Protocol I8F-MC-GPGE(a)

Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of LY3298176 in Healthy Subjects

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LY3298176

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1. Protocol Synopsis

Title of Study:
Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of LY3298176 in Healthy Subjects

Rationale:
A solution formulation of LY3298176 will be evaluated in upcoming Phase 3 studies. This solution formulation has a different composition from the lyophilized formulation for injection that was used in the Phase 1 study, and is being used in the ongoing Phase 2 studies.

Part A: Investigate the relative bioavailability of the solution formulation (test), compared to the lyophilized formulation (reference).

Part B: The pharmacokinetics (PK) of LY3298176 following administration via intravenous (IV) route will be investigated.

Part C: The safety, tolerability, and PK of LY3298176, following administration of up to a 10-mg dose via a titration regimen using a solution formulation.

Objective(s)/Endpoints:

Objectives	Endpoints
Part A: • **Primary**: To evaluate the PK of a single SC dose of LY3298176, administered as solution formulation (test) versus lyophilized formulation (reference) in healthy subjects • **Secondary:** To investigate the safety and tolerability of LY3298176, administered to healthy subjects	• PK parameters, including AUC and C_{max}, • AEs and injection site reactions
Part B: • **Primary:** To evaluate the PK of a single IV dose of LY3298176 in healthy subjects • **Secondary:** To investigate the safety and tolerability of LY3298176, administered to healthy subjects via IV formulation	• PK parameters, including AUC • AEs
Part C: • **Primary:** To evaluate the safety and tolerability of LY3298176, following multiple SC weekly doses of a solution formulation administered in healthy subjects. • **Secondary:** To evaluate the PK of LY3298176, administered as a solution formulation	• AEs and injection site reactions • PK parameters including AUC and C_{max}

Abbreviations: AEs = adverse events; AUC = area under the drug plasma concentration versus time curve; C_{max} = maximum observed concentration; IV = intravenous(ly); PK = pharmacokinetic(s); SC = subcutaneous(ly).

Summary of Study Design:
Study I8F-MC-GPGE is a single-center, Phase 1, Part A is a 2-period crossover study in healthy subjects to evaluate the relative bioavailability of a 5-mg solution formulation (test) administered subcutaneously (SC), compared to reconstituted lyophilized formulation (reference). Part B is a single-arm study in healthy subjects to evaluate the PK of 0.5-mg solution formulation of LY3298176 following IV administration. Part C will be conducted in healthy subjects evaluating safety, tolerability, and PK of doses up to 10 mg, administered via titration, using a solution formulation.

Treatment Arms and Planned Duration for an Individual:
Part A: Subjects will be screened over a 28 day period and will be randomized to 1 of 2 treatment sequences, according to the randomization table provided to the site. Each subject will receive a single SC injection of LY3298176 test formulation and a reference formulation in a 2 arm cross over design. Subjects will be admitted to the clinical research unit (CRU) on Day -1 and discharged on Day 8 of each period and will return to the CRU for Day 15, Day 21, and Day 35-37 procedures each period. Each dose will be separated by a minimum of 35 days. A follow-up (or early discontinuation) visit should occur 35-37 days after the last dose of the study drug.

Part B: Subjects will be screened over a 28-day period. Subjects will be admitted to the CRU on Day -1. On Day 1, following an overnight fast of at least 8 hours, subjects will receive a single IV dose of LY3298176 solution formulation, administered over 10 minutes. At a minimum, subjects will remain in the CRU for 8 days. Subjects may be required to remain in the CRU for longer than Day 8, at the investigator's discretion. Subjects will return to the CRU on Day 15, Day 35-37 and at greater than or equal to 70 days post-dose.

Part C: Subjects will be screened over a 28-day period. Subjects will be randomized to receive LY3298176 or placebo in doses of 5 mg (Day 1), 5 mg (Day 8), 7.5 mg (Day 15), and 10 mg (Day 22). Treatment will be administered via solution formulation at each of the doses. Subjects will be required to attend follow-up visits 35 days after the last dose and at least 70 days after the last dose.

Number of Subjects:
Up to 46 adult subjects will be enrolled to ensure that 34 complete the study:

- Up to 20 healthy subjects will be enrolled in order that at least 16 complete Part A
- Up to 10 healthy subjects will be enrolled in order that at least 6 complete Part B
- Up to 16 healthy subjects will be enrolled in order that at least 12 complete Part C

Statistical Analysis:

Safety:
Continuous safety variables will be summarized using descriptive statistics. Categorical safety variables will be summarized using count and percentage. Vital signs data will be analyzed and summarized for each Part.

Pharmacokinetic:
Part A: To evaluate the PK for the 2 formulations, area under the drug plasma concentration versus time curve from time zero to infinity ($AUC_{[0-\infty]}$), and maximum drug plasma concentration (C_{max}) will be log transformed and analyzed using a linear mixed-effects model with treatment, period, and sequence as fixed effects, and subject as a random effect. The treatment ratio and the corresponding 90% confidence intervals [CIs] of the ratios will be reported.

Part B: Pharmacokinetic parameters will be summarized descriptively.

Part C: Pharmacokinetic parameters will be summarized descriptively.

2. Schedule of Activities

2.1. Study Schedule Protocol I8F-MC-GPGE, Part A

Procedure (Part A)	Screening	Periods 1 and 2													ET	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**21**	**35 - 37 post dose period 1**	**35 - 37 post dose period 2**		**≥35 day washout between doses 1 and 2.**
Informed Consent	X															
Subject Admission to CRU		X														
Subject Discharge from CRU										X						Subjects may stay longer according to investigator discretion
Outpatient Visit	X										X	X	X	X	X	
Investigational Product Administration			X													There is a minimum of 35 days washout period between doses for Period 1 and Period 2. Study drug will be administered SC after an overnight fast of at least 8 hours.
Medical History	X															
Height	X															
Weight	X	X											X	X	X	
Vital Signs (BP/PR/T) (supine)	X	X	**P**	24	48					X	X	X	X	X	X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.

Procedure (Part A)	Screening	Periods 1 and 2													Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**21**	**35 - 37 post dose period 1**	**35 - 37 post dose period 2**	**≥35 day washout between doses 1 and 2.**
Clinical Laboratory Tests	X	X								X			X	X	X	See Appendix 2, Clinical Laboratory Tests, for details.
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Reaction Assessment			**P**, 0, 6h, 12h	24h	48h											0-hour assessment should be performed within 5 minutes after subcutaneous injection. Additional assessments may be performed if deemed necessary by the investigator. Visual analog scale (VAS) score will be recorded
PK Samples			**P**, 8h, 12h,	24h	48h	72h	96h	120h	144h	168h	336h	480h	X	X	X	Sampling times are relative to the start of dose administration (0 hr). Predose sample must be collected before dose administration. If a subject withdraws from the study prior to completion of scheduled PK sampling for a given period, every effort will be taken to draw an unscheduled blood sample for PK

Procedure (Part A)	Screening	Periods 1 and 2														Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**21**	**35 - 37 post dose period 1**	**35 - 37 post dose period 2**	**ET**	**≥35 day washout between doses 1 and 2.**
																assessment. This will not be required if a sample has already been taken within the previous 24 hours. For ET, a PK sample can be taken at any time during the visit timed close to the immunogenicity sample.
Pregnancy Test	X	X											X	X	X	All females only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at Day -1 for each period and at ET/Follow-up.
Physical Examination	X	X								X			X	X	X	After screening, medical assessment only performed to include medical review and targeted examination, as appropriate.
12-lead ECG	X	X								X			X	X	X	Single 12-lead ECG will be collected. ECGs must be recorded before collecting any blood samples. Subjects must be supine for

Procedure (Part A)	Screening	Periods 1 and 2														Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**21**	**35 - 37 post dose period 1**	**35 - 37 post dose period 2**	**ET**	**≥35 day washout between doses 1 and 2.**
																at least 5 minutes before ECG collection and remain supine but awake during ECG collection.
Genetic Sample			**P**													Single sample for pharmacogenetic analysis taken prior to dosing on Day 1 in Period 1 only.
Immunogenicity Samples			**P**								X		X	X	X	All samples for immunogenicity should be taken predose for period 1 and 2. Day ≥35 post dose 2 and at follow-up (Day ≥70). Time-matched PK sample should be collected at each time point.

Abbreviations: BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; h = hours; **P** = Predose; PK = pharmacokinetics; PR = pulse rate; T = Temperature; VAS = visual analog scale.

Note: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECGs, vital signs, and venipuncture.

2.2. Study Schedule Protocol I8F-MC-GPGE, Part B

Procedure (Part B)	Screening	Treatment												ET	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**35 - 37**	**≥70 days**		
Informed Consent	X														
Subject Admission to CRU		X													
Subject Discharge from CRU										X					Subjects may stay longer according to investigator discretion
Outpatient Visit	X										X	X	X	X	
Investigational Product Administration			X												Study drug will be administered after an overnight fast of at least 8 hours. Study drug will be administered over 10 min IV infusion
Medical History	X														
Height	X														
Weight	X	X										X		X	
Vital Signs (BP/PR/T) (supine) (hours)	X	X	**P**	24h	48h					X		X		X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Clinical Laboratory Tests	X	X								X		X		X	Requires an 8 hour fast. See Appendix 2, for details.
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure (Part B)	Screening	Treatment												ET	Comments
Days	-28 to -2	-1	1	2	3	4	5	6	7	8	15	35 - 37	≥70 days		
PK Samples			**P**, 5 min, 10 min, 30 min 1h, 2h, 4h, 8h, 12h,	24 h, 36 h	48 h	72h	96h	120h	144h	168h	336 h	X	X	X	All sampling times are from start of infusion. (0 hr). Predose sample must be collected before dose administration. If a subject withdraws from the study prior to completion of scheduled PK sampling, every effort will be taken to draw an unscheduled blood sample for PK assessment. This will not be required if a sample has already been taken within the previous 24 hours. For ET, a PK sample can be taken at any time during the visit timed close to the immunogenicity sample.
Pregnancy Test	X	X										X		X	All females only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at Day -1 and at ET/Follow-up.
Physical Exam	X	X								X		X		X	After screening, medical assessment only performed to include medical review and targeted examination, as appropriate.

Procedure (Part B)	Screening	Treatment												ET	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**35 - 37**	**≥70 days**		
12-lead ECG	X	X								X		X		X	Single 12-lead ECG will be collected. ECGs must be recorded before collecting any blood samples. Subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection.
Genetic Sample			**P**												Single sample for pharmacogenetic analysis taken prior to dosing on Day 1.
Immunogenicity Samples			**P**								X	X	X	X	All samples for immunogenicity should be taken predose and follow up. Time-matched PK sample should be collected at each time point.

Abbreviations: BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; hr = hour(s); IV = intravenous(ly); min = minute(s); **P** = Predose; PK = pharmacokinetic(s); PR = pulse rate; T= Temperature

Note: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

2.3. Study Schedule Protocol I8F-MC-GPGE Part C

Procedure (Part C)	Screen	Prestudy	Treatment																		ET/Follow-up
Days	**-28 to -2**	**Before −2**		**−1**	**1**	**2**	**3**	**4**	**8[a]**	**9**	**10**	**15[a]**	**16**	**17**	**18**	**22[a]**	**23**	**24**	**25**	**57**	**≥92**
Informed consent	X																				
Admission to CRU[c]				X					X			X				X					
Discharge from CRU							X				X			X				X			
Outpatient visits to CRU		X													X				X	X	X
Distribution of glucose meters, test strips, diary, and GM training		X																			
Distribution of **additional** test strips, and diary.									X			X				X					
Administer study drug[d]					X				X			X				X					
Medical history	X																				

Procedure (Part C)	Screen	Prestudy	Treatment																		ET/Follow-up
Days	**-28 to -2**	**Before −2**		**−1**	**1**	**2**	**3**	**4**	**8[a]**	**9**	**10**	**15[a]**	**16**	**17**	**18**	**22[a]**	**23**	**24**	**25**	**57**	**≥92**
Height and weight[e]	X			X	**P**				**P**			**P**				**P**					X
Physical examination	X																				
Medical assessment[f]	X				**P**				**P**			**P**				**P**					X
Vital signs (BP/PR/T)[g] (hours)	X			X	**P**	X	X		**P**	X	X	**P**	X	X		**P**	X	X			X
ECG[h]	X				**P**											**P**					X
PK sampling (hours)					**P**, 8h	24 h	48 h	72h	**P**			**P**, 8h	24 h	48 h	72 h	**P**, 8h	24 h	48 h	72 h	X	X
Clinical laboratory tests[i]	X				**P**											**P**					X
AEs/concomitant medications	X				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions[b]					**P**, 0, 6h , 12h	24 h			**P**, 0, 6h , 12 h	24		**P**, 0, 6, 12	24			**P**, 0, 6, 12	24				

Procedure (Part C)	Screen	Prestudy	Treatment																		ET/Follow-up
Days	**-28 to -2**	**Before −2**		**−1**	**1**	**2**	**3**	**4**	**8[a]**	**9**	**10**	**15[a]**	**16**	**17**	**18**	**22[a]**	**23**	**24**	**25**	**57**	**≥92**
Pharmacogenomic sample					X																
Immunogenicity					**P**							**P**								X	X

Abbreviations: AEs = adverse events; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; GM = glucose monitoring; h = hours; **P** = Predose; PK = pharmacokinetic(s); PR = pulse rate; T= temperature.

[a] Dosing day – subjects will be admitted to CRU the day prior to dosing.

[b] Visual analog scale (VAS) score will be recorded

[c] For each CRU admission, subjects must remain at the CRU at least 72 hours postdose or per medical judgment.

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

[e] Height measured at screening only. Weight will be measured twice in a consistent way, each predose. Scale needs to be calibrated (refer to Section 9.4.4).

[f] Medical assessment will include a physical examination.

[g] Vital signs(BP/PR/T) measurements: for each dose day: predose, 24 hr, 48 hr, and on or after Day 92 (follow-up/ET).

[h] Single local safety ECGs will be measured at screening, predose Day 1, predose Day 22, predose Day 50 and follow-up/ET to take place on or after Day 92 (follow-up). Electrocardiograms 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.

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

3. Introduction

3.1. Study Rationale

Study I8F-MC-GPGE is a single-center, Phase 1, 3-part study to be conducted in healthy subjects.

A new solution formulation of LY3298176 will be evaluated in upcoming Phase 3 studies. This formulation has a different composition from the lyophilized formulation for injection that was used in the Phase 1 study and is also being used in the ongoing Phase 2 studies.

In Part A of the study, the study will evaluate the relative bioavailability of a 5-mg dose of LY3298176, administered subcutaneously (SC) as solution formulation (test), compared to a 5-mg dose, administered after reconstituting a lyophilized formulation (reference). These data will support Phase 3 clinical development.

LY3298176 has not been administered to subjects via the intravenous (IV) route to date; therefore, in Part B of the study, we will evaluate the pharmacokinetics (PK) of LY3298176 following IV administration. This information will enable us to calculate the absolute bioavailability of LY3298176 following SC administration (using prior SC PK data from Phase 1), which was the route utilized in the Phase 1 study, and is the intended route of administration for this drug as a therapeutic.

Part C will evaluate the safety, tolerability, and PK of LY3298176 doses up to 10 mg. Doses will be administered via a weekly titration regimen in healthy subjects. These data will support Phase 3 clinical development.

3.2. Background

LY3298176 is being investigated for its potential use in the treatment of type 2 diabetes mellitus (T2DM). LY3298176 is a long-acting, dual incretin receptor co-agonist that binds to both the glucose-dependent insulinotropic polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor. As a co-agonist, LY3298176 combines the signaling of each receptor for potentially improved glycemic control. LY3298176 consists of a peptide component, which is based on the GIP sequence, conjugated to a C20 fatty acid moiety that prolongs the duration of action, allowing for once weekly (QW) SC administration. Because it is a co-agonist, LY3298176 has the potential of reaching high efficacy in target tissues (such as the insulin-producing pancreatic β-cells that express both GIP and GLP-1 receptors) before reaching its therapeutic limitation. Furthermore, LY3298176 may attain additional efficacy by recruiting metabolically active tissues (eg, adipose tissue) not targeted by classical GLP-1 receptor agonists. This may result in increased energy utilization and greater weight loss in T2DM patients than that observed with GLP-1 receptor agonists (GLP-1 RAs) alone (Baggio and Drucker 2007).

The safety, tolerability, and pharmacokinetics/pharmacodynamics (PK/PD) of LY3298176 were evaluated in the Phase 1 clinical pharmacology trial, I8F-MC-GPGA (GPGA). Preliminary data are available. In Study GPGA, LY3298176 was administered as an SC injection in a single dose (0.25 to 8 mg) and in 4 QW doses (0.5 to 10 mg with doses >5 mg reached through dose

titration) to healthy subjects. LY3298176 was also administered SC to patients with T2DM in 4 QW doses (0.5 to 15 mg with doses >5 mg reached through dose titration). In both healthy volunteers and patients with T2DM, there was a suppression of serum glucose and a reduction of postprandial glucose that was generally dose-dependent. There was also a decrease in body weight that was generally dose-dependent. Nausea, vomiting, and diarrhea were frequently reported adverse events (AEs). Higher doses were better tolerated using a dose titration scheme of administration. Increases in heart rate were observed following administration of LY3298176, compared with placebo. There were no clinically significant changes in systolic or diastolic blood pressure or QT/corrected QT (QTc) interval prolongation observed in either healthy volunteers or patients with T2DM. No subject appeared to develop neutralizing antibodies to LY3298176.

In summary, LY3298176 has exhibited the expected GLP-1 pharmacological effects on glucose suppression. The body weight loss may be due to pharmacology of higher GLP-1 doses or due to contribution of the GIP part of the molecule. The reported gastrointestinal- (GI-) related AEs are consistent with GLP-1 pharmacology and those observed previously following administration of GLP-1 RAs (Nauck et al. 2009; Dungan et al. 2014; Giorgino et al. 2015; Jendle et al. 2016; Nauck et al. 2016). The effects observed on heart rate have also been observed with other GLP-1 RAs and have not been associated with adverse cardiovascular (CV) outcomes (Herbst et al. 2017).

3.3. Benefit/Risk Assessment

The nonclinical data and preliminary clinical data (See Section 3.2) from Study GPGA support further clinical development for LY3298176.

Predicted exposure multiples were derived from repeat-dose toxicology studies, using the highest proposed clinical dose of 15 mg/week. CCI [redacted] The effects in rats and monkeys included decreases in body weight and/or body weight loss, decreases in food consumption, and dehydration. All of the changes were consistent with, or secondary to, GLP-1 pharmacology, and were easily monitored in clinical studies. Furthermore, there was no evidence of target organ toxicity in either species. For more information, reference the Investigator's Brochure (IB).

No clinically significant safety or tolerability concerns were identified up to the highest single dose level of 8 mg or following 4 QW doses titrated up to 10 mg in Study GPGA. Based on this information, doses to be administered in Study GPGE will be tolerable to healthy subjects.

Any identified potential risks are similar with the risks associated with currently available long-acting GLP-1 receptor agonists (See Section 3.2), are considered to be manageable, and are able to be monitored.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated AEs of LY3298176 is found in the compound IB.

4. Objectives and Endpoints

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

Table GPGE.4.1 Objectives and Endpoints

Objectives	Endpoints
Part A: • **Primary**: To evaluate the PK of a single SC dose of LY3298176, administered as solution formulation (test) versus lyophilized formulation (reference) in healthy subjects. • **Secondary:** To investigate the safety and tolerability of LY3298176, administered to healthy subjects.	• PK parameters, including AUC and C_{max}, • AEs and injection site reactions
Part B: • **Primary:** To evaluate the PK of a single IV dose of LY3298176 in healthy subjects. • **Secondary:** To investigate the safety and tolerability of LY3298176, administered to healthy subjects via IV formulation.	• PK parameters, including AUC • AEs
Part C: • **Primary:** To evaluate the safety and tolerability of LY3298176, following multiple SC weekly doses of a solution formulation administered in healthy subjects. • **Secondary:** To evaluate the PK of LY3298176, administered as a solution formulation.	• AEs and injection site reactions • PK parameters including AUC and C_{max}

Abbreviations: AEs = adverse events; AUC = area under the drug plasma concentration versus time curve; C_{max} = maximum observed concentration; IV = intravenous(ly); PK = pharmacokinetic(s); SC = subcutaneous(ly).

5. Study Design

5.1. Overall Design

Study I8F-MC-GPGE (GPGE) is a single-center, Phase 1 study conducted in healthy subjects in 3 parts: Part A is a 2-period, 2-treatment, crossover design evaluating the relative bioavailability of 2 formulations of LY3298176; Part B, a single-arm design evaluating LY3298176 PK with IV administration; and Part C is a placebo-controlled, single-arm design evaluating the safety, tolerability, and PK of LY3298176 titrated, once-weekly for 4 weeks.

Part A: Part A is a randomized, 2-period, crossover study in healthy subjects to evaluate the relative bioavailability of 5 mg LY3298176, administered as a solution formulation (test), compared to a 5-mg dose administered SC as lyophilized formulation (reference). Treatment sequences and randomization are described in Section 7.2.

Each subject will provide informed consent for study participation, and will undergo a screening examination within 28 days prior to enrollment.

In each treatment period, subjects will be admitted to the clinical research unit (CRU) on Day -1. On the morning of Day 1, following an overnight fast of at least 8 hours, subjects will receive a single SC dose of LY3298176, administered according to their assigned treatment sequences. Blood samples will be collected predose and up to 480 hours postdose to measure LY3298176 concentrations. At a minimum, subjects will remain in the CRU for 8 days. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on the morning of Day 8, provided that the subjects are deemed medically fit. Subjects may be required to remain in the CRU longer than Day 8, at the investigator's discretion. The subjects will return to the CRU for follow-up visits on Days 21 and 35-37.

There will be a washout period of at least 35 days between doses in Periods 1 and 2. Based on the PK properties of LY3298176 (terminal half-life: approximately 5 days), a washout period of at least 35 days between doses in Periods 1 and 2 is considered adequate. Period 2 will repeat the same schedule as Period 1 with the Day 35 visit being the final study visit, which will include an antidrug antibody (ADA) sample at least 10 weeks after the first dose.

Part B: Part B is a single, 0.5-mg IV dose of LY3298176 solution formulation (or lyophilized formulation in absence of solution formulation) administered to healthy subjects.

Each subject will provide informed consent for study participation, and will undergo a screening examination within 28 days prior to enrollment.

Subjects will be admitted to the CRU on Day -1. On the morning of Day 1, following an overnight fast of at least 8 hours, 2 subjects will receive a single IV dose of 0.5 mg LY3298176, administered over 10 minutes. This dose is expected to be safe while also providing plasma concentrations that can be adequately measured over the course of the sampling time period to enable adequate characterization of the PK profile.

- If the dose of 0.5 mg is found to be safe and well-tolerated, then a PK interim analysis will be performed. Based on the results of the interim analysis, if it is noted that

LY3298176 concentrations can be adequately quantified, then 4 more subjects will be dosed.

- If the dose of 0.5 mg is found to be safe and well-tolerated, then a PK interim analysis will be performed. Based on the results of the interim analysis, if it is noted that LY3298176 concentrations cannot be adequately quantified, then a dose adjustment (however less than 1 mg) may be considered for an additional 6 subjects.
- If the dose is not tolerated due to extensive GI events, a lower dose of 0.25 mg (infused over 10 minutes) may be administered to an additional 6 subjects.

Plasma samples will be collected multiple times, including predose and up to 336 hours postdose, to measure LY3298176 concentrations.

At a minimum, subjects will remain in the CRU for 8 days. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on the morning of Day 8, provided that the subjects are deemed medically fit. Subjects may be required to remain in the CRU longer than Day 8, at the investigator's discretion.

Each subject will be required to return to the CRU for a follow-up visit at least 35 days after the LY3298176 dose. In addition, subjects will need to attend a study visit on Day ≥70 for an ADA follow-up sample.

Part C: Part C is a randomized, titration study where healthy subjects will be assigned LY3298176 or placebo at a ratio of 3 LY subjects to 1 placebo subjects. The investigator and subject will be blinded to the treatment. .

Subjects will receive a treatment regimen of either LY3298176 or placebo to be given as a SC dose on Days 1, 8, 15, and 22, after an overnight fast (at least 8 hours). Subjects randomized to LY3298176 will receive a 5-mg dose on Day 1 and Day 8, a 7.5-mg dose on Day 15, and a 10-mg dose on Day 22, administered via solution formulation (treatment specifics can be found in Section 7.1).

Each subject will be required to return to the CRU for outpatient visits and for a follow-up visit on Day ≥92.

For all parts of this study pharmacokinetic sampling and safety assessments, including AE recording, medical assessments, clinical laboratory tests, vital signs measurement, and electrocardiograms (ECGs), will be performed according to the Schedule of Activities (Section 2).

Subjects will be admitted the day before dosing. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on Day 3 after the final study procedures, provided that the subjects are deemed medically fit. More information is outlined in the Schedule of Activities (Section 2.3).

5.2. Number of Participants

Part A: Approximately 20 healthy subjects will be enrolled so that at least 16 complete this part.

Part B: Approximately 10 healthy subjects will be enrolled so that at least 6 complete this part.

Part C: Approximately 16 healthy subjects will be enrolled so that at least 12 complete this part.

For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been finished.

5.3. End of Study Definition

The 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 subject entered into any part of the study.

5.4. Scientific Rationale for Study Design

In this study, a population of healthy subjects is selected based on the likelihood of less physiologic variability in the absence of disease states that may affect multiple organ systems and absence of other confounding factors, such as concomitant medications. Part A is a randomized, open-label, single-dose, crossover-design study. The use of a crossover design allows each subject to serve as his/her own control, thereby, reducing variability.

Part B, will investigate the PK of LY3298176 following administration via a single IV dose.

An interim analysis will be performed after dosing the first 2 subjects to review safety and tolerability, and to check if there is a need for dose adjustment prior to dosing the rest of the subjects.

Part C will evaluate the safety, tolerability, and PK of doses up to 10 mg attained via a 4-week titration regimen in healthy subjects, when administered via a solution formulation planned for use in the Phase 3 study, compared to placebo. The titration algorithms have been chosen based on safety and tolerability data from the Phase 1 study, GPGA.

5.5. Dose Justification

5.5.1. Part A

A 5-mg LY3298176 dose is selected for Part A of the study to enable comparison of the solution formulation (test) versus the lyophilized formulation (reference). A 5-mg dose has been previously studied in healthy subjects and T2DM patients (Study GPGA), and was found to be safe and tolerable.

5.5.2. Part B

A starting dose of 0.5 mg LY3298176 (administered IV over 10 minutes) is chosen because this dose is expected to lead to a measureable PK profile with a modest observed peak drug

concentration (C_{max}), while still leading to peak and overall exposures notably lower than those observed following administration of a 5-mg SC dose (which has been studied in the Phase 1 study, GPGA). This dose will be administered such that up to 2 subjects will receive an initial dose of 0.5 mg, administered over 10 minutes. If this dose is found to be safe in the first 2 subjects, an interim analysis will be performed to evaluate the PK data in these subjects.

After the interim analysis, it will be decided whether to administer the same 0.5-mg dose to all the remaining subjects in this arm or to evaluate a different dose. If it is noted that LY3298176 concentrations cannot be adequately quantified, then a dose adjustment may be considered for an additional 6 subjects.

If the 0.5-mg dose is not tolerated, a lower dose of 0.25 mg (infused over 10 minutes) may be administered to an additional 6 subjects.

5.5.3. Part C

The planned dose-titration scheme to be tested in healthy subjects in this part of the study will be comprised of a QW titration dosing regimen of 5 mg, 5 mg, 7.5 mg, and 10 mg, compared to placebo. The titration algorithms have been chosen based on safety and tolerability data from the Phase 1 study, GPGA.

6. Study Population

Eligibility of subjects for the study 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 prior to enrollment. 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

Subjects are eligible for inclusion in the study only if they meet **all** of the following criteria at screening:

[1] are overtly healthy males or females, as determined by medical history and physical examination.

[1a] Male 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 (see Appendix 8 for acceptable methods of contraception).

[1b] Female 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

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

OR

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

[2] are males or females between 18 and 70 years old.

[3] have a screening body mass index of >18.5 and ≤32.0 kg/m^2.

[4] have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.

[5] have blood pressure of <160/90 mmHg and pulse rate of 50 to 90 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] are able and willing to give signed informed consent.

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

6.2. Exclusion Criteria

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

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

[10] are Lilly employees.

[11] 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.

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

[13] have previously completed or withdrawn from this study or any other study investigating LY3298176, and have previously received the investigational product.

[14] have had any exposure to dulaglutide, other GLP-1 analogs, or other related compounds within the prior 3 months, or any history ever of allergies to these medications.

[15] 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.

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

[17] have evidence of significant active neuropsychiatric disease, as determined by the investigator.

[18] regularly use known drugs of abuse and/or show positive findings on drug screening.

[19] have evidence of human immunodeficiency virus (HIV) infection and/or are positive for HIV antibodies.

[20] have evidence of hepatitis C and/or are positive for hepatitis C antibodies.

[21] have evidence of hepatitis B and/or are positive for hepatitis B surface antigen.

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

[23] have used or plan to use over-the-counter or prescription medication, and/or herbal supplements (with the exception of vitamin/mineral supplements, any hormone replacement therapy, and/or thyroid replacement therapy) within 14 days prior to dosing and for the duration of the study, including any medications that reduce GI motility, including, but not limited to, anticholinergics, antispasmodics, 5-hydroxytryptamine-3 receptor antagonists, dopamine antagonists, and opiates.

[24] have had a blood donation of 450 mL or more in the last 3 months, or have had any blood donation within the last month prior to screening.

[25] have an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), or are unwilling to stop alcohol consumption 24 hours before dosing until discharge from CRU.

(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)

[26] 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]), GI disorder (eg, relevant esophageal reflux or gall bladder disease), or any GI disease which impacts gastric emptying (eg, gastric bypass surgery, pyloric stenosis [with the exception of appendectomy]) or could be aggravated by GLP-1 analogs or dipeptidyl peptidase IV (DPP-IV) inhibitors. Subjects with dyslipidemia and subjects who had cholecystolithiasis (with removal of gallstones) and/or cholecystectomy (removal of the gall bladder) in the past, with no further sequelae, may be included in the study, at the discretion of the investigator.

[27] 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).

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

[29] have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2X the ULN or total bilirubin (TBL) >1.5X ULN.

[30] have a history of malignancy within 5 years prior to screening.

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

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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Conflict of interest in study participants is outlined in Criteria [9] and [10]. Excluded medical conditions, medication intolerance, and concomitant medication use that may constitute a risk for the subject and/or may confound the assessment of study endpoints are described in Criteria [11] through [32].

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Subjects will be required to fast overnight for at least 8 hours before taking a SC or IV dose of LY3298176, and when clinical safety laboratory samples are taken (see Schedule of Activities [Section 2]). 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 for 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 consumption should not exceed 3 units for males and 2 units for females (a unit is defined in Exclusion Criterion [25], Section 6.2). No nicotine use will be permitted while in the CRU. While not resident in the CRU, subjects must consume no more than 10 cigarettes or the equivalent per day.

Subjects will be allowed to maintain their regular caffeine consumption throughout the study period.

6.3.3. Activity

Subjects should not engage in strenuous physical exercise or activities from 48 hours prior to the first dose, and for duration of the study. When certain study procedures are in progress at the site, 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.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of drug product LY3298176, for injection that is being used in the Phase 1 and ongoing Phase 2 trials to the intended solution formulation of LY3298176 drug product for Phase 3 trials over a planned dose range, administered by SC injection. In addition, the PK of a single IV dose of LY3298176 will be evaluated. Table GPGE.7.1 illustrates the treatment regimens.

7.1.1. LY3298176 for Injection

LY3298176 for injection, 5 mg, is supplied as lyophilized formulation in a glass vial for SC and IV infusion administration. CCI [redacted] The reconstituted product solution in the vial(s) may be held at room temperature and/or refrigerated (2°C to 8°C), and should be administered within 4 hours from the time of reconstitution. LY3298176 for injection, 5-mg vials, are intended for single-dose administration.

7.1.2. LY3298176 Solution Formulation Injection

LY3298176 injection is prepared by sterile compounding, and is for SC and IV administration. CCI [redacted] The LY3298176 drug product solution vials may be held refrigerated (2°C to 8°C) for not more than 72 hours. The drug product solution must be administered within 4 hours after it is removed from refrigerated (2°C to 8°C) storage. LY3298176 compounded sterile drug product vials are intended for single-dose administration.

All investigational product provided to the investigator will be stored in a secure location, 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 investigational product received, dispensed, and remaining at the end of the study will be maintained. Detailed instructions for the preparation and handling of LY3298176 will be provided by the Sponsor in a pharmacy manual.

Table GPGE.7.1 Treatments Administered

Treatment Name	LY3298176	LY3298176 Solution	Placebo to Match LY3298176 Solution
Dosage Formulation	Reference lyophilized powder in glass vial	Test solution formulation in a glass vial	Test solution formulation in a glass vial
Unit Dose Strength(s) / Dosage Level(s)	Each vial can deliver 5 mg LY3298176	Concentration ranging from 10 mg/mL to 30 mg/mL	Placebo
Route of Administration	Subcutaneous injection and intravenous infusion	Subcutaneous injection and intravenous infusion	Subcutaneous injection
Dosing Instructions	Single-dose administration	Single-dose administration	Single-dose administration

7.2. Method of Treatment Assignment

Part A: the treatment to be injected for each period will be determined according to a randomization schedule.

Part B: a fixed, single-arm treatment.

Part C: the treatment to be injected on a given treatment day will be determined according to a randomization schedule.

7.2.1. Selection and Timing of Doses

Part A: Subjects will be randomized to 1 of 2 treatment sequences to be administered over 2 consecutive study periods. Each treatment period will consist of the reference lyophilized formulation and a test-solution formulation. The sequence of treatments will be administrated according to the randomization schedule. The doses will be administered at approximately the same time of the day during both periods. The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF). Injections will be administered into the SC tissue of the abdominal wall.

Part B: A single, 0.5-mg IV dose of LY3298176 will be administered in the morning following an 8-hour, overnight fast. The actual start and stop time of IV dose administration will be recorded in the subject's eCRF.

Part C: Dosing will commence at approximately the same time of day at each dosing instance. The actual time of all dose administrations will be recorded in the subject's eCRF. All injections will be administered into the SC tissue of the abdominal wall. Injection sites will be alternated weekly between 4 sites (ie, right and left upper quadrants and right and left lower quadrants) on the abdominal wall.

7.3. Blinding

Parts A and B are open label. Part C is investigator- and subject-blinded.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the

investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dose Modification

Part B: An 0.5-mg LY3298176 dose is planned to be administered over 10 minutes to the first 2 subjects. If vomiting is noted in the first 2 subjects, to the extent that treatment with antiemetics and intravenous fluids is required, a reduced dose (0.25 mg) may be administered to the next 6 subjects planned in this part. If there are no safety concerns, then, following an interim PK analysis, the same planned dose of 0.5 mg will be administered to the next 4 subjects enrolled in this part. If, following the interim analysis, it is noted that the LY3298176 concentrations cannot be adequately measured, then a different dose may be considered for an additional 6 subjects.

7.4.1. Management of Intravenous Infusion

7.4.1.1. Premedication for Infusions

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used, as determined by the study investigator(s). If infusion reactions are observed, but a review of the data suggests that dose escalation may continue, administration of acetaminophen, 500 to 1000 mg, and/or an antihistamine may be administered orally, 30 to 60 minutes prior to the start of infusion for subsequent subjects.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and Sponsor, and recorded in the study documentation along with the dose-escalation decision.

Any premedications given will be documented as a concomitant therapy (see Section 7.7).

7.4.1.2. Management of Infusion Reactions

There is a risk of infusion reaction with any biological agent; therefore, all subjects should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness.

In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The investigational product infusion should be slowed (eg, reduce infusion rate by 50% [ie, an infusion rate of 12 mL/hr becomes 6 mL/hr or slower]) or stopped, depending on the symptoms/signs present:
    - If slowed, the infusion should be completed at the slower rate, as tolerated.
    - If determined by the investigator that the infusion should no longer continue, no further attempts to dose the subject should be made.
- Supportive care should be employed in accordance with the symptoms/signs.

- If a subject's infusion reaction is sufficiently severe to discontinue the infusion, subsequent infusions may be administered with premedication, at the discretion of the investigator, following agreement with the Lilly clinical research physician (CRP) or clinical pharmacologist.
- If a subject's infusion rate is reduced due to an infusion reaction, subsequent infusions may be administered, at the discretion of the investigator, following agreement with the Lilly CRP or clinical pharmacologist. If further infusions are administered, the infusion rate must not exceed the slowest rate used to complete the infusion on the occasion when the infusion reaction occurred. Premedication may be administered at the discretion of the investigator.
- If it is determined that the subject should not receive further doses of investigational product, the subject should complete AE and other follow-up procedures, per Section 2 of this protocol.

If the signs and symptoms indicate that a subject is suffering from possible infection(s), he/she will be clinically managed, treated, and followed up until resolution. Any AEs will be recorded, as appropriate.

7.5. Preparation/Handling/Storage/Accountability

The investigator (or designee) must confirm that appropriate temperature conditions have been maintained, as communicated by the Sponsor, during transit for all investigational product received, and that any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product.

All investigational product 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 of 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.

7.7. Concomitant Therapy

Subjects should not use over-the-counter or prescription medication, and/or herbal supplements, with the exception of vitamin/mineral supplements, any hormone replacement therapy, and/or thyroid replacement therapy, within 14 days prior to dosing and for the duration of the study. The use of topical medication may be permitted if no evidence of chronic dosing with the risk of systemic absorption exists.

Because LY3298176 may be associated with nausea and vomiting, symptomatic care (eg, antiemetic drugs [except 5-hydroxytryptamine 3 antagonists] and antacids) can be used as per usual standard of care, but should be avoided if possible. Signs and symptoms of dehydration should be evaluated and, if present, appropriately managed.

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

If the need for any other concomitant medication (eg, nonsteroidal anti-inflammatory drugs, acetaminophen, or antihistamines) arises, inclusion or continuation of the subject may be at the discretion of the investigator, preferably after consultation with a Lilly CRP or clinical pharmacologist. Any additional medication used during the course of the study must be documented in the eCRF.

7.8. Treatment after the End of the Study

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

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal pancreatic tests and liver function tests (LFTs) **should be considered** by the investigator when a subject meets any of the following conditions:

- ALT or AST >5X ULN in healthy subjects
- ALT or AST >3X ULN sustained for more than 2 weeks in healthy subjects
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio (INR) >1.5.
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Lipase and/or amylase are confirmed to be ≥3X ULN (please refer to algorithm for the monitoring of pancreatic events in Appendix 7)
- Drug-related vomiting requiring IV hydration treatment or causing severe distress (prevents daily activities and results in no appetite, or requires an emergency department visit or hospitalization)

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

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 Subjects

If the Sponsor or investigator identifies a 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 subject 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 subject to continue in the study, with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

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

- Investigator Decision:
    - The investigator decides that the subject should be discontinued from the study.
    - If the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.
- Subject Decision
    - The subject (or legal representative) requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits, and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for scheduled visits or who 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 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study, and for alerting Lilly (or its designee) to any events that seem unusual, even if those events may be considered an unanticipated benefit to the subjects.

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate healthcare option, AEs that are serious or, otherwise, medically important, considered related to the investigational product or the study, or which caused the subject to discontinue the investigational product before completing the study. The 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 informed consent form (ICF) is signed, study site personnel will record, via eCRF, the occurrence and nature of each 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 an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a potential cause-and-effect relationship between the investigational product, study device, and/or study procedure and the AE.

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

If a subject's investigational product is discontinued as the 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 (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization, but that may jeopardize the subjects or may require intervention to prevent one of the other outcomes listed in the definition above

Study site personnel must alert the Lilly CRP/clinical pharmacologist (or its designee) of any SAE as soon as practically possible. Additionally, study site personnel must alert Lilly Global Patient Safety (or its designee) of any SAE within 24 hours of investigator awareness of the event via a Sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

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

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 reports as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

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

Subjects should be instructed to contact the investigator as soon as possible if they have complaints or problems with the investigational product (or drug delivery system), so that the situation can be assessed.

9.3. Treatment of Overdose

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

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

For each subject, vital signs (blood pressure, pulse rate, temperature) measurements should be conducted, according to the Schedule of Activities (Section 2).

Blood pressure and pulse rate should be measured after the subject is supine for at least 5 minutes.

If orthostatic measurements are required, the subject should be supine for at least 5 minutes and stand for at least 3 minutes.

If the 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.

9.4.3. Electrocardiograms

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

For each subject, a single12-lead digital ECG will be collected, according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection, and remain supine, but awake, during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms 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

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

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT [QTc] interval from baseline) after enrollment, the investigator will determine whether the subject can continue in the study. The investigator (or qualified designee) is responsible for determining if any change in subject management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Body Weight

Weight will be measured, as indicated in the Schedule of Activities (Section 2). 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 the bowel and bladder, if possible. During the treatment period, weight will be measured twice on each scheduled occasion, with the subject stepping off the scale between measurements. Both weight measurements will be recorded in the source document and the eCRF. Wherever possible, the same scale will be used for all weight measurements throughout the study, and the scale will not be moved or recalibrated.

9.4.5. Safety Monitoring

The Lilly clinical pharmacologist or CRP 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 CRP will periodically review the following data:

- 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

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

9.4.5.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3X ULN, alkaline phosphatase (ALP) ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on consultation with the Lilly clinical pharmacologist or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.4.6. 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 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 (ALT, AST, complete blood count with percent eosinophils, and additional immunogenicity testing).

9.4.6.1. 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.

9.4.6.1.1. Pain Measurements Using the Visual Analog Scale

Pain measurements will be assessed using a 100-mm validated visual analog scale (VAS) for pain. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess injection-site pain. The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "no pain" and "worst imaginable pain." The subject will be asked to mark the 100-mm line to indicate pain intensity at time points according to the Schedule of Activities (Section 2) and as clinically indicated. A staff member will use a caliper to measure the distance from 0 to the mark that the subject placed on the VAS, and to record the measurement in the source document.

9.4.7. Glucose Monitoring (Part C)

Subjects will be instructed on how to use the glucose meter provided by the site, and to conduct self-blood glucose-monitoring tests; subjects will be also educated on the symptoms of hypoglycemia. Throughout their participation in the study, subjects will monitor blood-glucose

levels. Subjects will be provided a diary card and instructed to record blood-glucose results premeal and at bedtime on at least 2 days per week during the dosing phase of the study, and whenever the subject experiences symptoms of hypoglycemia. Investigator review of glucose results clinically indicative of hypoglycemia is required.

9.4.7.1. Hyperglycemia and Hypoglycemia Reporting

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

If the fasting plasma/serum glucose during the dosing period exceeds the acceptable level defined as hyperglycemia on 3 or more separate days over any 2-week period between screening and the end of the dosing period, the subject will be evaluated further at the study site. If fasting plasma/serum glucose continues to exceed the acceptable level, the investigational product will be discontinued, and treatment with an appropriate antidiabetic agent may be initiated by the investigator. If hyperglycemia occurs during the follow-up period, the subject will remain in the study until completion of the planned follow-up.

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

The main categories of hypoglycemia are outlined below:

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

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

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

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

Severe Hypoglycemia (Level 3):

- Severe hypoglycemia (in adults): Subjects had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma/Serum glucose measurements may not be available during such an event, but neurological recovery

attributable to the restoration of plasma/serum glucose concentration to normal is considered sufficient evidence that the event was induced by a low plasma/serum concentration (plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]).

- Severe hypoglycemia requiring medical attention: Severe hypoglycemic events when subjects require therapy by healthcare providers (emergency medical technicians, emergency room personnel, etc.) are of particular interest to payers. Therefore, some clinical trials may want to collect data on this subset of severe hypoglycemia episodes, especially if economic outcomes analyses may be based on trial results.

Other Hypoglycemia

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

If a hypoglycemic event meets the criteria of severe, it needs to be recorded as serious in the eECRF (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 eECRF, 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, skim 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.

9.4.8. Nausea and Vomiting

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

9.4.9. 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 7) for the monitoring of pancreatic events whenever lipase and/or amylase is confirmed to be ≥3X ULN at any visit postrandomization, even if the subject is asymptomatic.

9.4.10. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against LY3298176. To interpret the results of immunogenicity, a PK sample will be collected at the same time points. All samples for immunogenicity should be taken predose, when applicable. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3298176 at a laboratory approved by the Sponsor. Positive ADA samples may be evaluated for neutralizing antibodies to LY3298176. Positive ADA samples may also be tested for cross-reactivity with native GLP-1 and GIP, and, if positive, then, additional testing for neutralizing antibodies against native GLP-1 may also be conducted.

All subjects will have an ADA sample measured at early discontinuation or at the follow-up visit (date of visit outlined in the Schedule of Activities [Section 2]). A risk-based approach will be used to monitor subjects who have clinically significant treatment-emergent ADAs (TE-ADAs) at the last visit. CCI

[redacted] A PK sample may be collected at the follow up immunogenicity assessment(s), if warranted and agreed upon by the investigator and Sponsor.

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

Subjects followed for at least 1 year since last dose who have not returned to baseline, as defined above, will be assessed for safety concerns and, if no clinical sequelae are recognized by the clinical team, no further follow-up will be required. Subjects who have clinical sequelae that are considered potentially related to the presence of TE-ADAs may also be asked to return for additional follow-up testing.

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

9.5. Pharmacokinetics

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

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the Sponsor, and stored at a facility designated by the Sponsor. Concentrations of LY3298176 will be assayed using a validated liquid chromatography mass spectrometry (LC/MS) method. Analyses of samples collected from placebo-treated subjects are not planned. Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

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

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

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs/investigational review board (IRBs) 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

Not applicable.

9.9. Health Economics

Not applicable.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 20 healthy subjects may be enrolled in Part A in order that at least 16 subjects complete Part A. Up to 10 subjects will be enrolled in Part B in order that at least 6 subjects complete Part B. Approximately 16 healthy subjects may be enrolled in Part C in order that at least 12 subjects complete Part C (in a 3 LY3298176:1 placebo ratio).

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

Part A: CCI [redacted]

Parts B and C: The sample size is customary for Phase 1 studies evaluating safety and PK. The sample sizes are not based on statistical calculations. The sample sizes for each part of the study are considered sufficient to evaluate the primary objectives of this study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of subject disposition will be provided at the end of the study.
All 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 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).

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational product and who have evaluable PK.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Unless, otherwise, noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, and 90% CIs will be calculated.

Additional exploratory analyses of the data will be conducted, as deemed appropriate. Study results may be pooled with the results of other studies for post-hoc analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure 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 Dictionary for Regulatory Activities.

The number of investigational product-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include: safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed. Continuous safety variables will be summarized using descriptive statistics. Categorical safety variables will be summarized using count and percentage. Vital signs data will be analyzed and summarized for each Part. Body weight data will be summarized.

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

10.3.1.3. Injection Site Reaction

For Part A and Part C, incidence of erythema, induration, pain, itching, and swelling will be listed and summarized by treatment.

The post-injection pain score will be summarized by treatment. Additional analyses may be performed, if appropriate.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3298176 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be: C_{max}, and AUCf LY3298176 for Parts A, B, and C of the study. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported, as appropriate.

10.3.2.2. Pharmacokinetic Statistical Inference

10.3.2.2.1. Part A

To assess the relative bioavailability of a single SC dose of LY3298176 administered as a solution formulation (test), compared to a lyophilized formulation (reference), AUC from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of last measured concentration ($AUC_{0-t_{last}}$) and C_{max} will be log-transformed and analyzed using a linear mixed effects model

with treatment, period, and sequence as fixed effects and subject as a random effect. The difference in least squares means (LSMeans) between the test formulation and reference formulation for each parameter will be exponentiated to yield ratios of geometric LSMeans and their corresponding 90% CIs. Time to maximum observed concentration will be analyzed using a nonparametric method. The Wilcoxon rank-sum test will be performed. Median difference and 90% CI will be reported.

10.3.2.2.2. Part B

No formal statistical analysis will be performed for the IV formulation evaluation part of the study. A descriptive summary of PK parameters will be reported.

10.3.2.2.3. Part C

A descriptive summary of PK parameters, by treatment, will be presented.

10.3.3. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADAs, ADAs at any time postbaseline, and TE-ADAs to LY3298176 will be tabulated. Correspondingly, the frequency and percentage of subjects with preexisting or treatment-emergent neutralizing antibodies, and/or cross-reacting antibodies to LY3298176 may be tabulated.

The relationship between the presence of antibodies to LY3298176 and the PK parameters and safety (such as AEs, injection site reactions, formulation, and/or route of administration) may be assessed.

10.3.4. Data Review during the Study

An interim analysis is planned after dosing 2 subjects in Part B of the study.

The possible outcomes following IV administration of a 0.5-mg dose of LY3298176 over 10 minutes are:

- LY3298176 tolerability is adequate; LY3298176 concentrations are measurable in the 2 subjects.
- LY3298176 tolerability is inadequate. To improve tolerability, the dose of LY3298176 may be reduced to 0.25 mg, administered over 10 minutes.
- LY3298176 tolerability is adequate; however, if LY3298176 concentrations cannot be adequately quantified, then a dose adjustment may be considered.

Following completion of Parts A and B of this study, an interim database lock may be performed.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
AUC	area under the drug plasma concentration versus time curve
$AUC_{(0-\infty)}$	area under the drug plasma concentration versus time curve from time zero to infinity
$AUC_{(0-t_{last})}$	area under the drug plasma concentration versus time curve from time zero to the time of last measured concentration
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient/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	blood pressure
CBC	complete blood count
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed (peak) concentration
CNS	central nervous system
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.

Term	Definition
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CPK	creatinine phosphokinase
CRP	clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSE	clinically significant effect
CT	computed tomography
CV	coefficient of variation
DBP	diastolic blood pressure
DPP-IV	dipeptidyl peptidase IV
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a patient/subject to a treatment. Patients/Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients/Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FOIA	Freedom of Information Act
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide

Term	Definition
GLP-1	glucagon-like peptide 1
GLP-1 RA	glucagon-like peptide 1 receptor agonist
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
Ig	immunoglobulin
informed consent	A process by which a patient/subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient/subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board
IV	intravenous administration
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 a patient/subject, to the a patient/subject's participation in the clinical study.
LFT	liver function test
LSMean	least squares mean
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect level

Term	Definition
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.
PD	pharmacodynamic
PK	pharmacokinetic
PR	pulse rate
QTc	corrected QT interval
QW	once weekly administration
randomize	the process of assigning subjects/patients to an experimental group on a random basis
RBC	red blood cell
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous administration
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
T	temperature
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE-ADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event: any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
TG	triglyceride
ULN	upper limit of normal
US	United States
USP	United States Pharmacopoeia
VAS	Visual Analog Scale
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Clinical 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
Microscopy[a]	HIV antibody
	Pregnancy test (urine, serum) [d]
	Drug and alcohol screen[e]

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

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

[e] Drug screen and ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities (Section 2).

[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 subject understands the nature of the study, the potential risks and benefits of participating in the study, and that his/her participation is voluntary.
- Ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- Answering any questions, the subject may have throughout the study, and sharing, in a timely manner, any new information that may be relevant to the subject's willingness to continue his/her participation in the study.
- Providing a copy of the ICF to the participant or the participant's legal representative, and retaining a copy on file.

Recruitment

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

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

- Current Investigator's Brochure (IB) and updates during the course of the study
- Informed consent form
- Relevant curricula vitae

Regulatory Considerations

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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (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/her knowledge, the protocol accurately describes the planned design and conduct of the study.

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

Final Report Signature

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

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/her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

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

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

In addition, Lilly (or its representatives) will periodically check a sample of the 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.

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

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

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

Appendix 5. Blood Sampling Summary

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

Protocol I8F-MC-GPGE Sampling Summary Part A

Type of Sample	Volume per Sample (mL)	Number of Samples per Subject	Total Volume (mL)
Screening tests[a]	17.0	1	17.0
Clinical laboratory tests[a]	6.5	6	39.0
Pharmacokinetics	3.0	29	87.0
Immunogenicity	6.0	6	36.0
Genetic	10.0	1	10.0
Loss by use of indwelling, intravenous cannula	1.0	3	3.0
Total:			192.0

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

Protocol I8F-MC-GPGE Sampling Summary Part B

Type of Sample	Volume per Sample (mL)	Number of Samples per Subject	Total Volume (mL)
Screening tests[a]	17.0	1	17.0
Clinical laboratory tests[a]	6.5	4	26.0
Pharmacokinetics	3.0	23	69.0
Immunogenicity	6.0	4	24.0
Genetic	10.0	1	10.0
Loss by use of indwelling, intravenous cannula	1.0	9	9.0
Total:			155.0

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

Protocol I8F-MC-GPGE Sampling Summary Part C

Type of Sample	Volume per Sample (mL)	Number of Samples per Subject	Total Volume (mL)
Screening tests[a]	17.0	1	17.0
Clinical laboratory tests[a]	6.5	3	19.5
Pharmacokinetics	3.0	21	63.0
Immunogenicity	6.0	4	24.0
Pharmacogenomic	10.0	1	10.0
Loss by use of indwelling, intravenous cannula	1.0	6	6.0
Total:			139.5

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

Appendix 6. Clinically Significant Adverse Effects

The following table summarizes the type and severity of symptoms, clinical signs, and clinical laboratory findings that may qualify as a clinically significant effect (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 subjects 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 (eg, phlebotomy, nausea, bowel or bladder function), and are associated with orthostatic SBP decrease >20 mmHg or DBP decrease >10 mmHg 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 that is unresponsive to oral antihistamine.
Signs	
SBP	>30 mmHg increase from baseline values and an absolute level >190 mmHg.
DBP	>20 mmHg increase from baseline values and an absolute level >115 mmHg.
Heart rate	Resting (sitting or recumbent) >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 <1500/μL and >1000 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.
ALT	>5-fold above laboratory reference upper limit value.
AST	>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: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system, CSE = clinically significant effect, DBP = diastolic blood pressure, QTc = corrected QT interval; SBP = systolic blood pressure.

Appendix 7. Pancreatic Monitoring

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

To enhance understanding of the natural variability of pancreatic enzymes in the T2DM population and, in order 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 the upper limit of normal (ULN) at any visit after randomization, even in asymptomatic 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 gastrointestinal [GI] signs and/or symptoms), at the investigator's discretion.

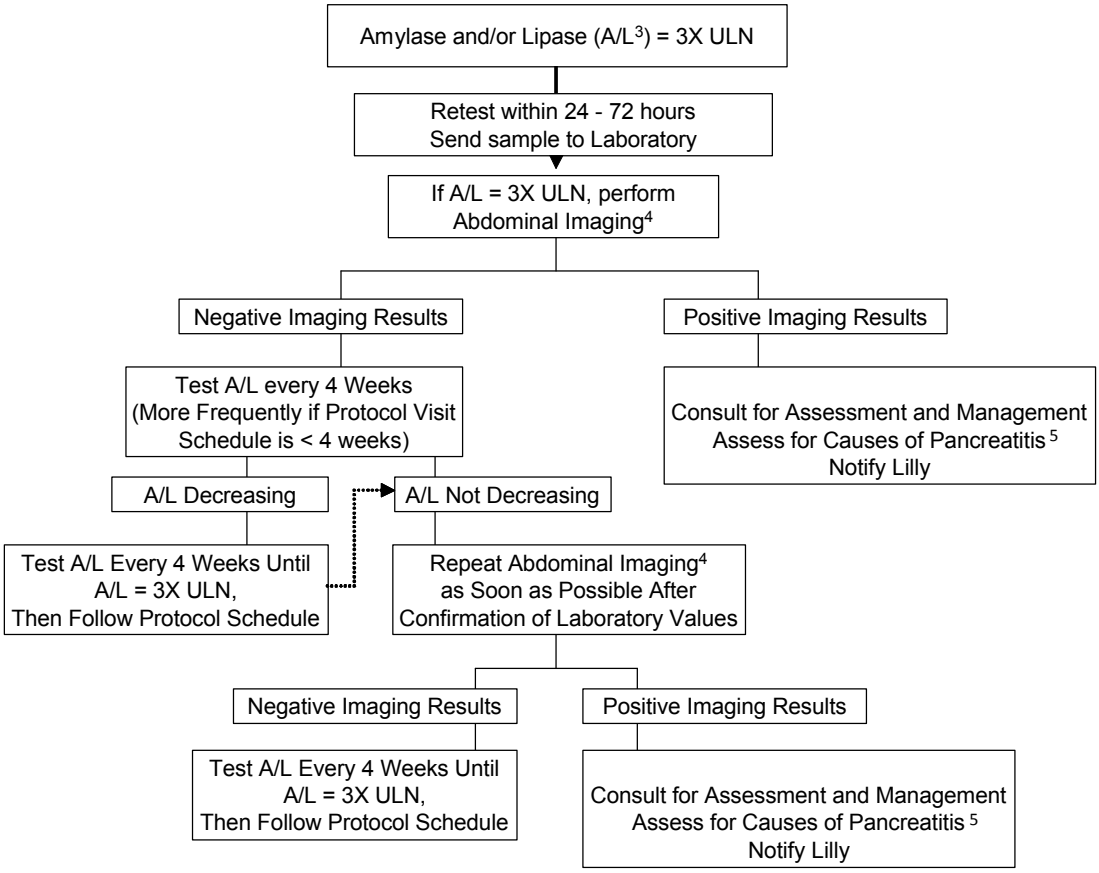
Acute pancreatitis is an adverse event (AE) defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems.
The diagnosis of acute pancreatitis requires 2 of the following 3 features:

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

Most subjects with acute pancreatitis experience abdominal pain that is located generally in the epigastrium, and radiates to the back in approximately one-half of the cases. The pain is often associated with nausea and vomiting. However, experience with GLP-1 agonists has demonstrated that some subjects asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase. For 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 subjects safely and to quickly reach (or not reach) a diagnosis of pancreatitis.

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

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



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

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

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

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

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

Abbreviations: CBC = complete blood count; CT = computed tomography; LFTs = liver function tests; MRI = magnetic resonance imaging.

Subjects diagnosed with pancreatitis will be discontinued from the study. Investigators will be responsible for following, through an appropriate healthcare option, these pancreatitis AEs until the events resolve or are explained. Adverse events that meet the diagnostic criteria of acute pancreatitis will be captured as serious adverse events (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 8. Contraceptive Methods

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

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

Men who have had a vasectomy with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate are not required to use contraception. In addition, Inclusion Criterion 1b provides a specific definition of women not of childbearing potential; these subjects will not be required to use contraception. Male subjects with a female partner meeting the definition of a woman not of childbearing potential will not be required to use contraception.

Appendix 9. Protocol Amendment I8F-MC-GPGE(a) Summary Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of LY3298176 in Healthy Subjects

Overview

Protocol I8F-MC-GPGE(a) Pharmacokinetics, Safety, and Tolerability of a Solution Formulation of LY3298176 in Healthy Subjects has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Part C of the protocol has been amended to remove any clinical activities occurring on Day -2.
- Reference to a study period in Part B of the protocol is misleading. Language in the protocol referencing a study period is removed.
- Clarify that clinical assessments will be taken on Day 92 as part of follow-up activities rather than Day 84 for Part C.
- Clarify that patients will return to the CRU for study days 35-37 inclusive consistent with the Schedule of Activities for Part A.
- Clarify that patients will be admitted to the CRU on Day -1 in order to fulfill the completion of study assessments scheduled to occur on Day -1.
- Added descriptor for each Part A – C to the top row for each SoA page to facilitate ease of use
- Clarified that LY will be administered subcutaneously for Part A

Revised Protocol Sections

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

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

2.1 Study Schedule Protocol I8F-MC-GPGE Part A

Procedure (Part A)	Screening	Periods 1 and 2													ET	Comments
Days	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**21**	**35 - 37 post dose period 1**	**35 - 37 post dose period 2**		**≥35 day washout between doses 1 and 2.**
Informed Consent	X															
Subject Admission to CRU		X														
Subject Discharge from CRU										X						Subjects may stay longer according to investigator discretion
Outpatient Visit	X										X	X	X	X	X	
Investigational Product Administration			X													There is a minimum of 35 days washout period between doses for Period 1 and Period 2. Study drug will be administered SC after an overnight fast of at least 8 hours.

2.2 Study Schedule Protocol I8F-MC-GPGE Part B

Procedure (Part B)	Screening	Treatment												ET	Comments
Days	-28 to -2	-1	1	2	3	4	5	6	7	8	15	35 - 37	≥70 days		
PK Samples			P, 5 min, 10 min, 30 min 1h, 2h, 4h, 8h, 12h,	24 h, 36 h	48 h	72h	96h	120h	144h	168h	336 h	X	X	X	All sampling times are from start of infusion. (0 hr). Predose sample must be collected before dose administration. If a subject withdraws from the study prior to completion of scheduled PK sampling ~~for a given period~~, every effort will be taken to draw an unscheduled blood sample for PK assessment. This will not be required if a sample has already been taken within the previous 24 hours. For ET, a PK sample can be taken at any time during the visit timed close to the immunogenicity sample.
Pregnancy Test	X	X										X		X	All females only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at Day -1 ~~for each period~~ and at ET/Follow-up.

2.3 Study Schedule Protocol I8F-MC-GPGE Part C

Procedure (Part C)	Screen	Prestudy	Treatment																		ET/Follow-up
Days	**-28 to -2**	**Before −2**	**~~−2~~**	**−1**	**1[a]**	**2**	**3**	**4**	**8[a]**	**9**	**10**	**15[a]**	**16**	**17**	**18**	**22[a]**	**23**	**24**	**25**	**57**	**≥92**
Informed consent	X		-																		
Admission to CRU[c]			~~X~~	X	~~X~~				X			X				X					
Discharge from CRU			-				X				X			X				X			
Outpatient visits to CRU		X	-												X				X	X	X
Distribution of glucose meters, test strips, diary, and GM training		X	-																		
Distribution of **additional** test strips, and diary.			-						X			X				X					
Administer study drug[d]			-		X				X			X				X					
Medical history	X		-																		

Procedure (Part C)	Screen	Prestudy	Treatment																		ET/Follow-up
Days	-28 to -2	Before −2	~~−2~~	−1	1[a]	2	3	4	8[a]	9	10	15[a]	16	17	18	22[a]	23	24	25	57	≥92
Height and weight[e]	X		-	X	P				P			P				P					X
Physical examination	X		-																		
Medical assessment[f]	X		-		P				P			P				P					X
Vital signs (BP/PR/T)[g] (hours)	X		-	X	P	X	X		P	X	X	P	X	X		P	X	X			X
ECG[h]	X		-		P											P					X
PK sampling (hours)			-		P, 8h	24 h	48 h	72h	P			P, 8h	24 h	48 h	72 h	P, 8h	24 h	48 h	72 h	X	X
Clinical laboratory tests[i]	X		-		P											P					X
AEs/concomitant medications	X		-		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site reactions[b]			-		P, 0, 6h , 12h	24 h			P, 0, 6h , 12 h	24		P, 0, 6, 12	24			P, 0, 6, 12	24				

Procedure (Part C)	Screen	Prestudy	Treatment																		ET/Follow-up
Days	-28 to -2	Before −2	~~−2~~	−1	1[a]	2	3	4	8[a]	9	10	15[a]	16	17	18	22[a]	23	24	25	57	≥92
Pharmacogenomic sample			-		X																
Immunogenicity			-		P							P								X	X

g Vital signs(BP/PR/T) measurements: for each dose day: predose, 24 hr, 48 hr, and on or after Day 92~~84~~ (follow-up/ET).

h Single local safety ECGs will be measured at screening, predose Day 1, predose Day 22, predose Day 50 and follow-up/ET to take place on or after D~~d~~ay 92~~84~~ (follow-up).

5.1 Overall Design

…

Part A: Part A is a randomized, 2-period, crossover study in healthy subjects to evaluate the relative bioavailability of 5 mg LY3298176, administered as a solution formulation (test), compared to a 5-mg dose administered SC as lyophilized formulation (reference). Treatment sequences and randomization are described in Section 7.2.

Each subject will provide informed consent for study participation, and will undergo a screening examination within 28 days prior to enrollment.

In each treatment period, subjects will be admitted to the clinical research unit (CRU) on Day -1. On the morning of Day 1, following an overnight fast of at least 8 hours, subjects will receive a single SC dose of LY3298176, administered according to their assigned treatment sequences. Blood samples will be collected predose and up to 480 hours postdose to measure LY3298176 concentrations. At a minimum, subjects will remain in the CRU for 8 days. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on the morning of Day 8, provided that the subjects are deemed medically fit. Subjects may be required to remain in the CRU longer than Day 8, at the investigator's discretion. The subjects will return to the CRU for follow-up visits on Days 21 and 35-37.

…

Part C: Part C is a randomized, titration study where healthy subjects will be assigned LY3298176 or placebo at a ratio of 3 LY subjects to 1 placebo subjects. The investigator and subject will be blinded to the treatment. .

Subjects will receive a treatment regimen of either LY3298176 or placebo to be given as a SC dose on Days 1, 8, 15, and 22, after an overnight fast (at least 8 hours). Subjects randomized to LY3298176 will receive a 5-mg dose on Day 1 and Day 8, a 7.5-mg dose on Day 15, and a 10-mg dose on Day 22, administered via solution formulation (treatment specifics can be found in Section 7.1).

Each subject will be required to return to the CRU for outpatient visits and for a follow-up visit on Day ≥92.

For all parts of this study pharmacokinetic sampling and safety assessments, including AE recording, medical assessments, clinical laboratory tests, vital signs measurement, and electrocardiograms (ECGs), will be performed according to the Schedule of Activities (Section 2).

~~For each dose after the first dose, the s~~Subjects will be admitted the day before dosing. The investigator (or qualified designee) will review all available inpatient safety data before discharging subjects from the CRU on Day 3 after the final study procedures, provided that the subjects are deemed medically fit. More information is outlined in the Schedule of Activities (Section 2.3).

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