a neutralization assay is performed, the frequency of neutralizing 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 (e.g., AEs, efficacy measures) may be assessed. Likewise, the relationship between antibody titers, the PK parameters, and PD response to LY3298176 may be assessed.

10.3.4.6. Electrocardiograms

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

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

In addition, LY3298176 concentration–response analysis of QTcF results will be performed as well as a categorical analyses of absolute and change from baseline QTc intervals. Any additional ECG analyses will be detailed in the SAP.

10.3.4.7. Adverse Events of Special Interest

Hypoglycemia, hypersensitivity reactions, injection site reactions, acute pancreatitis, major adverse CV events, and selected GI events such as nausea, vomiting, and diarrhea are defined as AESIs.

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

Continuous elements of AESIs, such as the durations of hypoglycemia and injection site reactions, will be analyzed using a similar MMRM-based model as for the secondary analysis on the primary endpoint.

Statistical analyses on categorical AESIs will be analyzed using a logistic regression analysis with fixed effects of treatment, metformin use, and HbA1c strata. Additional analyses will be run if necessary.

10.3.4.8. Hypoglycemic Episodes

Hypoglycemic episodes will be defined as follows: documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, relative hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia. Total or overall hypoglycemia is defined as any event meeting the criteria for documented symptomatic hypoglycemia, asymptomatic hypoglycemia, or probable symptomatic hypoglycemia.

The total hypoglycemia monthly rate per patient will be summarized where 1 month is defined as a 30-day period. This will be calculated by dividing the total number of hypoglycemic events by the total number of days between visits and multiplying by 30 days. This rate will also be calculated per patient for nocturnal hypoglycemia episodes, and summarized by treatment.

The incidence and rate of total hypoglycemic episodes and nocturnal hypoglycemic episodes will be presented for each visit (incidence between visits) and overall. Nocturnal hypoglycemia episodes are episodes that occur between bedtime and waking. The incidence of hypoglycemic episodes during a time period on treatment is defined as patients with at least 1 hypoglycemic episode occurring within that period of time. Statistical analyses will be performed for overall total hypoglycemia using a logistic regression analysis with fixed effects of treatment, metformin use, and HbA1c strata.

Listings of hypoglycemic episodes and severe hypoglycemic episodes will be presented by visit for each patient. If a sufficient number of severe hypoglycemic episodes are reported, then incidence summaries similar to incidence of hypoglycemic episodes will be included.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

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

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

10.3.6. Other Analyses

10.3.6.1. Health Outcome/Quality of Life Analyses

Each instrument is transformed to a single score on a scale from 0 to 100. Patient-reported outcomes endpoint change from baseline at Weeks 12 and 26 will be analyzed using ANCOVA with treatment, country, metformin use (Yes/No), gender, and baseline HbA1c as independent variables. Missing observations will be imputed with LOCF. Any additional analysis on patient-reported outcomes will be detailed in the SAP.

10.3.6.2. Subgroup Analyses

Subgroup analyses of important factors, including age, race, ethnicity, gender, duration of diabetes, baseline HbA1c (<8.5%, ≥8.5%), metformin use (Yes/No) at baseline, BMI, and other factors to be specified in the SAP are planned for the key outcomes of HbA1c.

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

Other exploratory subgroup analyses may be performed as deemed appropriate.

10.3.6.3. Exploratory Analyses

The change from baseline of 7-point SMBG profiles will be calculated using a similar MMRM-based model to the one used for the primary analysis. The corresponding baseline will be used in the model instead of the baseline HbA1c levels. The MMRM model will also include a term for the HbA1c stratification group.

Statistical analyses on categorical exploratory objectives like the effect of intrinsic factors, such as baseline levels of endogenous FGF-21, GLP-1, or GIP, on the pharmacologic effects of LY3298176 will be done using a logistic regression analysis with fixed effects of treatment, metformin use, and HbA1c strata.

Genetic markers will be evaluated for their contribution to the variability of LY3298176 pharmacology and will also be included as covariates in PK/PD model-based analyses if applicable.

LY3298176 concentration–response analyses of exploratory biomarkers may be performed.

Exploratory analysis on efficacy endpoints such as HbA1c and body weight may be performed on dataset that includes data from patients who received rescue therapy.

Other exploratory subgroup analyses may be performed as deemed appropriate.

10.3.7. Interim Analyses

There may be up to 3 interim analyses for this study. This study will not be stopped for either positive efficacy or futility at any interim analysis. No change in study design will occur based on these interim analyses.

The first interim analysis may occur to support evaluation of the titration scheme. The second interim analysis may occur to support Phase 3 dose selection. The third interim analysis may occur when all patients have completed the treatment part of the study (prior to completion of the follow-up phase for all patients) and will include all safety, efficacy, and PK data available through the 26-week treatment for all patients to confirm Phase 3 doses.

It is not considered a protocol deviation if one or more interim analysis is not performed. Detailed information on the interim analyses will be specified in an Assessment Committee charter or SAP.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibodies
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APPADL	Ability to Perform Physical Activities of Daily Living
AST	aspartate aminotransferase
Blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the 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 subjects are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CIOMS	Council for International Organizations of Medical Sciences
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.
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.
CRS	clinical research scientist
CT	computed tomography

CTX-1	carboxy-terminal telopeptide of type I collagen
CV	cardiovascular
Documented symptomatic hypoglycemia	Defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a plasma glucose level of ≤3.9 mmol/L (≤70 mg/dL)
DPP-4i	Dipeptidyl peptidase 4 inhibitor (an OAM)
ECG	electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
eGFR	estimated glomerular filtration rate
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FBG	fasting blood glucose
FGF-21	fibroblast growth factor-21
GCP	Good Clinical Practice
GI	Gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	Intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	Interactive Web Response System
IW-SP	Impact of Weight on Self-Perception
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LS	least squares
MAD	multiple ascending dose
MI	myocardial infarction
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
OAM	oral antihyperglycemic medication
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per protocol dataset: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PRO	patient-reported outcomes
QTc	corrected QT interval
QW	once weekly
SAD	single ascending dose
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SDP	single-dose pen
SMBG	self-monitoring of blood glucose
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus
TE-ADA	treatment-emergent antidrug antibodies
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
TIA	transient ischemic attack
ULN	upper limit of normal (reference range)
USPI	United States Package Insert
WHO	World Health Organization

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

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

Hemoglobin A1c

Urinalysis:
- pH
- Protein
- Glucose
- Blood
- Urine leukocyte esterase
- Urine albumin, creatinine, UACR

Lipid Panel (Fasting)
- Total Cholesterol
- Triglycerides
- HDL-C
- LDL-C (calculated)

Clinical Chemistry:

Serum Concentrations of:
- Sodium
- Potassium
- Total bilirubin
- Direct bilirubin
- ALP
- ALT
- AST
- BUN
- Creatinine
- Uric acid
- Calcium
- Total Protein
- Lipase
- Amylase
- eGFR[b]
- Glucose, fasting or random
- Albumin
- Calcitonin

Hormones (females):
- Pregnancy Test, serum and/or urine[c]
- Serum estradiol[d]
- Serum FSH[d]
- Serum LH[d]

Serology[e]
- Hepatitis B Surface Ag
- Hepatitis C Ab
- HIV Ab

Immunogenicity
- Anti-LY3298176 Antibodies
- Anti-LY3298176 antibody neutralization assay

Pharmacogenetics Sample

Pharmacokinetic Samples

Optional urine drug screen (local, at the discretion of the investigator)

Nonpharmacogenetic Stored Samples
- EDTA plasma
- Serum
- P800 plasma

Biomarkers
- Fasting insulin, C-peptide, glucagon
- β-hydroxy butyrate
- Adiponectin (Total and HMW)
- FGF-21 (active), GIP and GLP-1 (total and active), osteopontin, free fatty acids, glycerol, MCP-1, CTX-1, P1NP, osteocalcin

Abbreviations: Ab = antidrug antibody; Ag = antigen; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CTX-1 = carboxy-terminal telopeptide of type I collagen; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; FGF-21 = fibroblast growth factor-21; FSH = follicle-stimulating hormone; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; P1NP = procollagen type 1 N-terminal propeptide; RBC = red blood cells; UACR = urine albumin-to-creatinine ratio; WBC = white blood cells.

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

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

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

[d] Performed at screening by central laboratory to establish menopausal status.

[e] Performed at screening only.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his/her participation in the trial.

Appendix 3.1.2. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

- the current IB and dulaglutide Package Insert or dulaglutide SmPC, and updates during the course of the study
- ICF
- relevant curricula vitae

Appendix 3.1.3. Regulatory Considerations

This study will be conducted in accordance with:

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

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

Appendix 3.1.4. Investigator Information

Physicians with a specialty in diabetes/endocrinology, internal medicine, or family medicine will participate as investigators in this clinical trial.

Appendix 3.1.5. Protocol Signatures

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

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

Appendix 3.1.6. Final Report Signature

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

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

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

Appendix 3.2. Data Quality Assurance

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

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

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

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

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in InForm. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (e.g., a rating scale), a daily dosing schedule, or an event diary.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

The following hepatic monitoring tests should be considered for patients with treatment-emergent hepatic abnormalities in Lilly or its designee-sponsored clinical trials to ensure patient safety and comply with regulatory guidance.

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
ALP isoenzymes	
ALT	Antinuclear antibody[a]
AST	Anti-F actin antibody[a]
GGT	Anti-smooth muscle antibody[a]
CPK	

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

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

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

Appendix 5. World Health Organization Classification for Diabetes

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

Type 2 Diabetes Mellitus: Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine.

Coma is rare in type 2 diabetes, but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (e.g., severe infection or mesenteric artery thrombosis) due to acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with type 2 diabetes later progress to a state of absolute insulin deficiency.

References:

Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabetic Med*. 1998;15(7):539–553.

Bennett P. Classification and diagnosis of diabetes mellitus and impaired glucose tolerance. In: Pickup J, William G, editors. Textbook of diabetes. Vol. 1. Oxford: Blackwell Scientific Publications; 1991:p 37–44.

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1999;22(suppl 1):S5–S19.

Appendix 6. Pharmacokinetics Schedule of Events

Study Phase	Screen	Lead-in	Randomize	Treatment Phase													Follow-up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Month of treatment		0	0	0	0	0	0	1	1	2	3	3	4	5	6	6	(7)	
Week of treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)		±7d	0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		112/(17)	140/(21)	168/(25)	182/(27)		
PK-specific visit					X		X		X			X						
PK blood draw				X*	X		X		X	X*	X*	X				X*		X

[I] Predose PK samples will be collected at Visit 4 (Week 1), Visit 10 (Week 8), Visit 11 (Week 12), and Visit 16 (Week 26). X* = Predose sample.

[II] Postdose PK samples will be collected per the assigned schedule after dosing at Visit 5 (Week 1), Visit 7 (Week 2), Visit 9 (Week 4), and Visit 12 (Week 12), and at early termination from all patients. An early termination PK sample may be taken at any time during the visit.

1. At Visit 5 (Week 1), 1 predose PK sample should be collected prior to administering study drug from all patients. Later in the week (Visit 5), an additional PK sample should be taken within 1 to 48 hours (i.e., within 2 days of administrating study drug).
2. At Visit 7 (Week 2), 1 PK sample should be collected after administration of the study drug within 1 to 48 hours (i.e., within 2 days of administrating study drug).
3. At Visit 9 (Week 4), 1 PK sample should be collected after administration of the study drug within 48 to 72 hours (i.e., 2 to 3 days after the administration of study drug).
4. At Visit 12 (Week 12), 1 predose PK sample should be collected prior to administering the study drug from all patients. Later in the week (Visit 12), an additional PK sample should be taken within 96 to 168 hours (i.e., any time between 4 days after study drug administration up to just prior to the next dose of study drug administration).

Appendix 7. Contraceptive Methods

Male patients with female partners of childbearing potential will be required to use a condom in conjunction with a spermicidal gel, foam, cream, or suppository. In addition, the female partner, as well as female patients of child-bearing potential will be requested to use an additional effective form of contraception, which can be any of the following:

- female condom with spermicide
- diaphragm with spermicide
- cervical sponge
- cervical cap with spermicide
- combined oral contraceptive pill and mini-pill
- NuvaRing
- implantable contraceptives
- injectable contraceptives (such as Depo-Provera®)
- intrauterine device (such as Mirena® and ParaGard®)
- true abstinence, when in line with the preferred and usual lifestyle of the patient

Men who have had a vasectomy with appropriate postvasectomy documentation of the absence of sperm in the ejaculate are not required to use contraception. In addition, Inclusion Criterion 3b provides a specific definition of women not of childbearing potential; these subjects will not be required to use contraception. Male patients with a female partner meeting the definition of a woman not of childbearing potential will not be required to use contraception.

Appendix 8. World Health Organization Standardized Protocols for the Measurement of Height and Weight

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2008) (Available at: http://www.who.int/chp/steps/Part3_Section3.pdf. Accessed August 16, 2016).

Measuring Height

Step 1 Ask the patient to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the patient at every clinic visit when their weight is measured).

Step 2 Ask the patient to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the back board or the stadiometer or the wall.

Step 3 Ask the patient to look straight ahead without tilting their head up.

Step 4 Ask the patient to breathe in and stand tall. If using a stadiometer or fixed measuring device, move the device's measurement arm gently down onto the top of the patient's head. Record the patient's height in centimeters (cm).

Measuring Weight

Body weight measurements should be done in a consistent manner using a calibrated scale (mechanical or digital scales are acceptable). All weights for a given patient should be measured using the same scale, whenever possible, after the patient has emptied their bladder. Patients should be lightly clothed but not wearing shoes while their weight is measured.

Step 1 Ask the patient to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the patient at every clinic visit when their weight is measured).

Step 2 Make sure the scale is placed on a firm, flat, even surface (not on carpet or on a sloping surface or a rough uneven surface).

Step 3 Ask the patient to step onto the scale with one foot on each side of the scale.

Step 4 Ask the patient to stand still with their arms by their sides and then record their weight in kilograms (kg).

Appendix 9. Protocol Amendment I8F-MC-GPGB(a) Summary: A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus

Overview

Protocol I8F-MC-GPGB A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus 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 described in the following table:

Amendment Summary for Protocol I8F-MC-GPGB Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Visit 13 Study Day/(Dose number) changed from 98/(15) to 112/(17)	Math error
Section 6.3 Lifestyle Restrictions	30 days changed to 8 weeks	Typographical error. Changing to 8 weeks is consistent with Section 7.2.2. Specific Restrictions/Requirements
Section 7.6 Treatment Compliance	Added "intentionally" to the following sentence: A patient will be considered significantly noncompliant if he/she intentionally misses 4 or more doses of study medication.	Added to clarify from Section 8.1.2.
Section 8.1.1 Permanent Discontinuation from Study Treatment	Added "significant" to the following bullet: • Any significant study drug-related hypersensitivity reaction Added "intentionally" to the following sentence: • If the patient intentionally misses 4 or more doses (consecutive or not) of study medication or intentionally or repeatedly takes more than the prescribed dose of study medication (see Section 9.3).	Added to clarify and align with Section 9.2.1.2.2 Added to clarify from Section 8.1.2
Section 8.1.2 Temporary Discontinuation from Study Treatment	Added "a natural disaster" to the following sentence: After randomization, the investigator may temporarily discontinue study drug, for example, due to an AE (eg, nausea and vomiting), a clinically significant laboratory value, or a natural disaster.	Added because we had patients miss doses and visits due to hurricanes Irma and Maria, both of which have shut sites, resulted in loss of study drug due to lack of power/refrigeration, and made it a logistical challenge for patients to attend site visits or take study drug. Since this is not a patient compliance issue, we want to keep patients in the study.

Amendment Summary for Protocol I8F-MC-GPGB Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Section 8.1.2 Temporary Discontinuation from Study Treatment	Sentence deleted: If 4 or more doses of study medication (consecutive or not) are missed for any reason, then the patient should be permanently discontinued from study medication.	This sentence has been removed because we are allowing patients to miss 4 or more doses when the reason has been beyond their control, such as the length of time it has taken for follow up for abnormal laboratory results and due to natural disasters (hurricanes). Of note, because of hurricanes Irma and Maria we have had sites without power and issues of patient logistics that have necessitated patients missing doses fully beyond their control. We want to keep those patients in the study.
Appendix 6 Pharmacokinetics Schedule of Events	Visit 13 Study Day/(Dose number) changed from 98/(15) to 112/(17)	Math error

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

2. Schedule of Activities

Study Phase	Screen	Lead - in	Randomize	Treatment Phase													Follow up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Week of Treatment	−3	−2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study Day/(Dose number)			0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		~~98~~112/(~~15~~17)	140/(21)	168/(25)	182/(27)		
Visit Window (days)		±7				±3		±3		±3	±3		±3	±3	±3	±3	±3	
PK Specific Visit[a]					X		X		X			X						

6.3 Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study or for ~~30 days~~ 8 weeks following the study.

7.6 Treatment Compliance

During the study, patients will be asked to return their unused study drug materials and completed diaries to the site so that their compliance may be assessed.

Patients who are significantly noncompliant will be permanently discontinued from study medication. A patient will be considered significantly noncompliant if he/she intentionally misses 4 or more doses of study medication. Similarly, a patient will be considered significantly noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

8.1.1 Permanent Discontinuation from Study Treatment

- Any significant study drug-related hypersensitivity reaction

- If the patient intentionally misses 4 or more doses (consecutive or not) of study medication or intentionally or repeatedly takes more than the prescribed dose of study medication (see Section 9.3).

8.1.2 Temporary Discontinuation from Study Treatment

After randomization, the investigator may temporarily discontinue study drug, for example, due to an AE (e.g., nausea and vomiting), ~~or~~ a clinically significant laboratory value, or a natural disaster. If study drug discontinuation is due to an AE, the event is to be followed and documented. Every effort should be made by the investigator to maintain patients in the study and to restart study drug promptly after any temporary discontinuation, as soon as it is safe to do so. The dates of study drug discontinuation and restart will be documented. Patient noncompliance should not be recorded as temporary discontinuation of study drug on the eCRF. ~~If 4 or more doses of study medication (consecutive or not) are missed for any reason, then the patient should be permanently discontinued from study medication.~~

Appendix 6 Pharmacokinetics Schedule of Events

Study Phase	Screen	Lead-in	Randomize	Treatment Phase													Follow-up	Early Term
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	801	
Month of treatment		0	0	0	0	0	0	1	1	2	3	3	4	5	6	6	(7)	
Week of treatment	–3	–2	0	1	1	2	2	4	4	8	12	12	16	20	24	26	(30)	
Study day/(Dose number)		±7d	0/(1)	7/(2)		14/(3)		28/(5)		56/(9)	84/(13)		~~98~~112/(~~15~~17)	140/(21)	168/(25)	182/(27)		
PK-specific visit					X		X		X			X						
PK blood draw				X*	X		X		X	X*	X*	X				X*		X

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