I8F-MC-GPGA(f) Clinical Pharmacology Protocol

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

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Confidential Information

LY3298176

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1. Protocol Synopsis

Title of Study:

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

Rationale:

LY3298176 is CCI glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor coagonist being developed as a weekly treatment for type 2 diabetes mellitus (T2DM). This first-in-human study of LY3298176, I8F-MC-GPGA (GPGA), will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3298176 administered as subcutaneous (SC) injections in healthy subjects and in patients with T2DM.

Objectives/Endpoints:

Primary Objective	**Endpoints**
To investigate the safety and tolerability following single and multiple SC doses of LY3298176 administered to healthy subjects and patients with T2DM	Adverse event and safety glucose monitoring.
Secondary Objectives	**Endpoints**
To characterize the PK of LY3298176 following SC doses of LY3298176 in healthy subjects and patients with T2DM	Blood samples will be evaluated for LY3298176 concentration for the assessment of LY3298176 PK parameters using a noncompartmental method of analysis.
To investigate the PD effects of LY3298176 following multiple SC doses of LY3298176 administered to healthy subjects	Glycemic control (including fasting glucose; glucose and insulin during an OGTT), gastric emptying using acetaminophen, weight, lipids, adiponectin, blood urea nitrogen, and cortisol.
To investigate the PD effects of LY3298176 following multiple SC doses of LY3298176 administered to patients with T2DM	Glycemic control (including fasting glucose; glucose insulin during an OGTT, and hemoglobin A1C), gastric emptying using acetaminophen, weight, lipids, adiponectin, blood urea nitrogen, and cortisol.

Abbreviations: AUC = area under the concentration versus time curve; ECG = electrocardiogram; OGTT = oral glucose tolerance test; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous; T2DM = type 2 diabetes mellitus.

Summary of Study Design:

Study GPGA is a Phase 1, multiple-site, patient-/subject- and investigator-blind, placebo-controlled, randomized, parallel-dose group, single-ascending dose (SAD; Part A), and a 4-week multiple-ascending dose (MAD; Part B) study in healthy subjects, and a 4-week multiple-dose evaluation in patients with T2DM (Part C). Part B will evaluate Trulicity® (dulaglutide) as a positive control for PD of GLP-1 pharmacology.

Treatment Arms and Duration:
Part A will consist of up to 6 escalating single-dose levels of LY3298176 or placebo in healthy subjects. Approximately 48 subjects will be randomized into 6 groups (Cohorts A through F).

In Part B, approximately 40 healthy subjects in Cohorts A′ through E′ will be administered 4 weekly SC doses within the dose and exposure range of the SAD (Part A).

Up to 3 additional cohorts of approximately 8 subjects each may be utilized to explore the full single (Part A) or multiple (Part B) dose range planned or to evaluate dose titration regimens in Part B of the study. The additional cohorts will be assigned the next available letter designation.

Part C of the study will be a 4-week multiple-dose evaluation of LY3298176 in approximately 20 patients with T2DM.

Number of Patients/Subjects:
Approximately 143 healthy subjects and up to approximately 25 patients with T2DM may be enrolled so that approximately 112 healthy subjects and 20 patients complete the study.

Statistical Analysis:
PK and PD analyses will be conducted on the full analysis set. Safety analyses will be conducted for all enrolled patients/subjects whether or not they completed all protocol requirements.

Sample Size: Approximately 143 healthy subjects may be enrolled in Parts A and Part B to achieve the objectives of each part of the study. Approximately 25 T2DM patients may be enrolled in Part C to achieve study objectives. The replacement patient/subject will be assigned to receive the treatment of the dropout.

For each study part, any dropout may be replaced so that the targeted numbers of patients/subjects for safety review and data collection may be achieved. The replacement patient/subject will be assigned to receive the treatment of the dropout.

The sample sizes for each part of the study were chosen to provide adequate placebo control for each dosing occasion and are considered sufficient to evaluate the primary objective of this study.

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

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

For single- and multiple-dose parts of the study, PK dose proportionality will be assessed separately. Log-transformed C_{max} and AUC of LY3298176 will be evaluated using a power model to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals (CIs). The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality.

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

For Parts A, B, and C, all PK parameters will be summarized using descriptive statistics.

Pharmacodynamics: Inferences will be sought regarding the ability of LY3298176 to reduce fasting or dynamic glucose together with the effects on insulin. Such effects will be explored over different doses of LY3298176.

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

Gastric emptying of LY3298176 will be evaluated using acetaminophen parameters. The parameter estimates for acetaminophen will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be the C_{max}, the AUC, and the T_{max} of acetaminophen. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

The PD parameters from each part of the study will be analyzed separately. PD parameters from placebo-treated patients/subjects within each part of the study will be pooled for the final analysis. Absolute values as well as change from baseline in each parameter will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The main comparisons will be between each LY3298176-treated group and placebo group.

Baseline-adjusted C_{max} of acetaminophen (ratio to Day -1 value) will be calculated and log-transformed to compare the gastric emptying effect of LY3298176 to that of dulaglutide. A mixed-model repeated-measure with treatment, day, and treatment-by-day interaction as fixed effects, patient/subject as random effect, and baseline (Day -1) as covariate will be used to perform the analysis. Least-squares means as well as 95% CIs will be reported.

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

All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment group and day. Summary statistics will be provided.

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

Immunogenicity: The frequency of antibody formation to LY3298176 will be determined. If a neutralization assay is performed, the frequency of neutralizing antibodies will be determined. The relationship between the presence (or absence) of antibodies and clinical parameters will be assessed. Likewise, the relationship between the presence of antibodies and the PK parameters and PD response to LY3298176 will be assessed.

Interim Analysis: Access to the data is scheduled to occur after every dosing session. The purpose of these reviews is to review the safety data and determine the dose for the next dosing session. The investigator and the Lilly sponsor team will make the determination regarding dose escalation based upon their review of the safety and tolerability data. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

2. Schedule of Activities

Study Schedule Protocol I8F-MC-GPGA, Part A

Procedure	Screening[a]	Baseline	Treatment[a]								Follow-up[b]		
Days		**−1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**15 ± 1**	**29 ± 3**	**43 ± 3**	**ET[c]**
Study informed consent	X												
Medical history	X												
Physical examination	X												
Height and weight[d]	X		X						X	X	X	X	X
Admit to CRU		X											
Medical assessment[o]	X		Predose	X	X	X	X	X	X	X	X	X	X
Discharge from CRU[e]						X							
Clinical safety lab[f]	X		Predose		X				X	X	X	X	X
Glucose only[g] (hr)			8	X		X	X	X					
Vital signs (BP/PR)[h] (hr)	X		Predose, 1, 4, 8, and 12	X	X	X	X	X	X	X	X	X	X
Body temperature (hr)	X	X	Predose, 8										
ECGs[i] (hr)	X		Predose, 8	X	X	X	X	X	X	X	X	X	X
Administer study drug[j]			X										
PK sampling[k] (hr)			Predose, 8	X	X	X	X	X	X	X	X	X	X
Point of care safety glucose sampling[l]			X	X	X	X	X	X					
Lipid panel[m]			Predose		X								
Fasting insulin[m]			Predose						X				
Pharmacogenomic sample			X										
Nonpharmacogenetic sampling (storage)[n]			Predose		X								
Immunogenicity			X						X	X	X		X
AEs/concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; lab = laboratory; PK = pharmacokinetics; PR = pulse rate.

a Screening shall be completed up to 28 days before study enrollment. Clinical tests will be repeated if dosing is >28 days from initial screening.

b Follow-up visit shall be completed after at least 28 days from dose of study drug.

c Subjects who discontinue early will be encouraged to return for a follow-up visit at least 28 days after study drug administration.

d Height measured at screening only. Weight will be measured in a consistent way always predose. Scale needs to be calibrated (refer to Section 9.4.3.1).

e The day of discharge may be changed after review of preliminary safety and/or PK data. On Day 4, subjects may be discharged after the morning procedures are completed. Subjects may be retained in-house longer than Day 4 at the investigator's discretion.

[f] Clinical safety laboratory measures include chemistry, hematology, and urinalysis panels. Blood samples will be taken predose on the dosing day. Subjects will be required to fast for at least 8 hours before each blood sample is drawn.

[g] Nonfasting glucose samples will be taken with triplicate ECGs and PK time points on the days that no clinical safety laboratory samples are taken.

[h] Vital measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. BP and PR measurements will be taken after approximately 5 minutes in the supine position.

[i] A single local safety ECG will be measured at screening, Day 29, and Day 43 (follow-up) or ET visit. Triplicate ECGs will be obtained at predose (Day 1), and 8, 24, 48, 72, 96, 120, 168, and 336 hours postdose at a time matched to predose. The Day 1 predose ECGs will be taken in triplicates every 15 minutes for 1 hour to establish a baseline. ECGs must be recorded before collecting any blood for safety or PK samples and close to the time of the blood draw. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[j] Study drug will be administered after an overnight fast of at least 8 hours.

[k] PK samples will be obtained predose and 8 and 24 hours postdose, and approximately 48, 72, 96, 120, 168, and 336 hours postdose and at the follow-up visits on Days 29 and 43.

[l] Point of care safety glucose sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 3). Prebreakfast samples only will be collected on Days 4, 5, and 6.

[m] Subjects will be required to fast for at least 8 hours before each blood sample is drawn for lipid panel and fasting insulin. Lipid panel includes fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

[n] Nonpharmacogenetic samples will be collected predose and while fasting for at least 8 hours before each blood sample is drawn.

[o] Assessments of injection site reactions will be included in the medical assessments, except screening.

Study Schedule Protocol I8F-MC-GPGA Parts B and C

Procedure	Screen[a]	Prestudy	Baseline		Treatment[a]														Follow-up		
Days		**Before Day −2**	**−2**	**−1**	**1**	**2**	**3**	**4**	**8 ±1**	**12 ±1**	**15 ±1**	**18 ±1**	**22**	**23**	**25**	**27**	**28**	**29**	**ET[b]**	**36 ±2**	**57 ±2**
Informed consent	X																				
Admission to CRU			X										X				X				
Drug and alcohol screen	X[s]																				
Discharge from CRU[c]								X						X				X			
Outpatient visits to CRU		X							X		X				X				X	X	X
Distribution of glucose meters, test strips, and diaries/SMBG training	X[d]	X							X		X		X								
Administer study drug[e]					X				X		X		X								
Phone calls for safety/ immune monitoring										X		X									
Medical history	X																				
Height and weight[f]	X				Predose				Predose		Predose		Predose					X	X		
Physical examination	X																				
Medical assessment[t]	X				Predose			X	Predose		Predose		Predose		X			X	X		X
Hemoglobin A1C[g,h]	X				Predose													X	X		
Vital signs (BP/PR)[i,j] (hr)	X			X	Predose, 1, 4, 8, and 12	X	X	X	X		X		X		X			X	X	X	X
ECG[j,k] (hr)	X				Predose, 8	X	X	X	Predose				Predose, 8	X	X			X	X	X	X
PK sampling[l] (hr)					Predose, 8	X	X	X	X				Predose, 8	X	X			X	X	X	X
Body temperature	X			X	X													X			
Clinical safety lab[m]	X				X	X	X	X	X		X		X					X	X	X	X
Glucose only (hr)[n]					8								8	X	X						
AEs/concomitant medications	X				X	X	X	X	X		X		X		X		X	X	X	X	X
7-point glucose profile			X						X		X		X			X					
OGTT[o]				X		X								X							

Procedure	Screen[a]	Prestudy	Baseline		Treatment[a]														Follow-up		
Days		Before Day −2	−2	−1	1	2	3	4	8 ±1	12 ±1	15 ±1	18 ±1	22	23	25	27	28	29	ET[b]	36 ±2	57 ±2
Acetaminophen test for gastric emptying[p]				X		X								X							
Lipid panel[q]					Predose													X	X		
Adiponectin[q]					Predose				Predose									X			
Cortisol[q]					Predose				Predose									X			
Bone markers: P1NP, osteocalcin, CTX-1[g,h]					Predose													X	X		
Pharmacogenomic sample					X																
Nonpharmacogenetic sampling (storage)[r]					Predose				Predose		Predose		Predose					X	X		
Immunogenicity					X				X		X		X					X	X	X	X

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; CTX-1 = carboxy-terminal telopeptide fragments of Type I collagen; ECG = electrocardiogram; ET = early termination; lab = laboratory; OGTT = oral glucose tolerance test; P1NP = N-terminal propeptide of Type I collagen; PK = pharmacokinetic; PR = pulse rate; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus.

a Screening shall be completed up to 28 days before study enrollment. For Part C, the screening period will be longer for patients with T2DM treated with sulfonylureas; these patients will be required to stop their treatment and have a 6-week washout period before dosing with study drug. Clinical tests will be repeated if dosing would be >28 days from initial screening.

b For early termination, the patient/subject will complete Day 29 predose time frame pharmacodynamic, PK, and safety laboratory collections and a single ECG and vital signs measurement if during the treatment period, and Day 57 procedures if during the follow-up. Patients/subjects who are discontinued early from the study will be asked to complete a follow-up visit with Day 57 procedures after a washout period of at least 28 days from the last dose of study drug.

c For the initial CRU admission, patients must remain at the CRU at least until the morning of Day 4.

d Patients with T2DM (Part C) who were taking sulfonylureas at screening will be required to monitor their glucose during the 6-week washout period.

e Study drug will be administered after an overnight fast of at least 8 hours.

f Height measured at screening only. Weight will be measured in a consistent way, always predose. Scale needs to be calibrated (refer to Section 9.4.3.1).

g Part C only.

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

i Vital signs sampling: Day 1: predose, and 1, 4, 8, and 12 hours; Days -1, 2, 3, 4, 8, 15, 22, 25, 29, and 37 at a time matched to predose; and follow-up, Days 37 and 57. Triplicate measurements will be done in Part C only (patients with T2DM).

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

[k] A single local safety ECG will be measured at screening and Day 57 (follow-up) or ET visit; triplicate ECGs will be measured at predose and 8 hours after dose administration on Days 1 and 22 and on Days 2, 3, 4, 8, 23, 25, 29, and 36 at a time matched to predose. The Day 1 predose ECG will be taken in triplicates every 15 minutes for 1 hour to establish a baseline. ECGs must be recorded before collecting any blood for safety or PK samples and close to the time of the blood draw. Patients/subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[l] PK sampling for LY3298176 on Day 1 at predose, 8, and 24 (Day 2) hours postdose, and approximately 48 (Day 3), 72 (Day 4), and 168 (Day 8) hours after the first dose (168-hour sample to be collected before the second dose of LY3298176); additional PK samples to be collected at Week 4 after the fourth dose (Day 22) at predose, 8, and 24 (Day 23) hours postdose, and approximately 72 (Day 25) and 168 (Day 29) hours postdose, and at the follow-up visits on Day 36 and Day 57.

[m] Clinical safety laboratory measures include chemistry, hematology, and urinalysis panels. Blood samples will be taken predose on all dosing days. Patients will be required to fast for at least 8 hours before each blood sample is drawn.

[n] Nonfasting glucose samples will be taken with triplicate ECGs and PK time points on the days and/or time points that no clinical safety laboratory samples are taken.

[o] OGTT (insulin and glucose) sampling schedule: Pre-glucose dose (75 g) and 0.5, 1, 1.5, and 2 hours post glucose dose. Patients/subjects will be required to fast for at least 8 hours before OGTTs.

[p] Acetaminophen PK sampling schedule: Pre-acetaminophen dose and 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12, and 24 hours post acetaminophen dose. For the second CRU admission, D22, subjects may be discharged on Day 23 or Day 24 after the 24 hours acetaminophen sample is collected.

[q] Patients/subjects will be required to fast for at least 8 hours before each blood sample is drawn for lipid panel, adiponectin, and cortisol. Lipid panel includes high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglycerides. Triglyceride and total cholesterol concentrations in the safety panel will not be required on the days that the lipid panel is performed.

[r] Nonpharmacogenetic samples will be collected predose and while fasting for at least 8 hours before each blood sample is drawn.

[s] Performed only at site(s) located in the United States, and procedures may be repeated throughout the study as deemed necessary by the investigator.

[t] Assessments of injection site reactions will be included in the medical assessments.

3. Introduction

3.1. Study Rationale

LY3298176 is CCI glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor coagonist being developed as a weekly treatment for type 2 diabetes mellitus (T2DM). This first-in-human study of LY3298176, I8F-MC-GPGA (GPGA), will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3298176 administered as subcutaneous (SC) injections in healthy subjects and in patients with T2DM.

3.2. Background

In normal physiology, the incretins GLP-1 and GIP are secreted from enteroendocrine cells in the gut following a meal to enhance the physiological responses to food intake including sensation of satiety, insulin secretion, and nutrient disposal. It is now well known that T2DM patients have impaired incretin responses (Nauck et al. 2004) and pharmacologic interventions providing either GLP-1 receptor agonistic peptides or dipeptidyl peptidase (DPP)-IV inhibitors (which delay degradation of endogenous GIP and GLP-1) are successfully used in the treatment of T2DM (Drucker and Nauck 2006; Amori et al. 2007; Baynes 2010). Although GLP-1 is regarded as the incretin of therapeutic utility, published data demonstrated that overexpression of GIP may lead to improved body weight and glycemic control and the combination of GLP-1 and GIP may result in improved glycemic efficacy and weight management compared with GLP-1 agonists alone in T2DM patients (Kim et al. 2012; Finan et al. 2013).

CCI [redacted] By combining the 2 incretin pharmacologies, improved glycemic control may be expected based on potential additive or synergistic effects on glycemic and weight benefits (Irwin et al. 2009).

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

Based on nonclinical PK data, LY3298176 PK is expected to be linear and dose proportional. A half-life of 3 to 5 days in humans is projected, supporting the desired once weekly dosing regimen with $\leq$2-fold in peak to trough ratio and accumulation at steady-state within 2 to 4 weeks. The time to maximum concentration (T_{max}) is predicted to be approximately 24 hours after an SC dose administration.

In vivo safety pharmacology assessments conducted in accordance with International Conference on Harmonisation (ICH) S6 guidelines using LY3298176 did not reveal any substantive clinical risk to the central nervous system, respiratory system, or cardiovascular function in cynomolgus monkeys. Consistent with GLP-1 pharmacology previously observed in nonclinical studies with this drug class (Goodwill et al. 2014), effects of LY3298176 on the cardiovascular system in monkeys were increased blood pressure and heart rate and decreased cardiac contractility. There

were no effects on QT corrected for heart rate (QTc) at any dose in monkeys given a single dose or after repeated doses in the 1-month toxicology study. No adverse effects on neurobehavior or respiratory function were observed. Cardiovascular function will be monitored in the clinical trial.

One-month studies were conducted in rat and cynomolgus monkey. All of the effects in both species were consistent with GLP-1 pharmacology and no target organ toxicity was identified. In the rat study, effects were limited to decreased food consumption and body weights. No clinical pathology effects considered toxicologically important were observed and there were no LY3298176-related histopathology findings. The top dose of 1.5 mg/kg was the no-observed-adverse-effect level (NOAEL) in rats. In monkeys, effects included body weight loss and decreased food consumption at ≥0.15 mg/kg and thin clinical condition at 0.5 mg/kg. One monkey given the high dose of 0.5 mg/kg required veterinary treatment (supplemental fluids) due to decreased food consumption, body weight loss, and clinical condition. No adverse histopathology effects were noted at any dose. Due to the need for veterinarian intervention (administration of SC fluids) at 0.5 mg/kg, the NOAEL in monkeys was 0.15 mg/kg.

Preliminary draft safety and tolerability data:

In Part A (single-ascending dose [SAD] portion) of this study, more than 50 healthy subjects received study drug with doses of LY3298176 ranging from 0.25 mg to 8 mg. Single doses of study drug were generally well tolerated. Gastrointestinal (GI) events (loss of appetite, bloating, nausea, vomiting, etc.) were the most commonly reported adverse events (AEs). At the 8-mg dose level, the majority of subjects experienced drug-related GI events Two of the subjects who received 8 mg reported AEs of nausea and vomiting that required treatment with antiemetics and intravenous fluids. Further dose escalation was therefore stopped.

In Part B (multiple-ascending dose [MAD] portion) of this study, more than 30 healthy subjects have been dosed in cohorts of 4 weekly SC fixed doses of 0.5 mg, 1.5 mg, and 4.5 mg; and an additional titration regimen cohort of 5 mg for 2 doses (Weeks 1 and 2), 8 mg (Week 3), and 10 mg (Week 4). Similar to Part A, the most commonly reported AEs have been GI events, including loss of appetite, nausea, bloating, heartburn, and vomiting. A majority of the AEs have been reported following the first week of dosing, with fewer AEs being reported after the third and fourth doses. The 8-mg dose was better tolerated in this titration approach as compared with the single 8-mg dose evaluated in Part A The limits of tolerability were not reached in the multiple-dose escalation in healthy subjects.

Part C of this study is currently ongoing. A group of T2DM patients has received a fixed dose of 5 mg for 4 weeks. GI events were the most commonly reported adverse events in these patients. LY3298176 appears to be better tolerated by T2DM patients who received 5 mg doses compared to healthy subjects who received 4.5 mg in Part B of the study. A second group of T2DM patients is currently being evaluated in Part C using a titration approach with a dosing scheme of 5 mg (Week 1), 5 mg (Week 2), 10 mg (Week 3), and 10 mg (Week 4). GI events (decreased or loss of appetite, feeling bloated, nausea, vomiting, etc) have been reported following the first

two doses of 5 mg. Preliminary data regarding the 10 mg dose indicates that LY3298176 appears to be tolerated in this titration approach.

3.3. Benefit/Risk Assessment

The nonclinical safety information for LY3298176 adequately supports the transition from preclinical status to a clinical development. On the basis of the nonclinical data, LY3298176 is not considered to be a high-risk compound. LY3298176 has not been administered to humans previously, and to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the European Medicines Agency (EMEA 2007) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. Any identified risks are considered to be monitorable and manageable at the planned dose range for LY3298176 in healthy subjects and patients with T2DM.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3298176 are to be found in the Investigator's Brochure (IB). Known and expected benefits and risks of dulaglutide may be found in the package insert for dulaglutide (Trulicity package insert, 2015).

4. Objectives and Endpoints

Table GPGA.4.1 shows the objectives and endpoints of the study.

Table GPGA.4.1 Objectives and Endpoints

Primary Objective	**Endpoints**
To investigate the safety and tolerability following single and multiple SC doses of LY3298176 administered to healthy subjects and patients with T2DM	Adverse event and safety glucose monitoring.
Secondary Objectives	**Endpoints**
To characterize the PK of LY3298176 following SC doses of LY3298176 in healthy subjects and patients with T2DM	Blood samples will be evaluated for LY3298176 concentration for the assessment of LY3298176 PK parameters using a noncompartmental method of analysis.
To investigate the PD effects of LY3298176 following multiple SC doses of LY3298176 administered to healthy subjects	Glycemic control (including fasting glucose; glucose and insulin during an OGTT), gastric emptying using acetaminophen, weight, lipids, adiponectin, blood urea nitrogen, and cortisol.
To investigate the PD effects of LY3298176 following multiple SC doses of LY3298176 administered to patients with T2DM	Glycemic control (including fasting glucose; glucose insulin during an OGTT, and hemoglobin A1C), gastric emptying using acetaminophen, weight, lipids, adiponectin, blood urea nitrogen, and cortisol.
Exploratory Objective	**Endpoints**
To investigate LY3298176 effects on markers of bone metabolism (formation and resorption) following multiple SC doses of LY3298176 administered to patients with T2DM	Markers include: P1NP, osteocalcin, CTX-1.

Abbreviations: AUC = area under the concentration versus time curve; CTX-1 = carboxy-terminal telopeptide fragments of Type I collagen; ECG = electrocardiogram; OGTT = oral glucose tolerance test; P1NP = N-terminal propeptide of Type I collagen; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous; T2DM = type 2 diabetes mellitus.

5. Study Design

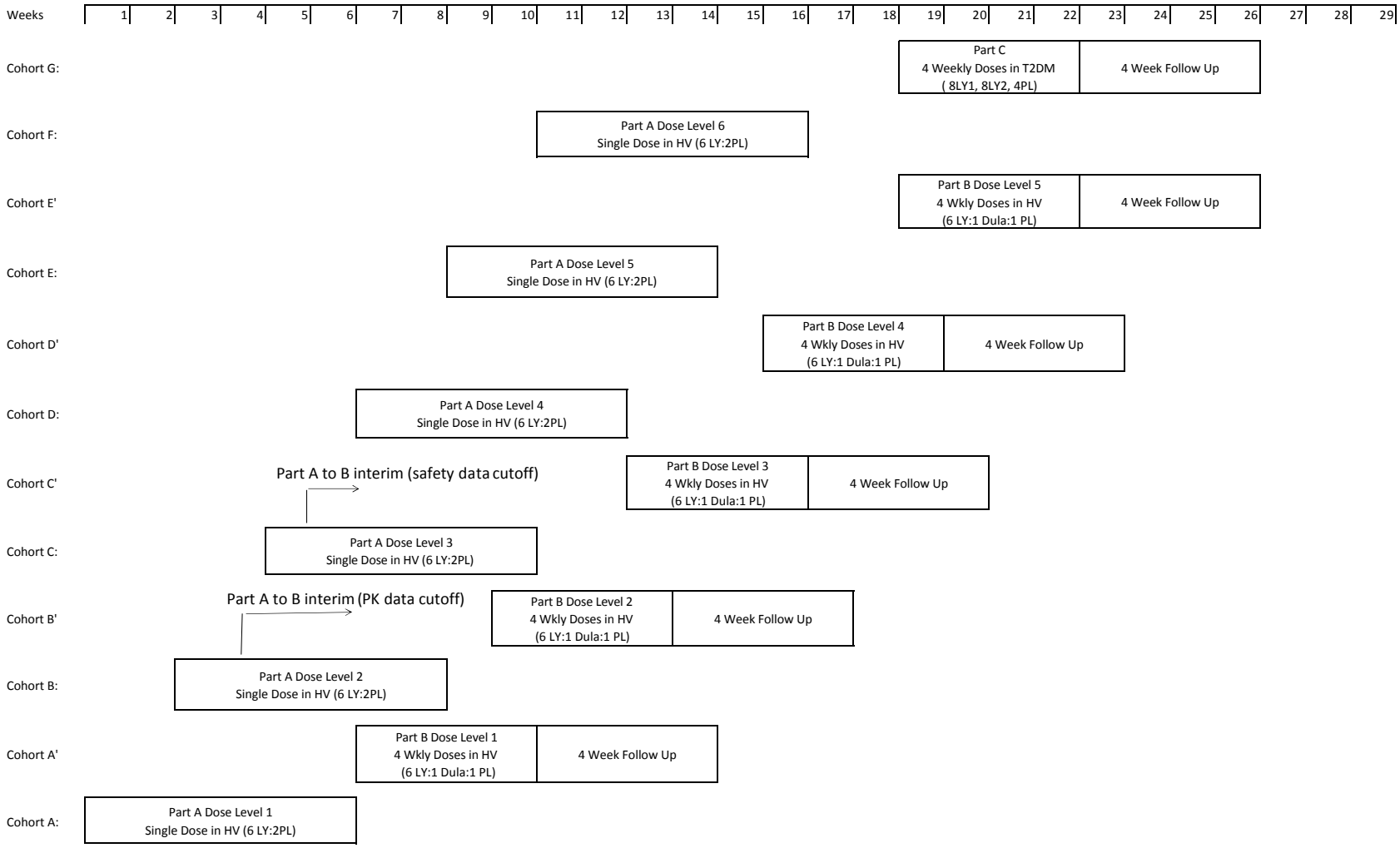
5.1. Overall Design

Study GPGA is a Phase 1, multiple-site, patient-/subject- and investigator-blind, placebo-controlled, randomized, parallel-dose group, single-ascending dose (SAD; Part A), and a 4-week multiple-ascending dose (MAD; Part B) study in healthy subjects, and a 4-week multiple-dose evaluation in patients with T2DM (Part C). Part B will evaluate Trulicity® (dulaglutide) as a positive control for PD of GLP-1 pharmacology.

The planned LY3298176 doses for this study range from 0.25 mg up to 15 mg LY3298176 (Section 5.5). Initially, it was planned to explore doses up to 10 mg; however, based on a preliminary review of safety, tolerability, and PK data, the upper end of the dose range was increased from 10 mg to 15 mg. Dulaglutide will be provided as a 1.5-mg SC dose.

Figure GPGA.5.1 illustrates the study design.

A follow-up visit will be performed according to the Schedule of Activities (Section 2).



Abbreviations: Dula = dulaglutide; HV = healthy volunteers; LY = LY3298176; PL = placebo; T2DM = type 2 diabetes mellitus; Wkly = weekly.

This is a general schematic of the study design, but dose levels may be repeated or cohorts added.

Figure GPGA.5.1. General study design for Protocol I8F-MC-GPGA.

Patient/subject eligibility for this study will be determined at a screening visit. Eligible patients/subjects will be admitted to the clinical research unit (CRU) on Day −1 (Part A) or on Day -2 (Parts B and C). If the investigator decides not to administer the first dose to a patient/subject or not to enroll a patient/subject on a particular day, the patient/subject may be rescheduled to participate in the same part of the study and any procedures performed up to that point may be repeated. Alternatively, the patient/subject may be rescheduled to participate in another part of the study if he/she consents to doing so and meets the inclusion/exclusion criteria.

Patients/subjects will be given an SC dose of LY3298176 (or placebo or dulaglutide) on Day 1 (Parts A, B, and C) and Days 8, 15, and 22 (Parts B and C only) after an overnight fast (at least 8 hours). PK sampling and safety assessments, including AE, medical assessments, clinical laboratory tests, vital signs, and electrocardiograms (ECGs), will be performed according to the Schedule of Activities (Section 2). PK or PD sampling schedules may be modified based on the available safety and PK data.

The investigator or qualified designee will review all available inpatient safety data before discharging patients/subjects from the CRU on the morning of Day 4, provided they are deemed medically fit by the investigator. Patients/subjects may be required to remain at the CRU longer than Day 4 at the investigator's discretion. Safety, as assessed by AEs, clinical safety laboratory tests, vital signs, 12-lead ECGs, concomitant medications, and medical assessments, will be reviewed by the sponsor and investigator before each dose-escalation decision.

During the study, patients/subjects may remain at the CRU as needed for safety follow-up based on clinical judgment of the principal investigator.

A Safety Review Panel (SRP) will be established and composed of experts in early phase medicine independent of the study team and investigative site. When the study team recommends a dose that differs from that anticipated by the protocol in Part A, and for the doses for Parts B and C, the SRP will review the recommendation(s) of the study team and provide a recommendation in return to the study team.

Patients/subjects will be discharged after the review of all final safety assessments from the last follow-up visit is completed by the investigator.

5.1.1. Single-Ascending Dose Study in Healthy Subjects (Part A)

Part A will consist of up to 6 escalating single-dose levels of LY3298176 or placebo in healthy subjects. Approximately 48 subjects will be randomized into 6 groups (Cohorts A through F) as follows:

- Cohorts A through F: approximately 8 subjects per cohort, with a ratio of 6 LY3298176:2 placebo.

Each new dose level will be initiated only if safety results through Day 8 from at least 5 subjects receiving LY3298176 in the preceding dose level are deemed acceptable by the investigator and the Lilly clinical pharmacologist.

5.1.2. Multiple-Ascending Dose Study in Healthy Subjects (Part B)

The MAD portion of the study will be initiated after review of safety and PK data from Day 8 of the second SAD dose level and safety data through Day 8 of the third SAD dose level. In Part B, approximately 40 healthy subjects in Cohorts A′ through E′ will be administered 4 weekly SC doses within the dose and exposure range of the SAD as follows:

- Cohorts A′ through E′: approximately 8 subjects per cohort, with a ratio of 6 LY3298176:1 placebo:1 dulaglutide.

The dose levels in Part B will be determined on the basis of safety, tolerability, and PK data from Part A. Dose escalations will be based on the evaluation of preliminary safety and tolerability data from at least 5 subjects receiving LY3298176 through Day 15 of the previous MAD dose level.

Amendment to Parts A and B

The protocol has been amended to allow the addition of up to three cohorts of approximately 8 subjects each. These additional cohorts may be utilized to explore the full single (Part A) or multiple (Part B) dose range planned or to evaluate dose titration regimens in Part B of the study. The additional cohorts will be assigned the next available letter designation.

5.1.3. Multiple-Dose Evaluation in Patients with Type 2 Diabetes Mellitus (Part C)

Part C of the study will be a 4-week multiple-dose evaluation of LY3298176 in approximately 20 patients with T2DM. Patients will be administered 4 weekly SC doses of LY3298176 or placebo in a ratio of 16 LY3298176:4 placebo (Cohort G). Patients receiving LY3298176 will be randomized into 1 of 2 different dose levels (8 patients per dose level). Dose levels will be determined based on safety, tolerability, and PD data from Part B.

Part C may be initiated based on the evaluation of safety and tolerability data from Part B (MAD).

Amendment to Part C

The protocol has been amended to allow the addition of up to 2 cohorts (up to 15 patients each) of T2DM patients to enable assessment of doses up to 15 mg through dose titration.

5.2. Number of Participants

Approximately 143 healthy subjects and up to approximately 55 patients with T2DM may be enrolled so that approximately 112 healthy subjects and up to approximately 40 patients complete the study.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

Safety and tolerability assessments will be made over all dose levels. Although only a modest glucose-lowering effect is expected in healthy subjects due to LY3298176 action on glucose-dependent insulin secretion, a preliminary assessment of the PD effects of LY3298176 will be based on gastric emptying (acetaminophen test) and insulin response following oral glucose tolerance tests (OGTTs).

The study is intended to estimate a maximum-tolerated dose (MTD) or establish that doses exceeding the expected therapeutic dose are tolerated. Preliminary PK, PD, safety, and tolerability data in healthy subjects and patients with T2DM will assist in identifying an appropriate dose range for subsequent clinical studies.

To establish a quantitative range for the GLP-1 pharmacology, dulaglutide will be used as a positive control and placebo will also be used as a comparator to allow interpretation of PD, safety, and tolerability data.

5.5. Justification for Dose

The planned doses in this study are selected to provide a full evaluation of the safety and tolerability of LY3298176 at doses ideally 3-fold beyond the expected therapeutic dose range to allow characterization of the PK and preliminary assessment of the PD effects of LY3298176 in the target patient population over a wide dose and exposure range to support dose selection in future clinical trials. The anticipated dose-limiting safety and tolerability profile (nausea and vomiting) of LY3298176 has been consistently demonstrated with the GLP-1 drug class.

Based on PK and PK/PD modeling of nonclinical data, the starting dose of 0.25 mg may provide detectable LY3298176 exposure expected to demonstrate minimal to no pharmacological response in healthy subjects in Part A (SAD). Based on the allometry-based projected human exposure, the exposure at the NOAEL from the rat and monkey repeat-dose studies is >10-fold margin of safety to the starting dose of 0.25 mg (Table GPGA.5.1). Furthermore, the starting dose of 0.25 mg is predicted to achieve maximum drug concentration (C_{max}) of approximately 4- and 30-fold below the inhibitory constant (Ki) of GIP and GLP-1 human receptor binding, respectively, based on the in vitro pharmacology studies. Doses at 1 mg or higher are expected to achieve concentrations above these Ki values.

In Part A of the study, the planned dose levels to be evaluated are: 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, and 10 mg.

The clinical dose range to be studied in Part B (MAD) will be selected based on safety, tolerability, and PK data from Part A (SAD). The starting dose planned for Part B (MAD) is 0.25 mg once weekly for 4 weeks. The maximum dose planned is 10 mg.

Doses may be adjusted before each dose escalation in both Part A and Part B based on safety, tolerability, and available PK/PD data during the course of the study. Any changes to the planned dose levels, together with the supporting data, will be reviewed by SRP (refer to Section 5.1). The doses to be evaluated in Part C in patients with T2DM will be selected based

on safety, tolerability, and pharmacology from Parts A and B (SAD and MAD) and reviewed by the SRP.

The margin of safety for SC administration of LY3298176 is presented in Table GPGA.5.1.

Table GPGA.5.1. Margin of Safety for Subcutaneous Administration of LY3298176 Based on Body Surface Area and Predicted Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple to Human Starting Dose	Dose Multiple to Human Maximum Dose[a]	AUC (µg•hr/mL)	Exposure Multiple to Human Starting Dose	Exposure Multiple to Human Maximum Dose
Human starting dose (0.25 mg)	0.0036[b]	0.132	-	-	8.62	-	-
Human maximum dose (10 mg)[b]	0.143[b]	5.29	-	-	345[c]	-	-
Rat NOAEL[d]	1.5	8.85	67	1.67	134[h]	27[e]	0.68[e]
Monkey NOAEL[f]	0.15	1.80	14	0.34	115[i]	13[g]	0.33[g]

Abbreviations: AUC = area under the plasma concentration versus time curve; AUC(0-96) = AUC from time 0 to 96 hours; AUC(0-168) = AUC from time 0 to 168 hours; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetic.

a Dose multiple is calculated as dose in animals (mg/m^2)/dose in humans (mg/m^2).

b Typical body weight of 70 kg was assumed for a healthy subject.

c Plasma PK parameters shown were computed based on PK model-predicted LY3298176 concentration-time profile. Dose shown is the highest proposed clinical dose.

d NOAEL determined in a 1-month repeat dose toxicity study (Study 8325822).

e Exposure multiple is calculated as the ([AUC(0-96) in rats]/96 hr)/([AUC(0-168) in humans]/168 hr).

f NOAEL determined in a 1-month repeat dose toxicity study (Study 82325823).

g Exposure multiple is calculated as the ([AUC(0-168) in monkeys]/168 hr)/([AUC(0-168) in humans]/168 hr).

h Animal AUC(0-96) is mean Male + Female from Study 8325822, Day 29 toxicokinetic data.

i Animal AUC(0-168) is mean Male + Female from Study 8325823, Day 29 toxicokinetic data.

Protocol Amendment (f)

Healthy subjects were given single doses up to 8 mg near the limits of tolerability in Part A, and 4 fixed weekly doses of 0.5 mg, 1.5 mg, and 4.5 mg and up to 10 mg as part of a titration scheme in Part B. The limits of tolerability were not reached in either Part A or B of this study. In Part C, LY3298176 was given to patients with T2DM in a fixed 5-mg weekly dose cohort and a titration cohort of 5 mg, 5 mg, 10 mg, and 10 mg over 4 weekly doses. Based on better tolerability of LY3298176 in T2DM patients compared with healthy subjects and updated margins of safety based on human exposure data from Parts A and B of this study (see Table GPGA.5.2), the protocol is amended to evaluate a maximum dose of LY3298176 up to 15 mg in T2DM patients as part of up to 2 additional titration schemes in Part C of this study.

Table GPGA.5.2. Updated Margin of Safety for Subcutaneous Administration of LY3298176 Based on Preliminary Human PK Data

	Dose (mg/kg)	Dose (mg/m^2)	AUC (µg•hr/mL)	Exposure Multiple to Human Starting Dose	Exposure Multiple to Human Maximum Dose
Human maximum dose (15 mg)[b]	0.214[b]	7.92	342[c]	-	
Rat NOAEL[d]	1.5	8.85	134[h]		0.68[e]
Monkey NOAEL[f]	0.15	1.8	115[i]		0.33[g]

Footnote: Refer to Table GPGA.5.1.

6. Study Population

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

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

Screening may occur up to 28 days before enrollment. However, the screening period will be longer for patients with T2DM treated with sulfonylureas; these patients will be required to stop their treatment and have a 6-week washout period before dosing with study drug. Patients/subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

6.1.1. All Study Participants

[1] are overtly healthy males or females, as determined by medical history and physical examination (Parts A and B only) or have T2DM diagnosed at least 1 year before enrollment (Part C only)

[1a] male patients/subjects:

agree to use an effective method of contraception for the duration of the study and for 3 months following the last dose of investigational product

[1b] female patients/subjects:

women 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

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

OR

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

[2] are males or females between the ages of 21 and 70 years, inclusive

[3] have a screening body mass index of >18.5 and ≤40.0 kg/m^2 (healthy subjects) or ≥25 kg/m^2 (T2DM patients), inclusive

[4] have clinical laboratory test results within the normal range for the population or investigator site, or with abnormalities deemed clinically insignificant by the investigator

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

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

[7] have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site

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

6.1.2. Patients with T2DM (Part C only)

Patients are eligible for enrollment in Part C of the study only if they meet all of the following additional criteria:

[9] have T2DM controlled with diet and exercise alone or are stable on a single oral antidiabetic medication (metformin for at least 8 weeks or sulfonylureas). However, patients receiving sulfonylureas may participate only if this treatment is stopped for at least 6 weeks before dosing with study drug

[10] are taking stable doses of over-the-counter or prescription medications (for example, antihypertensive agents, aspirin, lipid-lowering agents) for treatment of concurrent medical conditions are permitted to participate providing they have been stable on their treatment regimen for at least 4 weeks

[11] have an hemoglobin A1c (HbA1c) ≥7.0% and ≤11.0%, and for the patients who have washed off of sulfonylureas, HbA1c ≥7.0% and ≤8.5%, at the screening visit

[12] have abnormalities of serum glucose, serum lipids, urinary glucose, and urinary protein consistent with T2DM are acceptable

6.2. Exclusion Criteria

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

6.2.1. All Study Participants

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

[14] are Lilly employees

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

[16] have known allergies to LY3298176, GLP-1 analogs, or related compounds, or acetaminophen (Parts B and C only)

[17] are persons who have previously completed or withdrawn from this study

[18] have a significant history of or current cardiovascular (for example, myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolis, etc), respiratory, hepatic, renal, gastrointestinal (GI), endocrine (except T2DM patients), hematological (including history of thrombocytopenia), or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs or of constituting a risk when taking the study medication or interfering with the interpretation of data

[19] have a history of heart block or a PR interval >200 msec or any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study

[20] intended use of over-the-counter or prescription medications 7 and 14 days before planned dosing (Parts A and B, respectively) and 4 weeks before planned dosing (Part C), apart from occasional intake of vitamin/mineral supplements, allowable antiemetics, and acetaminophen 14 days before the first dose. If this situation arises, inclusion of an otherwise suitable patient/subject may be at the discretion of the investigator (refer to Section 7.7)

[21] have a history of drug or alcohol abuse

[22] evidence of hepatitis B or positive hepatitis B surface antigen and/or evidence of hepatitis C or hepatitis C antibody (United States [US] only) (at screening)

[23] evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies (at screening)

[24] blood donation of 450 mL or more in the last 3 months or any blood donation within the last month from screening

[25] have an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females) (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits), or patients/subjects unwilling to stop alcohol consumption 24 hours before dosing until discharge from the CRU

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

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

[28] have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase (>1.5-fold the upper limit of normal [ULN]) or GI disorder (for example, relevant esophageal reflux or gall bladder disease) or any GI disease which impacts gastric emptying (for example, gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs or DPP-IV inhibitors. Patients with dyslipidemia, and patients who had cholecystolithiasis (removal of gall stones) and/or cholecystectomy (removal of gall bladder) in the past, with no further sequelae, may be included in the study at the discretion of the investigator

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

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

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

[32] are deemed unsuitable by the investigator for any other reason

[38] have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2x the ULN or total bilirubin >1.5x ULN

[39] have a history of malignancy within five years prior to screening

[40] have serum triglyceride (TG) ≥5 mmol/L (442.5 mg/dL) at screening

6.2.2. Patients with T2DM (Part C only)

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

[33] have taken any glucose-lowering medications other than metformin and or sulfonylureas (refer to inclusion criterion [9]), including insulin, in the past 3 months before screening

[34] have had more than 1 episode of severe hypoglycemia, as defined by the American Diabetes Association criteria, within 6 months before entry into the study or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any patient that cannot communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia prior to the first dose of study drug should also be excluded

[35] impaired renal function (serum creatinine >124 µmol/L [1.4 mg/dL] in women, >133 µmol/L [1.5 mg/dL] in men, or estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) in patients with T2DM on metformin

[36] have had a blood transfusion or severe blood loss or have known hemoglobinopathy (alpha-thalassemia), 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

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

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Patients/subjects will be required to fast overnight for at least 8 hours before taking a SC dose of LY3298176 (or placebo) on Day 1 (Part A) and Days 1, 8, 15, and 22 (Parts B and C), and for each subsequent study day when clinical safety laboratory and PD samples are taken and OGTTs are administered. Water may be consumed freely. Standard meals will be administered in the CRU.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed at least 24 hours before each CRU admission and each outpatient visit and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 3 units for males and 2 units for females (a unit is defined in Exclusion Criterion [25], Section 6.2.1). No nicotine use will be permitted while at the CRU. While not resident in the CRU, patients/subjects must consume no more than 10 cigarettes or equivalent per day. Patients/subjects will be allowed to maintain their regular caffeine consumption throughout the study period.

6.3.3. Activity

Patients/subjects 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/subjects may be required to remain recumbent or sitting.

6.4. Screen Failures

Subjects who do not meet the criteria for participation in this study (screen failure) may not be rescreened; however, T2DM patients in Part C may be rescreened once. The interval between rescreenings should be at least 2 weeks. Each time rescreening is performed, the patient must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

CCI [redacted] Doses will be dispensed in accordance with the randomization scheme provided by the sponsor. Patients/subjects assigned to placebo treatment will receive SC injections of normal saline with the volume matching the investigational drug at each dose level. Please refer to the pharmacy binder for detailed instructions.

Dulaglutide will be provided as a 1.5-mg/0.5-mL single-use pen. Dulaglutide will be injected subcutaneously into the abdomen.

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

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

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the patient/subject/site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product dispensing and collection,
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if during the investigative site selection the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

7.1.1. Packaging and Labeling

Materials for this study are as follows:

- LY3298176 will be provided in a vial and provided in a carton.
- Placebo will be provided as sodium chloride (saline) in a vial.
- Dulaglutide will be provided in a carton with 4 single-dose pens per carton.

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

7.2. Method of Treatment Assignment

For Parts A and B, randomization tables for allocation of LY3298176, dulaglutide, or placebo will be prepared by the statistician for the study and provided to the site pharmacists involved in dose preparation. For Part C, patients will be assigned to LY3298176 or placebo by a computer-generated, randomized sequence using an interactive web response system (IWRS). The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained by the site pharmacist.

7.2.1. Selection and Timing of Doses

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

7.3. Blinding

For LY3298176 and placebo, the dosing is a patient-/subject- and investigator-blind. Dulaglutide dosing will be open-label. To preserve the blinding of the study for LY3298176 and placebo, all study site personnel, except pharmacy staff who prepare and dispense study medication, will be blinded to treatment allocation.

Blinding of LY3298176 and placebo will be maintained throughout the conduct of the trial until all data are cleaned to an acceptable level of quality and locked. The details are included in the blinding/unblinding plan.

The site pharmacist who prepares and dispenses study medication will receive a randomization table for Parts A and B, and use of an IWRS for Part C, with treatment codes to enable preparation of blinded placebo doses. The pharmacist will assign treatment.

If a patient's/subject's study treatment assignment (LY3298176 or placebo) is unblinded, the patient/subject must be discontinued from the study unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician for the study participant to continue in the study.

For Parts A and B, emergency codes will be available to the investigator. A code, which reveals the treatment group for a specific study patient/subject, may be opened during the study only if the patient's/subject's well-being requires knowledge of the patient's/subject's treatment assignment. For Part C, unblinding of study drug treatment will be conducted through the use of an IWRS. Site personnel will be able to unblind patient treatment at any time using the IWRS.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's/subject's treatment assignment is warranted for medical management of the event. Patient's/subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical pharmacologist or clinical research physician before unblinding a study patient's/subject's treatment assignment unless this could delay emergency treatment of

the patient/subject. If a study patient's/subject'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. Dose Modification

Dose levels or increments, sampling schedule, and length of CRU stay may be adjusted in view of emerging safety or PK data during the study. Dose increments may be reduced (but not increased), a dose level may be repeated, or a lower dose may be administered. Dose escalations will not exceed a half-log (3.3-fold) increase in dose. The timing of the sampling may be adjusted, but the number of samples will not increase. The duration of the CRU stay or the duration of safety follow-up may be increased (for example, if the half-life of LY3298176 is longer than anticipated) but not decreased. These changes must be appropriately documented and communicated by the sponsor to the investigator. Because these adjustments to timings or dose levels are allowable changes permitted by the protocol, they would not require a protocol amendment. However, any changes to the planned dose levels, together with the supporting data, will be reviewed by an SRP (refer to Section 5.1).

There will not be any dose modifications of dulaglutide.

7.5. Preparation/Handling/Storage/Accountability

All clinical trial material provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the investigational products will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained.

Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer study treatment. All study treatments should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

7.6. Treatment Compliance

The investigational product will be administered at the clinical site and documentation of treatment administration will occur at the site.

Every attempt will be made to select patients/subjects who have the ability to understand and comply with instructions. No doses can be missed. Noncompliant patients/subjects may be discontinued from the study and may be replaced upon consultation with Lilly clinical pharmacologist. The time and day of drug administration will be recorded. Drug accountability records will be maintained by the study site.

The specifications in this protocol for the timings of safety, PK, and PD sampling are given as targets and are to be achieved within reasonable limits. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

Failure to obtain samples due to clinical issues, such as problems with venous access or the patient/subject does not show up for a visit, will not be considered protocol violations. However, the site will still be required to notify the sponsor in writing to account for missing samples for data reconciliation purpose.

Any major modifications that might affect the conduct of the study, patient/subject safety, and/or data integrity will be detailed in a protocol amendment.

7.6.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is determined or stopping criteria have been met.

Safety data will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK or PD results will be used as supporting data for dose escalation, but such data are not required. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist.

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

After review of these data, escalation to the next dose level will be made by the investigator and sponsor. The magnitude of the dose escalation may be reduced (as low as 2-fold from the previous dose) following data review, but subsequent escalations cannot be increased by more than approximately 3-fold (a half-log increment) or dose levels may be repeated.

Based on tolerability data, a dose-titration regimen may be evaluated in Part B or C.

The dose escalation and further dosing at the same dose level will be terminated if 1 treatment-related SAE (unless due to anticipated pharmacology of LY3298176, for example, hypoglycemia in healthy subjects or T2DM) or 2 clinically significant events (CSEs) are reported or; ≥40% of patients/subjects in a dose level experience a symptomatic hypoglycemic episode with blood glucose values ≤2.8 mmol/L (50 mg/dL; corresponding to plasma glucose levels of ≤3.1 mmol/L [56 mg/dL]) and these events are deemed to be related to LY3298176 administration occur.

Additionally, the dose-escalation and further dosing at the same dose level will be terminated if ≥2 subjects experience an acute pancreatitis event as defined in Appendix 5.

Examples of unrelated events could include but are not limited to: events occurring before LY3298176 dosing; events experienced after receiving placebo; personal injury accidents that were not a result of hemodynamic changes or neurological symptoms (dizziness, visual

disturbance, numbness, loss of muscle control); events resulting from viral or bacterial infections; or changes in clinical chemistry or liver enzymes as a result of documented acute viral hepatitis, alcohol, or other hepatotoxic drug use.

Appendix 7 presents examples of AEs that are reasonably anticipated due to disease state and may not be considered related to LY3298176.

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

Dosing may continue, if deemed appropriate by the investigator, at doses lower than those resulting in termination of the escalation.

7.7. Concomitant Therapy

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

If the need for new or changes to concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator, preferably after consultation with a Lilly clinical pharmacologist or clinical research physician. Stable doses (refer to Section 6) of over-the-counter or prescription medications (for example, antihypertensive agents, aspirin, lipid-lowering agents) for treatment of concurrent medical conditions are allowed.

No start of new concomitant therapy, apart from occasional intake of vitamin/mineral supplements, allowable antiemetics, and acetaminophen, will be permitted for 14 days before the first dose of LY3298176 through the final poststudy follow-up visit. In the case of mild intercurrent illness during the study, concomitant treatment with paracetamol/acetaminophen may be allowed at the discretion of the investigator. This will be recorded in the CRF. However, acetaminophen should not be allowed after midnight and throughout the rest of the day on the day of the gastric-emptying test. Additional concomitant medications for treatment of T2DM are not permitted during the study.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. Any drug given for the treatment of an AE should be documented as such.

7.8. Treatment after the End of the Study

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

- lipase and/or amylase are confirmed to be ≥3X ULN. Please refer to algorithm for the monitoring of pancreatic events in Appendix 5.

The criteria for enrollment must be followed explicitly. If a patient/subject who does not meet enrollment criteria is inadvertently enrolled, that patient/subject is discontinued from the investigational product but may be allowed to continue in the study to provide the follow-up data.

Patients/subjects who discontinue the investigational product early will have procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients/Subjects

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

8.2. Discontinuation from the Study

Patients/subjects will be discontinued in the following circumstances:

- 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
- 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/subject should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of T2DM, discontinuation from the study occurs before introduction of the new agent
- patient/subject decision
    - the patient/subject or designee, (for example, parents or legal guardian) requests to be withdrawn from the study

- adverse event
    - if a CSE occurs, the investigational product is to be discontinued and appropriate measures taken. Lilly or its designee should be alerted immediately. A CSE will be defined as a moderate-to-severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the patient/subject
    - a clinically significant systemic hypersensitivity reaction occurs following administration of the investigational product (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction
- at the discretion of the investigator, if the participant has 2 or more symptomatic hypoglycemic episodes (defined as an event with typical hypoglycemic symptoms and a measured blood glucose ≤63 mg/dL [3.5 mmol/L], equivalent to plasma glucose ≤70 mg/dL [3.9 mmol/L], refer to Section 9.4.8.3)
- fasting plasma glucose values are >270 mg/dL (approximately 15 mmol/L, equivalent to a fasting blood glucose >241 mg/dL [13.4 mmol/L]) on 3 or more separate days over any 2-week period between screening and the end of the dosing period

Following the investigator's determination that CSE criteria have been met and after the investigator's judgment of relatedness to the investigational product is documented, a decision will be made between the investigator and Lilly or its designee regarding patient/subject discontinuation.

The nature of any conditions, clinical signs or symptoms, or abnormal laboratory values present at the time of discontinuation and any applicable follow-up procedures will be documented.

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

8.3. Patients/Subjects Lost to Follow-up

A patient/subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients/subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

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

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

Appendix 6 provides a summary of the maximum number and volume of invasive samples for all sampling during the study.

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

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients/subjects 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/subject.

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

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 caused the patient/subject to discontinue the investigational product before completing the study. The patient/subject 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.

After the ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each patient's/subject's preexisting conditions including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- events considered significant by the investigator based upon appropriate medical judgment

When a condition related to the dulaglutide single-use pen necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious criterion of "required intervention" will be assigned.

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

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

Investigators are not obligated to actively seek AEs or SAEs in patients/subjects once they have discontinued from and/or completed the study (the patient/subject summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient/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.

Pregnancy (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.

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. US 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.

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

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

Refer to the IB for LY3298176 and package insert for dulaglutide.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Study Schedule and as clinically indicated (Section 2).

9.4.3. Vital Signs

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

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

If orthostatic measurements are required, patients/subjects should be supine for approximately 5 minutes and stand for at least 3 minutes. If the patient/subject feels unable to stand, supine vital signs only will be recorded.

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

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

9.4.3.1. Body Weight

Weight will be measured as indicated in the Schedule of Activities (Section 2). Patients/subjects will be weighed in light clothing at approximately the same time in the morning before dosing and after an overnight fast and evacuation of bowel and the bladder, if possible. During the treatment period, weight will be measured twice on each scheduled occasion, with the patient/subject stepping off the scale between measurements. Both weight measurements will be recorded in the source document and the CRF. Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will not be moved or recalibrated.

9.4.4. Electrocardiograms

For each patient/subject, ECGs should be collected according to the Schedule of Activities (Section 2).

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

For each patient/subject, a single ECG will be collected at screening, Day 29 (Part A only), and follow-up according to the Schedule of Activities (Section 2). At all other scheduled times, consecutive replicate ECGs will be obtained in triplicate at approximately 1-minute intervals. ECGs (single) may be obtained at additional times when deemed clinically necessary (for example, to assess patient/subject safety). Collection of more ECGs (more replicates) than expected at a particular time point is allowed to ensure high quality records.

ECGs must be recorded before collecting any blood for safety or PK tests. Patients/subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

ECGs will 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/subject is still present to determine whether the patient/subject meets entry criteria at the relevant visit(s) and for immediate patient/subject management should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will assess the patient/subject for symptoms (for example, palpitations, near syncope, syncope)

to determine whether the patient/subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient/subject 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. Any new clinically relevant finding should be reported as an AE.

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

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

9.4.5. Safety Monitoring

The Lilly clinical pharmacologist or clinical research physician/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or research physician will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate and periodically review:

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

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3X ULN at any visit posttreatment sequence allocation even if the patient/subject is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Appendix 5) and, if pancreatitis is suspected, the case will be further defined during an adjudication process. Any patient/subject who develops symptoms of pancreatitis must not receive further administration of LY3298176.

To ensure patient/subject safety and compliance with regulatory guidance, the investigator is to consult with the Lilly designated clinical research physician regarding collection of specific recommended clinical information and follow-up laboratory tests.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the unblinding/blinding plan.

9.4.6. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected to determine antibody production against the investigational product. Additional samples may be collected if there is a possibility that an AE is immunologically mediated. Immunogenicity will be assessed by a validated assay designed to detect antidrug antibodies (ADAs) in the presence of the investigational product. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the investigational product.

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

9.4.7. Hypersensitivity Reactions

All hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Dosing should be temporarily discontinued in any individual suspected of having a severe or serious allergic/hypersensitivity reaction to investigational product. Investigational product 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 dosing is permanently discontinued, the patient/subject should remain in the study as needed per medical judgment.

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

9.4.7.1. Injection-Site Reactions

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

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

9.4.8. Glucose Monitoring

9.4.8.1. Part A

Blood glucose will be monitored for safety according the Schedule of Activities (Section 2).

9.4.8.2. Parts B and C

Patients/subjects will be instructed on how to use the glucose meter provided by the site and conduct self-blood glucose monitoring tests. In addition to the glucose monitoring and fasting glucose measurements, patients/subjects will be educated on the symptoms of hypoglycemia.

Throughout their participation in the study, patients/subjects will monitor blood glucose levels. Patients/subjects will be provided a diary card and instructed to record blood glucose results premeal and bedtime on at least 3 days per week during the dosing phase of the study and whenever the patient/subject experiences symptoms of hypoglycemia. Investigator review of glucose results clinically indicative of hypoglycemia or hyperglycemia is required.

Additionally, patients with T2DM (Part C) who were taking sulfonylureas at screening will be required to monitor their glucose during the 6-week washout period.

9.4.8.3. Hyperglycemia and Hypoglycemia Reporting

Episodes of hyperglycemia (fasting plasma glucose >270 mg/dL [15 mmol/L], equivalent to a fasting blood glucose >241 mg/dL [13.4 mmol/L]) or hypoglycemia (blood glucose ≤63 mg/dL [3.5 mmol/L], equivalent to plasma glucose 70 mg/dL [3.9 mmol/L]) will be reported by the investigator or designated physician who will be responsible for advising the patient/subject on what further actions to take. Additional monitoring may be requested at the investigator's discretion.

If the fasting glucose during the dosing period exceeds the acceptable level defined as hyperglycemia on 3 or more separate days over any 2-week period between screening and the end of the dosing period, the patient/subject will be evaluated further at the study site. If fasting glucose continues to exceed the acceptable level, study drug will be discontinued and treatment with an appropriate antidiabetic agent may be initiated by the investigator for patients with T2DM. The patient will continue to be followed in the study (for safety, PK, and immunogenicity assessment) for at least 28 days after his/her last dose. If hyperglycemia occurs during the follow-up period, the patient will remain in the study until completion of the planned follow-up.

Hypoglycemia episodes will be recorded on specific CRF pages. Hypoglycemia will be treated appropriately by the investigator and additional monitoring of blood glucose levels may be performed. The following definitions of the American Diabetes Association (ADA) and Endocrine Society Workgroup on Hypoglycemia and Diabetes (Seaquist et al. 2013) should be applied for reporting in the CRF and evaluating hypoglycemic events:

- **Severe Hypoglycemia:** An event during which the patient requires 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.
- **Documented Symptomatic Hypoglycemia:** An event during which typical symptoms of hypoglycemia are accompanied by a measured blood glucose concentration ≤63 mg/dL (3.5 mmol/L), equivalent to plasma glucose 70 mg/dL (3.9 mmol/L).

- **Asymptomatic Hypoglycemia:** An event not accompanied by typical symptoms of hypoglycemia but with a measured blood glucose concentration ≤63 mg/dL (3.5 mmol/L), equivalent to plasma glucose 70 mg/dL (3.9 mmol/L).
- **Probable Symptomatic Hypoglycemia:** An event during which symptoms of hypoglycemia are not accompanied by a blood glucose measurement but that was presumably caused by a blood glucose concentration ≤63 mg/dL (3.5 mmol/L), equivalent to plasma glucose 70 mg/dL (3.9 mmol/L).
- **Relative Hypoglycemia:** An event during which the patient reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia but with a measured blood glucose concentration >63 mg/dL (3.5 mmol/L), equivalent to plasma glucose 70 mg/dL (3.9 mmol/L).

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

9.4.9. Nausea and Vomiting

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

9.4.10. Elevated Lipase or Amylase

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing at time points specified in the Schedule of Activities (Section 2). Additional measurements may be performed at the investigator's discretion. Further diagnostic assessments will be recommended as per the algorithm (refer to Appendix 5) for the monitoring of pancreatic events whenever lipase and/or amylase is confirmed to be ≥3X ULN at any visit postrandomization, even if the patient/subject is asymptomatic.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 5 mL each will be collected to determine the plasma concentrations of LY3298176. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

9.5.1. Bioanalysis

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

Concentrations of LY3298176 will be assayed using validated liquid chromatography mass spectrometry (LC/MS) method. Analyses of samples collected from placebo-treated patients/subjects are not planned.

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

9.6. Pharmacodynamics

Preliminary assessment of LY3298176 pharmacology in healthy subjects in Part B will be evaluated based on glucose and insulin from the OGTT and acetaminophen for gastric emptying. LY3298176 PD assessment in patients with T2DM (Part C) may include fasting glucose, insulin, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, body weight, area under the concentration versus time curves (AUCs) for glucose, insulin associated with the OGTT, and acetaminophen for gastric emptying. Additional exploratory PD analysis may be analyzed as deemed appropriate.

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

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

9.6.1. Glucose Samples

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

9.6.1.1. Oral Glucose Tolerance Test (Parts B and C)

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

Patients/subjects shall maintain adequate carbohydrate intake 3 days before the scheduled OGTT. Patients/subjects shall fast for approximately 8 hours overnight before administration of the OGTT. A 75-gram glucose dose will be given orally. Patients should consume the glucose

load within 5 minutes. If patients develop symptoms of hypoglycemia, bedside blood glucose concentration may be measured and the patient will be treated per investigator discretion. Blood samples will be drawn for assessment of glucose and insulin pretest and at 0.5, 1, 1.5, and 2 hours after the initiation of the glucose load.

9.6.1.2. 7-Point Glucose Monitoring (Parts B and C)

Patients/subjects will be asked to perform a 7-point blood glucose profile according to the Schedule of Activities (Section 2). Patients will be asked to test their self-monitored blood glucose levels before each meal, approximately 2 hours after each meal, and at bedtime. Patients/subjects will be asked to record their self-monitored blood glucose levels in their diaries according to instructions. The complete 7-point blood glucose profile must be completed 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 except for the predose baseline on Day -2 that will need to be completed on that same day to avoid interference with the OGTT that will be administered on the subsequent day.

9.6.2. Gastric Emptying (Parts B and C)

Acetaminophen is a well-established marker for the rate and extent of gastric emptying (Young 2005). It is rapidly absorbed from the duodenum upon release from the stomach. A delay in gastric emptying is reflected in the alterations to the concentration-time profile of acetaminophen, specifically, decreasing its C_{max} and T_{max} without altering the extent (total drug amount) absorbed. A dose of approximately 1 g acetaminophen is considered to be sufficient for bioanalytical detection and will be administered on Day -1 and about 24 hours after first and fourth LY3298176 doses in Part B and Part C (refer to Schedule of Activities [Section 2]). The acetaminophen dose should be given soon after the 75-g glucose dose for the OGTT.

Venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of acetaminophen.

9.6.2.1. Bioanalysis

Concentrations of acetaminophen will be assayed using validated LC/MS method. Analyses of samples collected from placebo-treated patients/subjects are not planned.

9.6.3. Bone Biomarkers

To investigate the effects of LY3298176 on bone metabolism (absorption and resorption) following multiple doses in T2DM (Part C), the following biomarkers will be assessed: serum carboxy-terminal telopeptide fragments of Type I collagen (CTX-1), N-terminal propeptide of Type I collagen (P1NP), and osteocalcin.

9.7. Genetics

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

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

investigate genetic variants thought to play a role in T2DM and related complications. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

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

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

9.8. Biomarkers

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

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

Samples will be used for research on the drug target, disease process, variable response to LY3298176, pathways associated with T2DM, mechanism of action of LY3298176, and/or research method, or for validating diagnostic tools or assay(s) related to T2DM.

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

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

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 143 healthy subjects may be enrolled in Parts A and Part B to achieve the objectives of each part of the study. Approximately 25 T2DM patients may be enrolled in Part C to achieve study objectives. The replacement patient/subject will be assigned to receive the treatment of the dropout.

For each study part, any dropout may be replaced so that the targeted numbers of patients/subjects for safety review and data collection may be achieved. The replacement patient/subject will be assigned to receive the treatment of the dropout.

The sample sizes for each part of the study were chosen to provide adequate placebo control for each dosing occasion and are considered sufficient to evaluate the primary objective of this study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

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

PK and PD analyses will be conducted on the full analysis set. This set includes all data from all enrolled patients/subjects receiving at least 1 dose of the study drug according to the treatment the patients/subjects actually received. Safety analyses will be conducted for all enrolled patients/subjects whether or not they completed all protocol requirements.

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

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur before the first study drug dosing will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters.

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

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

ECG parameters, including the PR, QT, RR, and QTc using Fridericia's formula (QTcF) intervals, QRS duration, and heart rate, will be summarized. The number and percentage of patients/subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment group according to the following categories: >30 msec and >60 msec. In addition, the number and percentage of patients/subjects with QTcF postdose values according to the following categories: >450 msec, >480 msec, and >500 msec, will be summarized by treatment group. Analyses may be performed to determine the effects of PK and PD parameters on QTcF.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3298176 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max}, AUC, and T_{max} of LY3298176. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported. If deem necessary, additional model-based analysis may be performed.

10.3.2.2. Pharmacokinetic Statistical Inference

For single- and multiple-dose parts of the study, PK dose proportionality will be assessed separately. Log-transformed C_{max} and AUC of LY3298176 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% confidence intervals (CIs). The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will

be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach.

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

For Parts A, B, and C, all PK parameters will be summarized using descriptive statistics.

10.3.3. Pharmacodynamic Analyses

Inferences will be sought regarding the ability of LY3298176 to reduce fasting or dynamic glucose together with the effects on insulin. Such effects will be explored over different doses of LY3298176.

10.3.3.1. Pharmacodynamic Parameter Estimation

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

The parameter estimates for acetaminophen will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be the C_{max}, the AUC, and the T_{max} of acetaminophen. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

10.3.3.2. Pharmacodynamic Statistical Inference

The PD parameters from each part of the study will be analyzed separately. PD parameters from placebo-treated patients/subjects within each part of the study will be pooled for the final analysis. PD parameters may be transformed before statistical analyses, if deemed necessary. Absolute values as well as change from baseline in each parameter will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The model will include treatment, day, and treatment-by-day interaction as fixed effects and patient/subject as a random effect. Baseline (Day −1) values, as well as other influencing variables, may be used as covariates. The main comparisons will be between each LY3298176-treated group and placebo group.

Baseline-adjusted C_{max} of acetaminophen (ratio to Day -1 value) will be calculated and log-transformed to compare the gastric emptying effect of LY3298176 to that of dulaglutide. An MMRM with treatment, day, and treatment-by-day interaction as fixed effects, patient/subject as random effect, and baseline (Day -1) as covariate will be used to perform the analysis. Least-squares means as well as 95% CIs will be reported.

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

All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment group and day. Summary statistics will be provided.

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

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

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

10.3.5. Evaluation of Immunogenicity

The frequency of antibody formation to LY3298176 will be determined. If a neutralization assay is performed, the frequency of neutralizing antibodies will be determined. The relationship between the presence (or absence) of antibodies and clinical parameters (for example, AEs, efficacy measures) will be assessed. Likewise, the relationship between the presence of antibodies and the PK parameters and PD response to LY3298176 will be assessed.

10.3.6. Interim Analyses

The Lilly sponsor team is unblinded. Data may be analyzed while the trial is ongoing. An assessment committee will not be formed.

Access to the data is scheduled to occur after every dosing session. The purpose of these reviews is to review the safety data for the next dosing session. The investigator and the Lilly sponsor team will make the determination regarding dose escalation based upon their review of the safety and tolerability data. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

The first interim analysis supporting initiation of the MAD portion of the study (Part B) will be based on review of safety and PK data from Day 8 of the second SAD dose level and safety data through Day 8 of the third SAD dose level. These data may be used to update PK sampling times and dose selection for the remaining cohorts. The second interim analysis supporting initiation of Part C will be based on available data from Part B (MAD).

The third interim analysis will include data through Day 29 of the highest MAD dose level (Part B) and Day 29 of the T2DM cohort (Part C), excluding ADA assessment. The data will include but are not limited to available safety, PK of LY3298176 and acetaminophen (Parts B and C only), and OGTT (Parts B and C only).

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AUC	area under the concentration versus time curve
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient/subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient/subject are not. A double-blind study is one in which neither the patient/subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BP	British Pharmacopeia or blood pressure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF	case report form
CRU	clinical research unit
CSE	clinically significant event

CTX-1	carboxy-terminal telopeptide fragments of Type I collagen
DPP	dipeptidyl peptidase
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient/subject to a treatment. Patients/subjects who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients/subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a patient/subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's/subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product (IP)	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.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IWRS	interactive web response system

Ki	inhibitory constant
LC/MS	liquid chromatography mass spectrometry
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient/subject, to the patient/subject's participation in the clinical trial.
MAD	multiple-ascending dose
MMRM	mixed-model repeated-measure
MTD	maximum-tolerated dose
NOAEL	no-observed-adverse-effect level
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical trial, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
OGTT	oral glucose tolerance test
P1NP	N-terminal propeptide of Type I collagen
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QTc	QT corrected for heart rate
QTcF	QTc using Fridericia's formula
SAD	single-ascending dose
SAE	serious adverse event
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 trial.
SRP	Safety Review Panel
SUSARs	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus
T_{max}	time to C_{max}

ULN	upper limit of normal
US	United States
USP	US Pharmacopeia

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology	**Clinical Chemistry (fasting)**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Serum creatinine
Mean cell hemoglobin concentration	Calcium
Leukocytes (WBC)	Phosphorus
Absolute counts of:	Glucose, fasting
Neutrophils	Blood urea nitrogen
Lymphocytes	Uric acid
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
Platelets	Alkaline phosphatase
	Alanine aminotransferase
Urinalysis	Aspartate aminotransferase
Specific gravity	Lipase, fasting
pH	Amylase
Protein	Triglyceride[b]
Glucose	Total cholesterol[b]
Ketones	
Bilirubin	**Serology[c]**
Urobilinogen	Follicle-stimulating hormone[a]
Blood	Hepatitis B surface antigen
Leukocytes	Hepatitis C antibody[d]
Microscopy[a]	HIV antibody
	Pregnancy test (urine, serum)[e]
	Drug and alcohol screen[f]

Abbreviations: HIV = human immunodeficiency virus; RBC = red blood cells, WBC = white blood cells.

Note: Results of these assays will be validated by the central or local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

a If clinically indicated, per investigator's discretion.

b Triglyceride and total cholesterol concentrations in the safety panel will not be required on the days that the lipid panel is performed.

c At screening only (unless previously performed within the last 6 months with reports available for review).

d United States only.

e Pregnancy tests (females, as appropriate) will be performed at the investigator's discretion.

f Performed at a local laboratory only at site(s) located in the United States.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient/subject understands the potential risks and benefits of participating in the study.
- ensuring that informed consent is given by each patient/subject 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/subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/subject's willingness to continue his or her participation in the trial.

Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

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

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

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 organization.

Protocol Signatures

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

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

Final Report Signature

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

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

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

Data Quality Assurance

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

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

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

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

Data Collection Tools/Source Data

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

Any data for which paper documentation provided by the patient/subject 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/subject may include, for example, a paper diary to collect patient/subject-reported outcome measures (for example, self-monitored glucose values), a daily dosing schedule, or an event diary.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Clinically Significant Adverse Effects

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

Clinically Significant Adverse Effects

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

Abbreviations: CNS = central nervous system, CSE = clinically significant effect, DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure.

Appendix 5. Pancreatic Monitoring

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

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

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

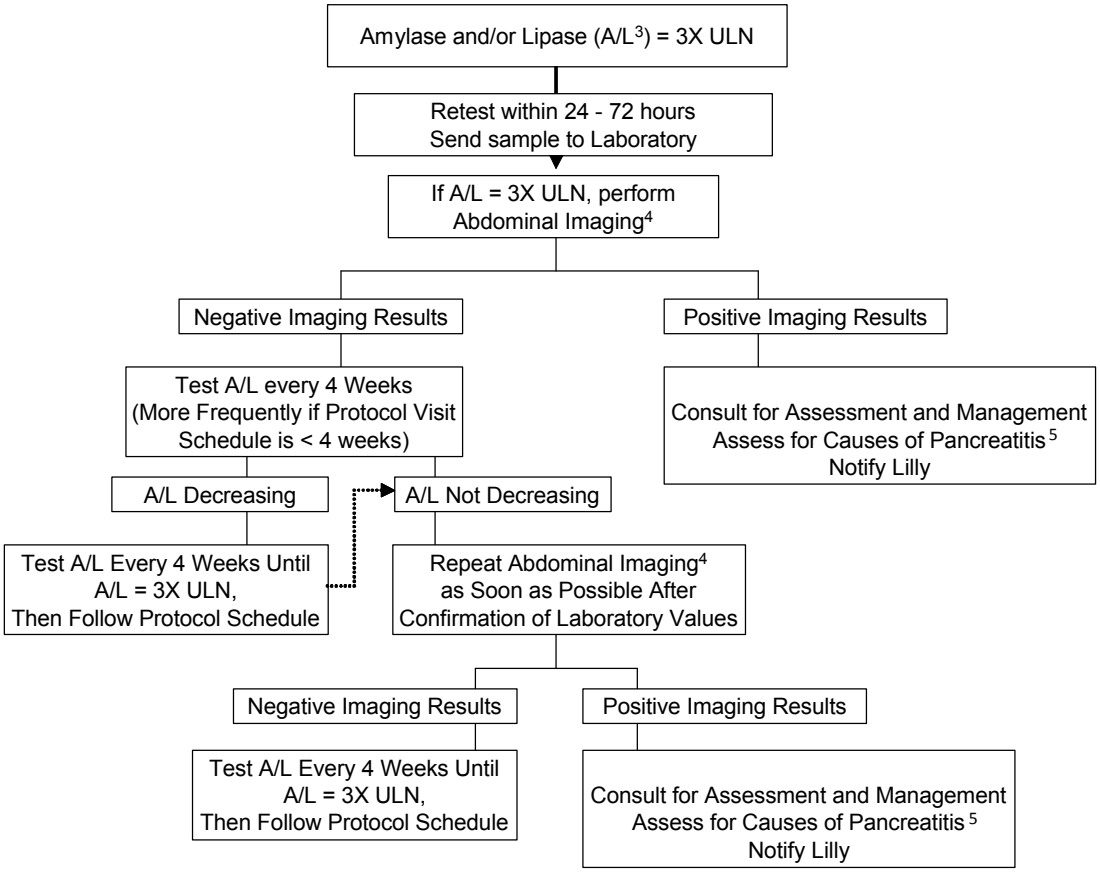
Acute pancreatitis is an AE defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

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

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

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

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



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

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

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

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

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

Abbreviations: GLP = glucagon-like peptide; HV = healthy volunteers; LY = LY3298176; PB = placebo; T2DM = type 2 diabetes mellitus; Wkly = weekly.

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

Appendix 6. Blood Sampling Summary

These tables summarize the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I8F-MC-GPGA Sampling Summary – Part A

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	17	1	17
Clinical laboratory tests[a]	11	6	66
LY3298176 pharmacokinetics	6	11	66
Potential additional LY3298176 pharmacokinetic samples	6	3	18
Blood discard for cannula patency	0.3	5	1.5
Glucose only samples	2	5	10
Point of care safety glucose	0.3	15	4.5
Pharmacodynamics			
Lipids	2.5	2	5
Fasting insulin	2	2	4
Immunogenicity	6	4	24
Pharmacogenetics	10	1	10
Storage sample	10	2	20
Total			246
Total for clinical purposes			250

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

Protocol I8F-MC-GPGA Sampling Summary – Part B

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	17	1	17
Clinical laboratory tests[a]	11	10	110
LY3298176 pharmacokinetics	6	13	78
Potential additional LY3298176 pharmacokinetic samples	6	3	18
Blood discard for cannula patency	0.3	28	8.4
Glucose only samples	2	4	8
Pharmacodynamics			0
Adiponectin	4	3	12
Lipids	2.5	3	7.5
Cortisol	2.5	1	2.5
Oral glucose tolerance test	4	15	60
Acetaminophen	2	33	66
Immunogenicity	6	7	42
Pharmacogenetics	10	1	10
Storage sample	10	5	50
Total			489.4
Total for clinical purposes			490

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

Protocol I8F-MC-GPGA Sampling Summary – Part C

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests[a]	7	10	70
LY3298176 pharmacokinetics	6	13	78
Potential additional LY3298176 pharmacokinetic samples	6	3	18
Blood discard for cannula patency	0.3	28	8.4
Glucose only samples	2	4	8
Pharmacodynamics			0
Adiponectin	4	3	12
Lipids	2.5	3	7.5
Cortisol	2.5	1	2.5
Oral glucose tolerance test	4	15	60
Acetaminophen	2	33	66
Hemoglobin A1c	2	4	8
Bone Biomarkers	8	2	16
Immunogenicity	6	7	42
Pharmacogenetics	10	1	10
Storage sample	10	5	50
Total			481.4
Total for clinical purposes			490

[a] Additional samples may be drawn if needed for safety purposes. Part C laboratory samples will be analyzed at the central laboratory.

Appendix 7. Reasonably Anticipated Serious Adverse Events

Reasonably Anticipated Serious Adverse Events

Indication or Study Population: Type 2 Diabetes Mellitus

Group 1: Anticipated comorbidities expected to be reported as serious adverse events in clinical studies:

- Myocardial infarction (fatal and nonfatal)[a]
- Cerebral vascular accident (fatal and nonfatal)[b]
- Myocardial ischemia[c]
- Peripheral vascular disease[d]
- Infections

Group 2: Events which may or may not be anticipated comorbidities of type 2 diabetes mellitus, may infrequently be reported as serious adverse events in clinical studies:

- Retinopathy[e]
- Nephropathy[f]
- Neuropathy[g]
- Sudden death and cardiovascular death not due to myocardial infarction or stroke
- Cardiac failure
- Diabetic ketoacidosis
- Diabetic foot
- Fractures
- Neoplasia
- Hypoglycemia
- Hyperglycemic hyperosmolar syndrome or state

Examples of terms in the categories above include, but are not limited to:

[a] Acute myocardial infarction, myocardial infarction.

[b] Cerebrovascular accident, stroke, cerebral infarct, ischemic cerebral infarction, ischemic stroke, transient ischemic attack.

[c] Angina, unstable angina, acute coronary syndrome, coronary artery disease, coronary artery bypass graft, percutaneous coronary intervention, coronary angioplasty.

[d] Peripheral vascular disease, diabetic peripheral vascular disease, diabetic vascular disease, carotid endarterectomy, peripheral revascularization.

[e] Blindness, proliferative retinopathy, nonproliferative (background) retinopathy, diabetic retinopathy, retinal laser coagulation, photocoagulation, loss of vision.

[f] Diabetic nephropathy, renal failure, acute renal failure, renal insufficiency. Should not include terms associated with prerenal azotemia due to dehydration.

[g] Peripheral neuropathy, mononeuropathy, autonomic neuropathy, orthostatic or postural hypotension.

Appendix 8. Protocol Amendment I8F-MC-GPGA(f) Summary
A Single- and Multiple-Ascending Dose Study in Healthy Subjects to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176 and Multiple Doses in Patients with Type 2 Diabetes Mellitus

Overview

Protocol I8F-MC-GPGA, A Single- and Multiple-Ascending Dose Study in Healthy Subjects to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176 and Multiple Doses in Patients with Type 2 Diabetes Mellitus, has been amended. The new protocol is indicated by Amendment (f) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Addition of text summarizing preliminary safety and tolerability data from the completed Parts A and B of this study.
- Addition of language to expand the upper end of the dosing range from 10 mg to 15 mg.
- Clarified that patients/subjects may remain at the CRU as needed for safety follow-up based on clinical judgment of the principal investigator.
- Updated numbers of participants enrolled and needed to complete to allow for the addition of up to two additional cohorts.
- Updated the margins of safety table based on human exposure data from Parts A and B of this study.

Revised Protocol Sections

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

3.2 Background

Preliminary safety and tolerability data:

In Part A (single-ascending dose [SAD] portion) of this study, more than 50 healthy subjects received study drug with dosesof LY3298176 ranging from 0.25 mg to 8 mg. Single doses of study drug were generally well tolerated. Gastrointestinal (GI) events (loss of appetite, bloating, nausea, vomiting, etc.) were the most commonly reported adverse events (AEs). At the 8-mg dose level, the majority of subjects experienced drug-related GI events Two of the subjects who received 8 mg reported AEs of nausea and vomiting that required treatment with antiemetics and intravenous fluids. Further dose escalation was therefore stopped.

In Part B (multiple-ascending dose [MAD] portion) of this study, more than 30 healthy subjects have been dosed in cohorts of 4 weekly SC fixed doses of 0.5 mg, 1.5 mg, and 4.5 mg; and an additional titration regimen cohort of 5 mg for 2 doses (Weeks 1 and 2), 8 mg (Week 3), and 10 mg (Week 4). Similar to Part A, the most commonly reported AEs have been GI events, including loss of appetite, nausea, bloating, heartburn, and vomiting. A majority of the AEs have been reported following the first week of dosing, with fewer AEs being reported after the third and fourth doses. The 8-mg dose was better tolerated in this titration approach as compared with the single 8-mg dose evaluated in Part A The limits of tolerability were not reached in the multiple-dose escalation in healthy subjects.

Part C of this study is currently ongoing. A group of T2DM patients has received a fixed dose of 5 mg for 4 weeks. GI events were the most commonly reported adverse events in these patients. LY3298176 appears to be better tolerated by T2DM patients who received 5 mg doses compared to healthy subjects who received 4.5 mg in Part B of the study. A second group of T2DM patients is currently being evaluated in Part C using a titration approach with a dosing scheme of 5 mg (Week 1), 5 mg (Week 2), 10 mg (Week 3), and 10 mg (Week 4). GI events (decreased or loss of appetite, feeling bloated, nausea, vomiting, etc) have been reported following the first two doses of 5 mg. Preliminary data regarding the 10 mg dose indicates that LY3298176 appears to be tolerated in this titration approach.

5.1. Overall Design

The planned LY3298176 doses for this study range from 0.25 mg up to ~~10~~ 15 mg LY3298176 (Section 5.5). Initially, it was planned to explore doses up to 10mg; however, based on a preliminary review of safety, tolerability, and PK data, the upper end of the dose range was increased from 10 mg to 15 mg. Dulaglutide will be provided as a 1.5-mg SC dose.

The investigator or qualified designee will review all available inpatient safety data before discharging patients/subjects from the CRU on the morning of Day 4, provided they are deemed medically fit by the investigator. Patients/subjects may be required to remain at the CRU longer than Day 4 at the investigator's discretion. Safety, as assessed by AEs, clinical safety laboratory tests, vital signs, 12-lead ECGs, concomitant medications, and medical assessments, will be reviewed by the sponsor and investigator before each dose-escalation decision.

During the study, patients/subjects may remain at the CRU as needed for safety follow-up based on clinical judgment of the principal investigator.

5.1.3. Multiple-Dose Evaluation in Patients with Type 2 Diabetes Mellitus (Part C)

Part C may be initiated based on the evaluation of safety and tolerability data from Part B (MAD).

Amendment to Part C

The protocol has been amended to allow the addition of up to 2 cohorts (up to 15 patients each) of T2DM patients to enable assessment of doses up to 15 mg through dose titration.

5.2 Number of Participants

Approximately 143 healthy subjects and up to approximately ~~25~~ 55 patients with T2DM may be enrolled so that approximately 112 healthy subjects and up to approximately ~~20~~ 40 patients complete the study.

5.5 Justification for Dose

Protocol Amendment (f)

Healthy subjects were given single doses up to 8 mg near the limits of tolerability in Part A, and 4 fixed weekly doses of 0.5 mg, 1.5 mg, and 4.5 mg and up to 10 mg as part of a titration scheme in Part B. The limits of tolerability were not reached in either Part A or B of this study. In Part C, LY3298176 was given to patients with T2DM in a fixed 5-mg weekly dose cohort and a titration cohort of 5 mg, 5 mg, 10 mg, and 10 mg over 4 weekly doses. Based on better tolerability of LY3298176 in T2DM patients compared with healthy subjects and updated margins of safety based on human exposure data from Parts A and B of this study (see Table GPGA.5.2), the protocol is amended to evaluate a maximum dose of LY3298176 up to 15 mg in T2DM patients as part of up to 2 additional titration schemes in Part C of this study.

Table GPGA.5.2. Updated Margin of Safety for Subcutaneous Administration of LY3298176 Based on Preliminary Human PK Data

	Dose (mg/kg)	Dose (mg/m^2)	AUC (µg•hr/mL)	Exposure Multiple to Human Starting Dose	Exposure Multiple to Human Maximum Dose
Human maximum dose (15 mg)[b]	0.214[b]	7.92	342[c]	-	
Rat NOAEL[d]	1.5	8.85	134[h]		0.68[e]
Monkey NOAEL[f]	0.15	1.8	115[i]		0.33[g]

Footnote: Refer to Table GPGA 5.1.

Appendix 6. Blood Sampling Summary

Protocol I8F-MC-GPGA Sampling Summary – Part A

Purpose	~~Maximum~~ Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	17	1	17
Clinical laboratory tests[a]	11	6	66
LY3298176 pharmacokinetics	6	11	66
Potential additional LY3298176 pharmacokinetic samples	6	3	18
Blood discard for cannula patency	0.3	5	1.5
Glucose only samples	2	5	10
Point of care safety glucose	0.3	15	4.5
Pharmacodynamics			
Lipids	2.5	2	5
Fasting insulin	2	2	4
Immunogenicity	6	4	24
Pharmacogenetics	10	1	10
Storage sample	10	2	20
Total			246
Total for clinical purposes			250

Protocol I8F-MC-GPGA Sampling Summary – Part B

Purpose	~~Maximum~~ Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	17	1	17
Clinical laboratory tests[a]	11	10	110
LY3298176 pharmacokinetics	6	13	78
Potential additional LY3298176 pharmacokinetic samples	6	3	18
Blood discard for cannula patency	0.3	28	8.4
Glucose only samples	2	4	8
Pharmacodynamics			0
Adiponectin	4	3	12
Lipids	2.5	3	7.5
Cortisol	2.5	1	2.5
Oral glucose tolerance test	4	15	60
Acetaminophen	2	33	66
Immunogenicity	6	7	42
Pharmacogenetics	10	1	10
Storage sample	10	5	50
Total			489.4
Total for clinical purposes			490

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

Protocol I8F-MC-GPGA Sampling Summary – Part C

Purpose	~~Maximum~~ Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	25	1	25
Clinical laboratory tests[a]	7	10	70
LY3298176 pharmacokinetics	6	13	78
Potential additional LY3298176 pharmacokinetic samples	6	3	18
Blood discard for cannula patency	0.3	28	8.4
Glucose only samples	2	4	8
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Adiponectin	4	3	12
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Cortisol	2.5	1	2.5
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