Protocol I8F-MC-GPGG(b)

Title: Pharmacokinetics of LY3298176 Following Administration to Subjects with Impaired Renal Function

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Pharmacokinetics of LY3298176 Following Administration to Subjects with Impaired Renal Function

Confidential Information

LY3298176

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1. Protocol Synopsis

Title of Study:
Pharmacokinetics of LY3298176 Following Administration to Subjects with Impaired Renal Function

Rationale:
LY3298176 is a balanced glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor co-agonist being developed as a weekly treatment of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). Renal failure is a common sequelae of diabetes; it is therefore important to understand the influence of differing degrees of renal impairment on the pharmacokinetics (PK) of LY3298176.

Objectives/Endpoints:

Objectives	Endpoints
Primary To estimate the PK parameters of LY3298176 in subjects with mild, moderate, or severe renal impairment, and in subjects with ESRD after a single 5-mg SC dose of LY3298176 compared to control subjects with normal renal function.	• LY3298176 PK parameters, including $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max}
Secondary To assess the tolerability of LY3298176 in subjects with mild, moderate, or severe renal impairment, and in subjects with ESRD after a single 5-mg SC dose of LY3298176 compared to control subjects with normal renal function.	• Adverse events

Abbreviations: $AUC_{0-\infty}$ = area under the concentration versus time curve from time zero to infinity; $AUC_{0-tlast}$ = area under the concentration versus time curve from time zero to the time of last measured concentration; C_{max} = maximum drug concentration; ESRD = end-stage renal disease; PK = pharmacokinetic; SC = subcutaneous.

Summary of Study Design:
Study I8F-MC-GPGG is a Phase 1, multicenter, nonrandomized, open-label, parallel-design study in subjects with mild, moderate, or severe renal impairment, or end-stage renal disease (ESRD), and control subjects with normal renal function. Renal function will provide the basis for assignment to treatment group.

- Group 1: control subjects with normal renal function (estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73m^2)
- Group 2: subjects with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2)
- Group 3: subjects with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2)
- Group 4: subjects with severe renal impairment (eGFR <30 mL/min/1.73m^2 and not requiring dialysis)
- Group 5: subjects with ESRD (have received dialysis for at least 3 months).

Subjects with T2DM and renal impairment will be permitted to enroll in the study. Subjects with T2DM will not be included in Group 1.

Treatment Arms and Planned Duration for an Individual Subject:
Subjects will be screened over a 28-day period prior to dosing. Subjects will be admitted to the clinical research unit (CRU) on Day -1, receive a single subcutaneous injection of LY3298176 on Day 1, remain at the CRU until discharge on Day 5, and return to the CRU on Days 8 and 15 for PK blood sampling and other study procedures. Subjects will also return to the CRU for a follow-up visit at least 28 days postdose for final PK and study assessments.

Subjects will receive either 5 mg LY3298176 or, depending on interim analysis results, a dose of LY3298176 reduced by approximately 50%.

Number of Subjects:
Approximately 58 subjects will be enrolled so that approximately 48 subjects complete the study, such that approximately 8 subjects per group complete Groups 2 through 5. Approximately 16 completers are needed from Group 1 in order to facilitate demographic matching with the subjects in other groups.

Statistical Analysis:
Pharmacokinetics: The primary parameters for analysis are area under the concentration versus time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of last measured concentration ($AUC_{0-tlast}$), and maximum drug concentration (C_{max}); log transformation will be applied. An analysis of variance model with subject group as fixed factor will be used in the main analyses. The 90% confidence interval of the ratio between each impaired renal function group versus the control group will be estimated. Additional supportive analysis is the evaluation of the relationship between the PK of LY3298176 and mean eGFR, as determined by the Modification of Diet in Renal Disease abbreviated equation. Scatter plots of PK parameter versus eGFR will be produced and analyzed using either a mixed-effects linear or a nonlinear regression approach with eGFR as a continuous covariate on PK parameters.

Safety: Descriptive statistics will be used to summarize safety parameters.

2. Schedule of Activities

Study Schedule Protocol I8F-MC-GPGG

	Screening	Study Days								Follow-up or ED	Comments
Procedure	Days -28 to -1	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day ≥28	
Informed Consent	X										
Subject Admission to CRU		X									
LY3298176 Administration			X								Study drug will be administered after an overnight fast of at least 8 hours.
Subject Discharge from CRU							X				Subjects may stay longer at the investigator's discretion.
Outpatient Visit								X	X	X	
Medical History	X										
Physical Examination	X	X						X	X	X	After screening, medical assessment only performed to include medical review and targeted examination, as appropriate.
Weight	X	X								X	
Height	X										
Temperature	X	X									
Urine Drug Screen	X	X						X	X		
Ethanol Testing		X						X	X		
Safety 12-lead ECG (hours)	X		Predose		48		X			X	Single ECG will be collected. ECGs 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.
Supine Vital Signs (hours)	X	X	Predose, 12	24	48	72	96	168	336	X	Time points may be added, if warranted and agreed upon between Lilly and the investigator.
Clinical Laboratory Tests	X	X			X		X	X	X	X	See Appendix 2 for details.
Estimated Glomerular Filtration Rate	X	X									
Pregnancy Test	X	X						X	X		Female subjects only. See Appendix 2 for details.
AEs/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Pharmacogenomic Sample			Predose								Single sample for pharmacogenetic analysis.

	Screening	Study Days								Follow-up or ED	Comments
Procedure	Days -28 to -1	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day ≥28	
Anti-LY3298176 Antibodies (hours)			Predose						336	X	Time-matched PK sample should be collected at each time point. In the event of drug hypersensitivity reactions (immediate or non-immediate), samples will be collected as close to event onset as possible, at event resolution, and 30 days following the event. Subjects with TE ADA at follow-up/ED will undergo additional follow-up. See Section 9.6.1 for details.
Glucose Monitoring (hours)			Predose, 12	24	48	72	96	168	336	X	Performed using a bedside glucose monitor. Additional measurements may be taken at the discretion of the investigator as clinically indicated.
PK Sampling (hours)			Predose, 8, 12	24	48	72	96	168	336	X	Up to a 10% deviation from the nominal collection time is permissible.
Assessment of Injection-site Reactions (hours)			Predose, 0, 6, 12	24	48						0-hour assessment should be performed within approximately 5 minutes after subcutaneous injection. Additional assessments may be performed if deemed necessary by the investigator.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; PK = pharmacokinetic(s); T2DM = type 2 diabetes mellitus; TE ADA = treatment-emergent antidrug antibodies.

Note: All sampling times are given relative to dosing with LY3298176 (predose or hours postdose).

Note: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECGs, vital signs, clinical laboratory sample, and PK sample, with PK sampling time the priority.

3. Introduction

3.1. Study Rationale

Study I8F-MC-GPGG is a Phase 1, multicenter, nonrandomized, open-label, parallel-design study in subjects with mild, moderate, or severe renal impairment, or end-stage renal disease (ESRD), and control subjects with normal renal function.

LY3298176 is currently being investigated for its use in the treatment of hyperglycemia in patients with type 2 diabetes mellitus (T2DM). Renal failure is a common sequelae of diabetes; it is therefore important to understand the influence of differing degrees of renal impairment on the pharmacokinetics (PK) of LY3298176. The primary purpose of this study is to determine the PK of a single subcutaneous (SC) dose of LY3298176 in subjects with renal impairment compared to subjects with normal renal function. The results of this study will be used to support appropriate dose recommendations in patients with T2DM with varying degrees of renal impairment.

3.2. Background

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

LY3298176 is a long-acting, dual incretin receptor co-agonist that binds to both the GIP receptor and the GLP-1 receptor. LY3298176 consists of a peptide component based on the GIP sequence. CCI [redacted] The unique co-agonist properties of LY3298176 allow for pharmacological effects to be realized at metabolically active tissues (such as pancreatic β-cells and adipose tissue) that express both GIP and GLP-1 receptors. This could maximize the intended therapeutic benefit of increased energy utilization and greater weight loss while also improving glycemic control in patients with T2DM (Baggio and Drucker 2007).

The safety, tolerability, and PK/pharmacodynamics of LY3298176 were evaluated in a 3-part, Phase 1 clinical pharmacology trial, I8F-MC-GPGA (GPGA) in healthy subjects and patients with T2DM. In Study GPGA, LY3298176 was administered by SC injection as a single dose of 0.25 to 8 mg to healthy subjects (Part A); as multiple doses of 0.5 to 10 mg to healthy subjects (Part B); and as multiple doses of 0.5 to 15 mg administered to patients with T2DM (Part C).

Following administration of a single dose of LY3298176, the maximum drug concentration (C_{max}) was observed to occur between 8 and 96 hours. The mean terminal half-life was approximately 5 days, thus supporting a QW dosing regimen. Pharmacokinetic data from the Phase 1 study supports apparent dose-proportionality of LY3298176.

Based on preliminary data, 52 subjects (out of 142 subjects dosed in this study) received 4.5 mg (6 healthy subjects) to 5 mg as a single dose or as the first dose (32 T2DM out of 47 subjects). There were no reported LY3298176-related SAEs.

Overall, gastrointestinal events (eg, vomiting, abdominal distension, nausea, diarrhea) were the most frequently reported adverse events (AEs). These AEs increased in number and severity with increasing doses, and higher doses appeared to be better tolerated when LY3298176 was administered via dose titration. The reported gastrointestinal- (GI-) related AEs are consistent with GLP-1 pharmacology and those observed previously following administration of GLP-1 receptor agonists (RAs) (Nauck et al. 2009; Dungan et al. 2014; Giorgino et al. 2015; Jendle et al. 2016; Nauck et al. 2016).

In Part A (SAD) of Study GPGA, with increasing doses there was an increase in the number and severity of AEs related to LY3298176. At the 5-mg dose, 6 subjects reported a total of 23 AEs that were all mild in severity. At the 8-mg dose, 7 subjects reported a total of 31 AEs, 21 of which were mild and 10 moderate in severity. Two of 6 subjects who received the 5-mg dose reported 5 mild AEs of vomiting and 1 subject reported a mild AE of nausea, whereas at the 8-mg dose, 3 of 7 subjects reported 12 episodes of vomiting, and 4 of 7 subjects reported 4 AEs of nausea. Two subjects who received 8 mg as a single dose and reported AEs of vomiting and nausea required treatment with antiemetics and IV fluids. Further dose escalation was stopped and the 5-mg dose was considered the maximum tolerated dose.

Based on preliminary data from Study GPGA, the most commonly observed cardiovascular changes included increased heart rate. Consistent with other GLP-1 RAs, dose-dependent increases in pulse rate were observed with administration of LY3298176 in healthy subjects and patients with T2DM. In Part A, the largest least squares (LS) mean time-averaged pulse rate change from baseline to 168 hours compared to placebo was an increase of 8.42 bpm for the single 8-mg dose group. For the multiple dose groups, the largest LS mean increases in pulse rate compare to placebo for the time-averaged change from baseline to 72 hours were 5.24 bmp in the 10-mg titration dose group in Part B, and 10.28 bmp in the 15-mg titration dose group in Part C. However, the increases did not result in any subject discontinuations. There were no clinically significant changes in systolic or diastolic blood pressure (BP) or QT/corrected QT (QTc) interval prolongation observed in either healthy subjects or patients with T2DM.

3.3. Benefit/Risk Assessment

Preclinical data and the preliminary clinical data (see Section 3.2) from Study GPGA support further clinical development for LY3298176.

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 15 mg in Study GPGA. Based on this information, 5 mg doses to be administered in Study GPGG are reasonably anticipated to be tolerable in subjects with renal impairment and in control healthy subjects. Subjects will reside in the clinical research unit (CRU) under close monitoring for at least 5 days, with the option of being kept for longer; discharge from the CRU will be per investigator discretion. An interim analysis safety, tolerability, and PK data is planned to determine whether dose adjustments are needed (see Section 10.3.7).

For safety purposes, blood glucose levels will be monitored for all subjects. Section 9.4.3.1 describes glucose monitoring procedures and how episodes of hypoglycemia or hyperglycemia will be treated, if necessary.

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

There is no anticipated therapeutic benefit for the subjects in this study.

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

4. Objectives and Endpoints

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

Table GPGG.1. Objectives and Endpoints

Objectives	Endpoints
Primary To estimate the PK parameters of LY3298176 in subjects with mild, moderate, or severe renal impairment, and in subjects with ESRD after a single 5-mg SC dose of LY3298176 compared to control subjects with normal renal function.	• LY3298176 PK parameters, including $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max}
Secondary To assess the tolerability of LY3298176 in subjects with mild, moderate, or severe renal impairment, and in subjects with ESRD after a single 5-mg SC dose of LY3298176 compared to control subjects with normal renal function.	• Adverse events
Exploratory To evaluate the formation of ADA to LY3298176 after a single 5-mg SC dose administered to subjects with mild, moderate, or severe renal impairment, and in subjects with ESRD.	• Presence of ADA to LY3298176

Abbreviations: ADA = antidrug antibodies; $AUC_{0-\infty}$ = area under the concentration versus time curve from time zero to infinity; $AUC_{0-tlast}$ = area under the concentration versus time curve from time zero to the time of last measured concentration; C_{max} = maximum drug concentration; ESRD = end-stage renal disease; PK = pharmacokinetic; SC = subcutaneous.

5. Study Design

5.1. Overall Design

This is a Phase 1, parallel-design, open-label, multicenter, single-dose study to assess PK and tolerability of a single dose of LY3298176 in subjects with mild, moderate, or severe renal impairment, or ESRD, and control subjects with normal renal function. Control Group 1 will be healthy subjects with normal renal function. Subjects with T2DM will not be included in Group 1. Subjects with T2DM and renal impairment will be permitted to enroll in Groups 2 to 5, whereas subjects with T2DM and normal renal function will not be permitted. Subjects will be assigned to 1 of 5 groups (Groups 1 to 5) based on criteria outlined in Table GPGG.2. For description of enrollment order and interim analysis, see Section 10.3.7. Estimated glomerular filtration rate (eGFR) will be determined by the Modification of Diet in Renal Disease (MDRD) abbreviated equation (Appendix 8) using serum creatinine levels obtained at Screening and on Day -1; subjects will be assigned to groups based on values from Day -1. See Sections 5.2 and 10.1 for sample size information.

The control subjects (Group 1) will be selected in order that the mean and distribution of Group 1 are comparable to the mean and distribution for each group with renal impairment (Groups 2 through 5) for age (±10 years), sex, race, weight (± 10 kg), and body mass index (BMI) (±20%), as far as is practically possible (additional information will be provided to the investigators in a separate document) (FDA 2010). An effort will be made to enroll control subjects that are representative of the races of the impaired subjects. One-to-one matching of subjects (1 impaired subject matched to 1 healthy subject in 1 or more impairment groups using the same criteria previously described) may be used to facilitate interim analysis.

Table GPGG.2. Subject Groups based on Renal Impairment Status

	Classification	eGFR (mL/min/1.73m^2)
Group 1	Control (normal renal function)	≥90
Group 2	Mild renal impairment	60-89
Group 3	Moderate renal impairment	30-59
Group 4	Severe renal impairment	<30 and not requiring dialysis
Group 5	End-stage renal disease	Requiring dialysis

Abbreviations: eGFR = estimated glomerular filtration rate (as determined by the Modification of Diet in Renal Disease abbreviated equation).

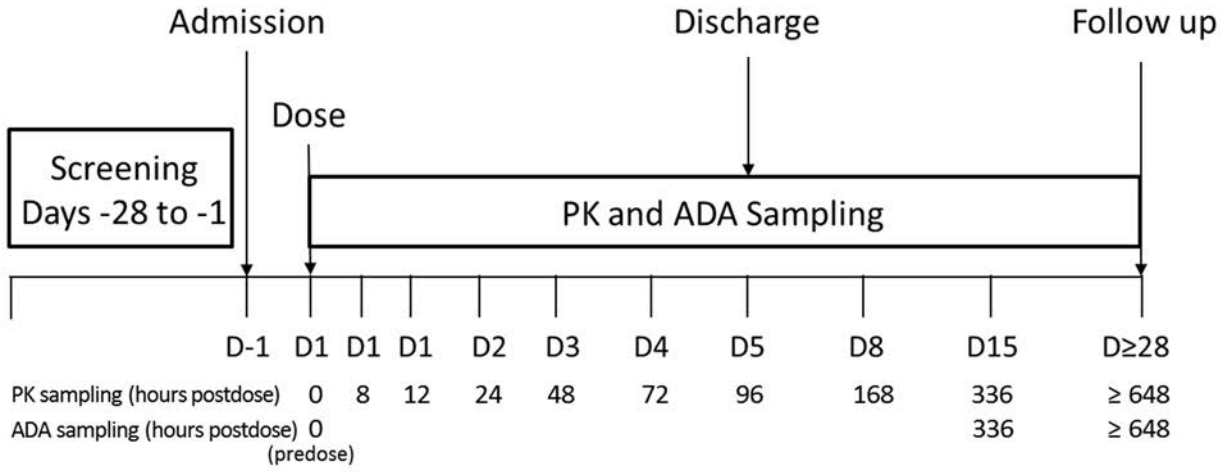
Figure GPGG.1 and Figure GPGG.2 illustrate the study design.

Subjects will visit the CRU to sign the informed consent document and undergo screening procedures up to 28 days prior to dosing.

Subjects will be admitted to the CRU on Day -1. Subjects will be administered a single dose of LY3298176 on Day 1 and will remain in the CRU until after assessments are completed on Day 5. Subjects will return for study visits on Days 8 and 15 and for a final follow-up visit at least 28 days postdose. Clinical laboratory tests, physical examination, vital signs, 12-lead electrocardiograms (ECGs), injection-site reactions, glucose monitoring, AEs, and antidrug antibodies (ADA) will be monitored to assess safety and tolerability. Blood samples for PK and immunogenicity analysis will be collected predose through the final follow-up visit.

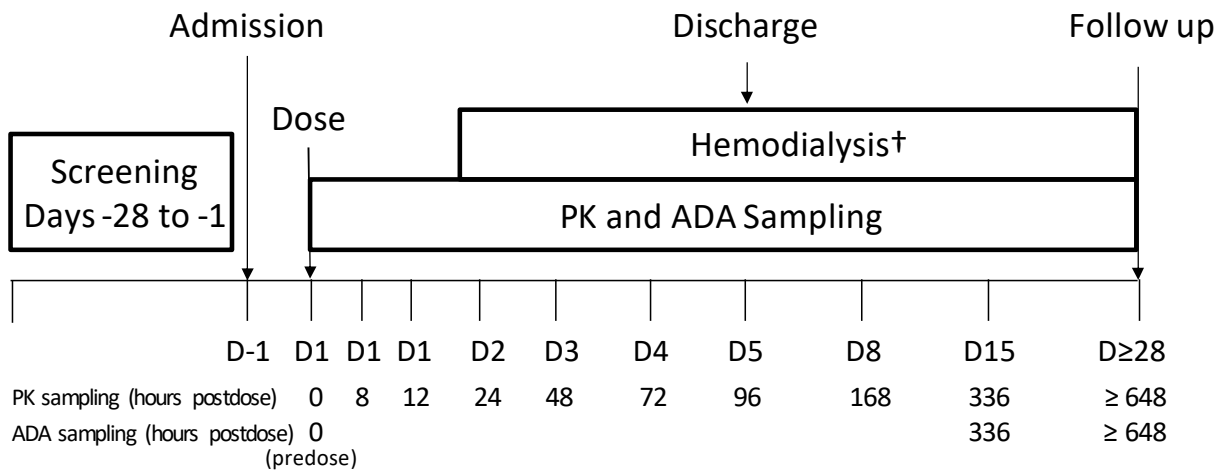
For subjects with ESRD, administration of LY3298176 should occur at least 24 hours prior to the next planned dialysis session. The time and dates of dialysis sessions from the session immediately prior to dose through Day 8 will be recorded in the case report form (CRF). To eliminate potential variation between different types of dialysis membrane, only high-flux polysulfone membranes will be used.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: ADA = antidrug antibodies; D = Day; PK = pharmacokinetic.

Figure GPGG.1. Illustration of study design for Groups 1 to 4.



† The first postdose dialysis session should be scheduled to start at least 24 hours after administration of LY3298176. Subsequent dialysis sessions should be scheduled as clinically appropriate.

Abbreviations: ADA = antidrug antibody; D = Day; PK = pharmacokinetic.

Figure GPGG.2. Illustration of study design for Group 5.

5.2. Number of Participants

Approximately 58 subjects will be enrolled so that approximately 48 subjects complete the study, such that approximately 8 subjects per group complete Groups 2 through 5 (EMEA CHMP 2016). Approximately 16 completers are needed from Group 1 in order to facilitate demographic matching with the subjects in other groups.

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

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

A comprehensive range of renal impairment is necessary to fully characterize the impact of renal impairment on the PK of LY3298176. Subjects undergoing dialysis (Group 5) will be included to determine the effect of dialysis on drug removal.

This study has been designed in accordance with the current regulatory guidances (EMEA CHMP 2016; FDA 2010) for the study of PK in subjects with impaired renal function. LY3298176 has shown linear and dose-proportional PK, based on preliminary SAD and MAD data in the Phase 1 Study GPGA. Per FDA guidance "a single-dose study is satisfactory for cases where there is clear prior evidence that single-dose studies accurately describe the PK for the drug and potentially active metabolites" (FDA 2010). This renal impairment study will be conducted as a single-dose study.

This study will be open-label. As the primary endpoints are objective rather than subjective, investigators and subjects do not need to be blinded.

Based on the molecular weight of LY3298176, its PK may be impacted by renal impairment. However, LY3298176 is expected to bind to albumin (because of the C20 fatty acid conjugation structure), thus systemically resulting in a larger molecular size and decreasing the likelihood that PK will be meaningfully impacted by renal impairment. Thus the same dose of LY3298176 is planned to be administered to subjects in all groups.

An interim analysis each are planned following dosing of at least 2 subjects in Groups 2 and 3 and appropriate matched-control subjects in Group 1, and following dosing of at least 2 subjects in Groups 4 and 5 and appropriate matched-control subjects in Group 1. An additional interim analysis will be done after completion of the Group 3 (see Section 10.3.7). The purpose of the interim review(s) is to determine the dose level(s) for subsequent subjects, based on safety, tolerability, and PK data. The dose of LY3298176 for subsequent subjects (any or all groups) may be adjusted accordingly after each interim. Data from the additional interim (completion of Group 3) will support Phase 3 enrollment.

5.5. Justification for Dose

A 5-mg dose was selected based on preclinical pharmacology and toxicology data. In addition, preliminary results from Study GPGA indicate the 5-mg dose was relatively well tolerated by healthy subjects and patients with T2DM, and is expected to be a clinically meaningful dose. In Study GPGA Part A (SAD), 5 mg was considered the maximum tolerated dose.

An interim review of data from at least 2 subjects in each of the mild and moderate renal impairment groups and appropriate matched-control subjects will be used to determine whether to continue administering the 5-mg dose to the remaining subjects (see Section 10.3.7). Another review will be performed following dosing of 2 subjects in the severe renal impairment and ESRD groups and appropriate matched-control subjects. Both reviews will assess safety and tolerability data. The PK data will also be analyzed during these reviews. If it appears that the PK are influenced by renal impairment and the exposure in subjects with impairment is higher than expected or if there are safety/tolerability events that manifest at a higher than expected rate in these subjects, then the dose would be reduced by approximately 50%.

6. Study Population

Eligibility of subjects for study enrollment will be based on the results of a screening medical history, physical examination, clinical laboratory tests, and ECG. 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 dosing.

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

6.1. Inclusion Criteria

All subjects must meet the following criteria for enrollment (Inclusion Criteria [1] through [6]). Additional subgroupings of inclusion criteria below are specific to the subjects' renal function (Inclusion Criteria [7] through [12]) and diabetic status (Inclusion Criteria [13] through [16]).

6.1.1. Inclusion Criteria for All Subjects

[1a] Male subjects:

Men, regardless of their fertility status, with non-pregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be approximately 30 days following dose of study drug (below the no-observed-adverse-effect level [NOAEL]/10).

- Men and their partners may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential (below the NOAEL/10).

Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be approximately 30 days following dose of study drug (below the NOAEL/10).

[1b] Female subjects:

Women of childbearing potential are excluded from the study.

Women not of childbearing potential may participate and include those who are:

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

B. postmenopausal – defined as either:

i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either:

a) cessation of menses for at least 1 year, or

b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 IU/mL; or

ii. A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[2] Are between the ages of 18 and 85 years, inclusive.

[3] Are between the BMI of 19.0 and 40.0 kg/m^2, inclusive, at screening.

[4] Have venous access sufficient to allow blood sampling as per the protocol.

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

[6] Have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

6.1.2. Additional Inclusion Criteria for Control Subjects

[7] Healthy males or females as determined by medical history, physical examination, and other screening procedures, with normal renal function, assessed by eGFR ≥90 mL/min at screening.

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

[9] Have normal BP and pulse rate, as determined by the investigator.

6.1.3. Additional Inclusion Criteria for Subjects with Mild to Severe Renal Impairment or ESRD

[10] Males or females with stable mild to severe renal impairment, assessed by eGFR or with ESRD (having received dialysis for at least 3 months).

[11] Clinical laboratory test results with deviations that are judged by the investigator to be compatible with the renal condition of the subject or of no additional clinical significance for this study.

[12] Have acceptable BP and pulse rate, as determined by the investigator.

6.1.4. Additional Inclusion Criteria for Subjects with T2DM and Renal Impairment or ESRD

[13] Have T2DM treated with diet or exercise alone or with stable doses of metformin and/or insulins for at least 8 weeks.

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

[15] Have a hemoglobin A1c (HbA1c) ≥6.0% and ≤11.0% at the screening visit.

[16] Have clinical laboratory test results within normal range or deemed clinically insignificant by the investigator. Abnormalities of serum glucose, serum lipids, urinary glucose, and urinary protein consistent with T2DM are acceptable.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment. For all subjects, Exclusion Criteria [17] through [42] apply; additional subgroupings of exclusion criteria below are specific to the subjects' renal function (Exclusion Criteria [43] through [45]) and diabetic status (Exclusion Criteria [46] through [49]).

6.2.1. Exclusion Criteria for All Subjects

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

[18] Are Lilly employees.

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

[20] Have known allergies to LY3298176 or related compounds.

[21] 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).

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

[23] Persons who have a current, functioning organ transplant. Nonfunctional renal allografts may be allowed.

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

[25] Febrile illness within 3 days prior to screening.

[26] Have a history of second- or third-degree heart block 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.

[27] Have a significant history or presence of cardiovascular (eg, myocardial infarction, cerebrovascular accident, etc. within the past 6 months), respiratory, hepatic, renal (applies to Group 1 only), GI, endocrine (except T2DM), hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study medication; or of interfering with the interpretation of data.

[28] Show evidence of significant active neuropsychiatric disease.

[29] Have a history of malignancy within 5 years prior to screening.

[30] Have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase or 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 DPP-IV inhibitors. Subjects with dyslipidemia and subjects who had cholecystolithiasis (removal of gall stones) and/or cholecystectomy (removal of gall bladder) in the past, with no further sequelae, may be included in the study at the discretion of the investigator.

[31] Have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× the upper limit of normal (ULN) or total bilirubin (TBL) >1.5× ULN.

[32] Have a serum triglyceride ≥5 mmol/L (442.5 mg/dL) at screening.

[33] Show evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies.

[34] Show evidence of hepatitis C and/or positive hepatitis C antibody.

[35] Show evidence of hepatitis B and/or positive hepatitis B surface antigen.

[36] Are women with a positive pregnancy test or women who are lactating.

[37] Regularly use known drugs of abuse and/or show positive findings on urinary drug screen that are not otherwise explained by permitted concomitant medications.

[38] Intend to use:

a. over-the-counter medication within 7 days prior to dosing.

b. prescription medication (other than those listed in Section 7.7 and Appendix 7) within 14 days prior to dosing.

c. herbal preparations within the 14 days prior to screening.

If this situation arises, an otherwise suitable subject may be included at the discretion of the investigator.

[39] Have donated blood of more than 450 mL within the last month.

[40] Have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males over 65 and females), and are unwilling to stop alcohol consumption 24 hours prior to dosing until discharge from the study or completion of all study procedures (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).

[41] Are unwilling to refrain from smoking on the day of LY3298176 administration or are unable to abide by CRU restrictions.

[42] Are determined to be unsuitable by the investigator for any reason.

6.2.2. Additional Exclusion Criteria for Subjects with Mild to Severe Renal Impairment or ESRD

[43] Have hemoglobin <8.5 g/dL or significant active hematological disease from causes other than underlying renal disease.

[44] Have used any drug indicated for medical care of the subject's renal impairment, which is not established in dose and administered for at least 7 days before LY3298176 administration.

[45] Positive findings on ethanol testing and use of drugs of abuse and/or positive findings on urinary drug screen except those prescribed for related complications (ie, pain, insomnia, anxiety) of renal disease. A serum or salivary drug screen may be performed on subjects who are unable to produce a urine sample.

6.2.3. Additional Exclusion Criteria for Subjects with T2DM and Renal Impairment or ESRD

[46] Have taken any glucose-lowering medications other than metformin and/or insulins (refer to Inclusion Criterion [13]) in the past 3 months before screening. In general, stable dosages of metformin and insulins will be continued; however, a washout period or dose modifications may be necessary to allow for optimal blood glucose monitoring throughout the dosing period at the discretion of the investigator.

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

[48] Have had a blood transfusion or severe blood loss or have known hemoglobinopathy (alpha-thalassemia), hemolytic anemia, sickle cell anemia, or any other condition known to interfere with HbA1c methodology.

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

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, 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 being given an SC dose of LY3298176, and when clinical laboratory test samples are taken (see Schedule of Activities [Section 2]). Water may be consumed freely. Standard meals will be administered while subjects are resident at the CRU.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed from 24 hours prior to dosing until discharge from the study or completion of all study procedures. 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 dosing until discharge from the study or completion of all study procedures. When certain study procedures are in progress at the site, subjects may be required to remain supine or sitting.

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

LY3298176 will be administered at the CRU as a single SC injection of either 5 mg or, depending on the results of interim analysis, a dose reduced by approximately 50%. Instructions for preparation and handling are summarized in Section 7.5.

Whenever possible, study drug administration should be carried out by the same personnel. Dosing will commence at approximately the same time of day in all dose groups. The actual time of dosing will be recorded in the subject's CRF.

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. LY3298176 will be supplied by Lilly or its representative in accordance with current good manufacturing practices and will be supplied with lot numbers.

LY3298176 is supplied as 5-mg lyophilized powder in a glass vial intended for single-dose administration. When reconstituted according to instructions, the LY3298176 solution should be clear, colorless, and free of any visible particulate matter.

A pharmacist at the site or other site personnel will use the vials provided to prepare the syringes.

7.2. Method of Treatment Assignment

Subjects will be assigned to groups based on mean eGFR as determined by the MDRD abbreviated equation using serum creatinine levels obtained on Day -1 (see Table GPGG.2). The allocation and dispensing of the IP will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained by the site pharmacist.

7.2.1. Selection and Timing of Doses

A single dose will be administered by site personnel to each subject in the morning of Day 1. The site of injection administration will be recorded.

7.3. Blinding

Not applicable. This will be an open-label study.

7.4. Dose Modification

The planned dose for subjects in this study is 5 mg. Following dosing of at least 2 subjects each with mild and moderate renal impairment (Group 2 and Group 3, respectively) and appropriate matched-control subjects (Group 1), an interim analysis, to include safety, tolerability, and PK data, is planned (Section 10.3.7 and Figure GPGG.3). Safety data will be reviewed by the Lilly study team on a regular basis while subjects are enrolled in the study. After dosing of the first 2 subjects with severe renal impairment and ESRD (Groups 4 and 5) and appropriate matched-control subjects (Group 1), another interim analysis will be performed. The purpose of the interim review(s) is to determine the dose level(s) for subsequent subjects. The dose of LY3298176 for subsequent subjects (any or all groups) may be adjusted accordingly after each interim review. The final dose determinations will be made by the investigator and the Lilly study team.

7.5. Preparation/Handling/Storage/Accountability

LY3298176 lyophilized powder is to be reconstituted with Sterile Water for Injection (United States Pharmacopoeia). 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. Detailed instructions for the preparation and handling of LY3298176 will be provided by the sponsor.

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

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

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Stable doses of over-the-counter or prescription medications (eg, antihypertensive agents, aspirin, lipid-lowering agents) for treatment of concurrent medical conditions are allowed for subjects with renal impairment. Refer to Appendix 7 for common medications prescribed to

patients with renal impairment. Subjects on stable concomitant medication(s) at the time of study entry should continue their regular, unchanged dose throughout the study.

Stable single oral doses of metformin and/or stable doses of insulins (for at least 8 weeks) are allowed for subjects with T2DM. Refer to Exclusion Criterion [46] in Section 6.2.3.

In the case of mild intercurrent illness during the study, concomitant treatment with paracetamol/acetaminophen may be allowed at the discretion of the investigator and is to be recorded in the CRF.

No start of new concomitant therapy, apart from occasional intake of vitamin/mineral supplements, allowable antiemetics, and acetaminophen, will be permitted for 14 days before the first dose of LY3298176 through the final poststudy follow-up visit. If the need for new or changes to concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator, preferably after consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP).

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

7.8. Treatment after the End of the Study

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

8. Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

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 CP/CRP 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 CP/CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with IP.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
- Investigator Decision
    - the investigator decides that the 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 T2DM, discontinuation from the study should occur prior to introduction of the new agent
- Subject Decision
    - the subject requests to be withdrawn from the study
- Adverse event
    - if a clinically significant event (CSE) occurs, the subject is to be discontinued and appropriate measures taken. Lilly or its designee should be alerted immediately. A CSE will be defined as a moderate-to-severe AE, abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the subject
    - a clinically significant systemic hypersensitivity reaction occurs following administration of the IP (eg, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) that requires parenteral medication, does not respond to symptomatic medication, or results in clinical sequelae or an anaphylactic reaction

- At the discretion of the investigator, if the participant has 2 or more symptomatic hypoglycemic episodes (defined as an event with typical hypoglycemic symptoms and a measured blood glucose ≤63 mg/dL [3.5 mmol/L], equivalent to plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]; refer to Section 9.4.3)
- Fasting plasma/serum glucose values are >270 mg/dL (approximately 15 mmol/L, equivalent to a fasting blood glucose >241 mg/dL [13.4 mmol/L]) on 3 or more separate days over any 2-week period between screening and the end of the dosing period
- Discontinuation for abnormal pancreatic tests should be considered by the investigator if a subject's lipase and/or amylase are confirmed to be ≥3× ULN. Please refer to the algorithm for the monitoring of pancreatic events in Appendix 6.

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

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

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

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

9.1. Efficacy Assessments

This section is not applicable for this study.

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 event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

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 health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the subject to discontinue the IP 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 is signed, study site personnel will record, via CRF, 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 or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the IP, 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.

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 may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly CRP/CP, or 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 CRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received IP. However, if an SAE occurs after signing informed consent, but prior to receiving IP, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

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

Pregnancy (maternal or paternal exposure to IP) 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 IP or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3298176 is considered any dose higher than the assigned dose. Treatment for overdose is supportive care (refer to IB for LY3298176).

9.4. Safety

9.4.1. Clinical Laboratory Tests

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

Additional blood draws may be drawn for safety purposes at the investigator's discretion.

9.4.2. Amylase and Lipase Measurements

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing and as specified in the Schedule of Activities (Section 2). Additional measurements may be performed at the investigator's discretion. Further diagnostic assessments will be recommended as per the algorithm (refer to Appendix 6) for the monitoring of pancreatic events whenever lipase and/or amylase is confirmed to be ≥3× ULN at any visit postdose, even if the subject is asymptomatic.

9.4.3. Glucose Monitoring

For safety purposes, blood glucose measurements will be performed using a bedside glucose monitor as specified in the Schedule of Activities (Section 2). Additional safety blood glucose measurements may also be taken during the study as deemed necessary by the investigator.

9.4.3.1. 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 IP 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 CRF 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 (ADA 2017) based on recommendations of the International Hypoglycaemia Study Group (IHSG 2017) should be applied for reporting in the CRF and evaluating hypoglycemic events.

Hypoglycemia will be described using the following definitions:

- **Documented Glucose Alert Level (Level 1), Plasma Glucose (PG) ≤70mg/dL (3.9 mmol/L):**
    - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
    - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (3.9 mmol/L)
    - **Unspecified hypoglycemia**: an event during which PG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycemia was recorded
- **Documented Clinically Significant Hypoglycemia (Level 2) PG <54 mg/dL (3.0 mmol/L):**
    - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG <54 mg/dL (3.0 mmol/L)
    - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG <54 mg/dL (3.0 mmol/L)
    - **Unspecified hypoglycemia:** an event during which PG <54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded
- **Severe hypoglycemia (Level 3):** an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. PG measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L])
    - **Severe hypoglycemia requiring medical attention:** a severe hypoglycemic event when subjects require therapy by healthcare professionals (eg, emergency medical technicians, emergency room personnel, etc.)

Other Hypoglycemia:

- **Nocturnal hypoglycemia:** any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking

- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, that do not require the assistance of another person, are accompanied by PG >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold
- **Overall (or total) hypoglycemia:** This optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category
- **Probable symptomatic hypoglycemia:** An event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

9.4.3.2. Severe Hypoglycemia

The determination of a hypoglycemic event as an episode of severe hypoglycemia as defined above will be made by the investigator based on the medical need of the subject to have required assistance and is not predicated on the report of a subject simply having received assistance.

All hypoglycemic events are AEs of special interest and will be recorded in the hypoglycemia module of the CRF (see Section 9.2 for details). All episodes of severe hypoglycemia must be reported as SAEs.

9.4.4. Vital Signs

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

Blood pressure and pulse rate should be measured after the subject has been supine for approximately 5 to 10 minutes.

During any AE of dizziness or posture-induced symptoms, unscheduled orthostatic vital signs should be assessed if possible. If the subject feels unable to stand, supine vital signs only will be recorded. Additional vital signs may be measured during the study if warranted.

9.4.5. Electrocardiograms

For each subject, single 12-lead digital ECGs should 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 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/QTc interval from baseline) after enrollment, the investigator will determine if 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 to Lilly or its designee via CRF.

9.4.6. Injection-site Reactions

For each subject, injection-site reactions should be assessed according to the Schedule of Activities (Section 2). Additional assessments may be performed if deemed necessary by the investigator.

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.

9.4.7. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study.

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

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

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3× ULN at any visit postdose even if the subject is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Appendix 6) and, if pancreatitis is suspected, the case will be further defined during an adjudication process.

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

9.4.7.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3× ULN, alkaline phosphatase (ALP) ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to

confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP 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 ≥5× ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.5. Pharmacokinetics

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

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

9.6. Pharmacodynamics

Not applicable.

9.6.1. Immunogenicity Assessments

For immunogenicity testing, venous blood samples of approximately 10 mL will be collected from each subject according to the Schedule of Activities (Section 2) to determine antibody production against LY3298176. Additional samples may be collected if there is a possibility that an AE is immunologically mediated. All samples for immunogenicity testing should have a time-matched sample for PK analysis. 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 24-hour clock time of each sampling will be recorded.

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of LY3298176. Antibodies may be further evaluated for their ability to neutralize the activity of LY3298176. Positive LY3298176 ADA samples may also be tested for cross-reactivity with native GLP-1 and GIP, and, if positive, may then be tested for neutralizing antibodies against native GLP-1 and GIP.

All subjects will have an ADA sample measured at early discontinuation or at the follow-up visit. A risk-based approach will be used to monitor subjects who develop treatment-emergent ADA (TE ADA), defined as a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay if no ADA were detected at baseline, or a 4-fold (2 dilutions) increase in titer, compared to baseline, if ADA were detected at baseline.

Clinically significant TE ADA will be defined as any TE ADA at the last visit with:

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

Subjects who have clinically significant TE ADA at early discontinuation or at the follow-up visit should be followed with ADA testing every 3 months for approximately 1 year or until the ADA titers have returned to the baseline ADA titer (defined as ADA titer within 2-fold of baseline). 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 ADA may also be asked to return for additional follow-up testing.

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

9.7. Genetics

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to LY3298176 and to investigate genetic variants thought to play a role in T2DM. 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 impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3298176 or after LY3298176 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 58 subjects will be enrolled so that approximately 48 subjects complete the study, such that approximately 8 subjects per group complete Groups 2 through 5. Approximately 16 completers are needed from Group 1 in order to facilitate demographic matching with the subjects in other groups.

The sample size is not selected to satisfy a priori statistical requirement. However, the sample size (16 subjects for the control group and 8 subjects per group for the other groups) will provide a 90% coverage probability of the half-width of the 90% confidence interval within 0.29 on a log-scale for comparison of each group to the control group for AUC or C_{max}. Assuming the variability (coefficient of variation [CV]) is 32%. In the natural scale, assuming the ratio is r, the 90% confidence interval for the ratio should be within (0.74r, 1.34r).

Subjects who are enrolled but not administered treatment may be replaced to ensure that a sufficient number of subjects complete the 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, smoking habits, or other demographic characteristics will be recorded and may be used in the PK and safety analyses as quantitative or classification variables. Study participants' renal status grouping will be determined using a mean of the eGFR estimates, determined by the MDRD abbreviated equation and based on measurements of serum creatinine levels obtained on Day -1.

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 one dose of the IP and have evaluable PK.

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

Immunogenicity analyses will be conducted for all subjects who receive at least one dose of IP.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IP 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 IP as perceived by the investigator. Symptoms reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety clinical laboratory parameters (including amylase, lipase, and blood glucose), vital signs, physical examinations, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Physical examinations and ECGs will be performed for safety monitoring purposes and will not be presented. If warranted, additional analysis will be performed upon review of the data.

10.3.1.3. Injection-site Reactions

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 area under the concentration versus time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the time of last measured concentration ($AUC_{0-tlast}$), and maximum drug concentration (C_{max}). Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

The main analysis is the evaluation of log-transformed $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} using an analysis of variance model with subject group as a fixed factor. The 90% confidence interval of the ratio between each impaired renal function group versus the control group will be estimated. The above analyses will be conducted twice, using different renal function group assignments (eGFR or creatinine clearance [CLcr] based on Day -1 measurements) (Table GPGG.3). The

analysis based on CLcr will be exploratory. Additionally an exploratory analysis based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method of renal impairment classification (Chronic Kidney Disease Epidemiology Collaboration, 2009) may also be performed.

Table GPGG.3. Renal Function Classification for Primary Analyses

Group	Classification	eGFR (mL/min/1.73 m^2)[a]	CLcr (mL/min)[b]
1	Control (normal renal function)	≥90	≥90
2	Mild renal impairment	60-89	60-89
3	Moderate renal impairment	30-59	30-59
4	Severe renal impairment	<30, not requiring dialysis	<30, not requiring dialysis
5	End-stage renal disease	Requiring dialysis	Requiring dialysis

Abbreviations: CLcr = creatinine clearance; eGFR = estimated glomerular filtration rate.

[a] Per enrollment classification; eGFR will be calculated using the Modification of Diet in Renal Disease abbreviated equation.

[b] CLcr will be calculated using the Cockcroft-Gault formula (Cockcroft and Gault 1976).

The supporting additional analysis is the evaluation of the relationship between the PK of LY3298176 and mean eGFR, as determined by the MDRD abbreviated equation. Scatter plots of PK parameter versus eGFR will be produced and analyzed using either a mixed-effects linear or a nonlinear regression approach with eGFR as a continuous covariate on PK parameters.

The time to C_{max} will be analyzed using a Wilcoxon rank sum test.

If a dose adjustment after interim is needed, descriptive statistics for the PK parameters will be summarized by dose and subject groups. Dose normalization or other methods may be employed for statistical analyses. Details of methods will be described in the Statistical Analysis Plan.

10.3.3. Pharmacodynamic Analyses

Not applicable.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.5. Evaluation of Immunogenicity

Subjects will be assessed for the development of TE ADA; the distribution of maximum titers will be described. If cross-reactivity with native GLP-1 and GIP or neutralizing antibodies against native GLP-1 and GIP assays are performed, the frequency of each will be reported.

The relationship between the presence of antibodies and the PK parameters and safety may be assessed.

10.3.6. Data Review During the Study

Data may be analyzed while the trial is ongoing. An assessment committee will not be formed. Safety data will be reviewed by the Lilly study team on a regular basis while subjects are enrolled in the study.

10.3.7. Interim Analyses

Interim analyses are planned to occur during Study GPGG. Figure GPGG.3 illustrates the interim data review decision tree.

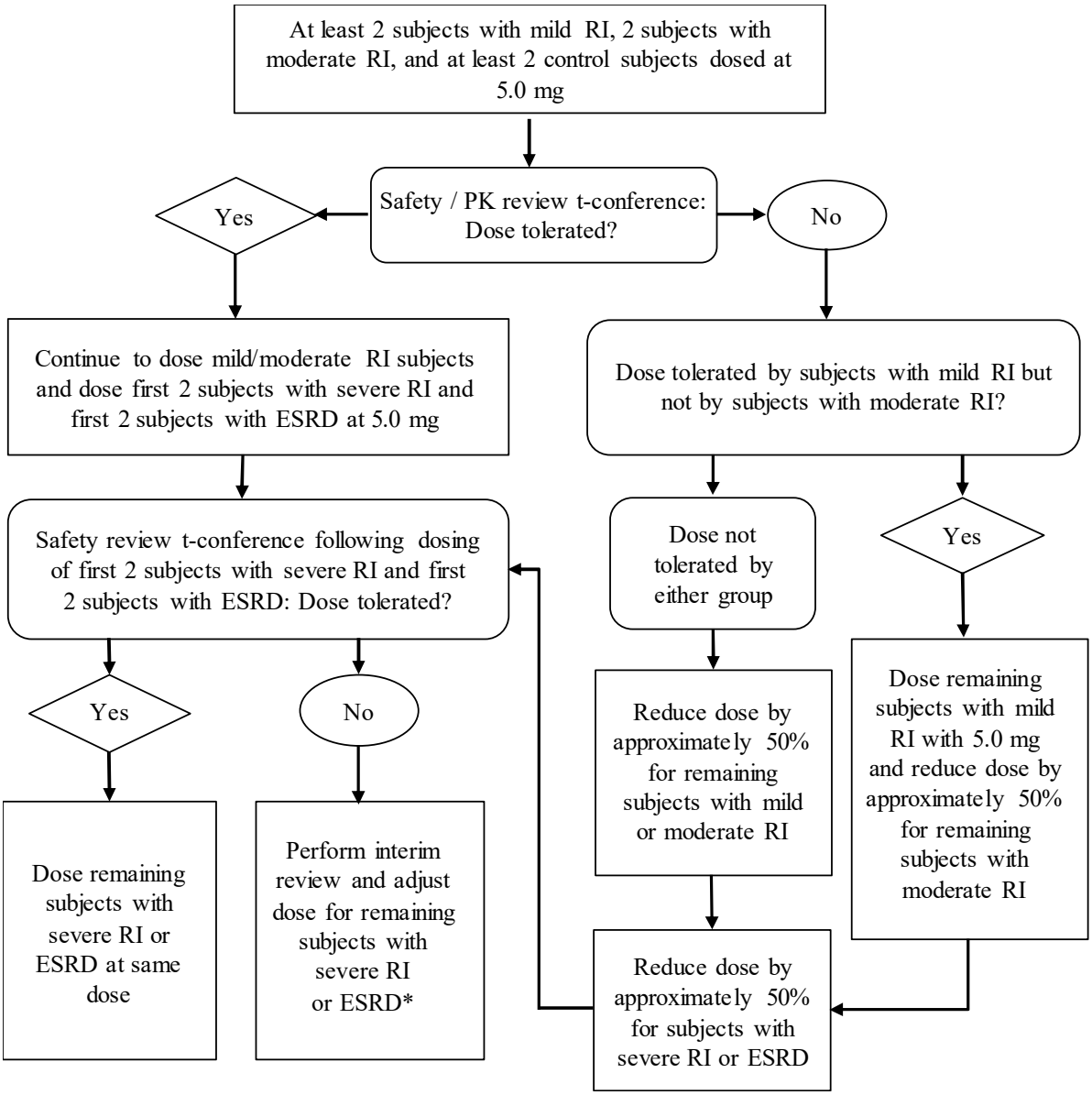
Two subjects each from Groups 2 and 3 (subjects with mild and moderate renal impairment, respectively) and at least 2 subjects in Group 1 (appropriate matched-control subjects with normal renal function) will be enrolled in parallel and dosed with 5 mg LY3298176, followed by an interim analysis to evaluate safety, tolerability, and PK data. Based on this interim analysis, a decision will be made about whether or not a dose adjustment is needed, and the study will continue with dosing of the remaining subjects in 2 and 3, along with the first 2 subjects from Groups 4 and 5 (subjects with severe renal impairment and ESRD, respectively) and appropriate matched-control subjects in Group 1.

A second interim analysis to evaluate safety, tolerability, and PK data will be performed for all subjects in Group 3 (moderate renal impairment) on completion of follow-up visit. Data from this interim will support Phase 3 enrollment.

After dosing of the first 2 subjects in each of Groups 4 and 5 and their appropriate matched-control subjects, a third interim analysis will be performed to evaluate safety, tolerability, and PK data. Based on data from the third interim review, a decision will be made regarding dose level. The study will then continue with the remaining subjects with severe renal impairment and ESRD (Groups 4 and 5, respectively) and their applicable matched-control subjects (Group 1).

The purpose of the interim review(s) is to determine the dose level(s) for subsequent subjects. The dose of LY3298176 for subsequent subjects (any or all groups) may be adjusted accordingly after each interim. A reduced dose of approximately 50% is planned, if needed. The final dose determinations will be made by the investigator and the Lilly study team.

If an additional unplanned interim analysis is deemed necessary, the Lilly CP, CRP, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.



Abbreviations: ESRD = end-stage renal disease; PK = pharmacokinetic; RI = renal impairment; t-conference = teleconference.

*If the subjects with severe RI or ESRD are already being administered a reduced dose, it may be necessary to discontinue enrollment of 1 or both of these groups.

Figure GPGG.3. Interim data review decision tree.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0-\infty}$	area under the concentration versus time curve from time zero to infinity
$AUC_{0-tlast}$	area under the concentration versus time curve from time zero to the time of last measured concentration
BP	blood pressure
BMI	body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLcr	creatinine clearance
C_{max}	maximum drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist

CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSE	clinically significant event
DPP	dipeptidyl peptidase
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
ESRD	end-stage renal disease
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
informed consent	A process by which a 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

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.
IP	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.
LS	least squares
MDRD	Modification of Diet in Renal Disease
NOAEL	no-observed-adverse-effect level
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.
PG	plasma glucose
PK	pharmacokinetic(s)
QTc	corrected QT interval
QW	once weekly
RA	receptor agonist
SAE	serious adverse event
SC	subcutaneous
S_{cr}	serum creatinine
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
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TE ADA	treatment-emergent antidrug antibodies
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology[a]:	Clinical Chemistry[a]:
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Magnesium
Absolute counts of:	Glucose, fasting
Neutrophils	Blood urea nitrogen
Lymphocytes	Uric acid
Monocytes	Total cholesterol
Eosinophils	Triglycerides
Basophils	Total protein
Platelets	Albumin
Cell morphology[b]	Total bilirubin
	Alkaline phosphatase
	Aspartate aminotransferase
	Alanine aminotransferase
Urinalysis[a]:	Creatinine
Specific gravity	Gamma-glutamyl transferase
pH	Amylase
Protein	Lipase
Glucose	
Ketones	Ethanol testing[d]
Bilirubin	Urine drug screen[d]
Urobilinogen	Hepatitis B surface antigen[c]
Blood	Hepatitis C antibody[c]
Nitrite	HIV[c]
Microscopic examination of sediment[b]	Pregnancy test[e]
	FSH[c,f]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

a Performed by local laboratory at screening and by central laboratory at all other time points.

b If clinically indicated, per investigator's discretion.

c Performed by local laboratory at screening only.

d Urine drug screen performed in clinic or by local laboratory at screening and repeated prior to admission to the clinical research unit. Ethanol testing will be performed at admission to the clinical research unit. Urine drug screen and ethanol level will be repeated at other times indicated in the Schedule of Activities. A serum or salivary drug screen may be performed on subjects who are unable to produce a urine sample.

e Female subjects only. Serum pregnancy test performed by local laboratory at screening; urine pregnancy test performed in clinic at all other times.

f Female subjects only. To confirm postmenopausal status as needed.

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 their 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 or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly 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 Council for Harmonization (ICH) guidelines and other applicable laws and regulations.

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

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

- the current Investigator's Brochure and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

Final Report Signature

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

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the 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.

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 (direct) 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]**
CK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; 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-GPGG Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12	5	60
Pharmacokinetics[a]	3	13	26
Immunogenicity[a]	10	3	30
Pharmacogenetics	10	1	10
Glucose monitoring[a]	0.5	9	4.5
Total			175.5
Total for clinical purposes rounded up to nearest 10 mL			180

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

Appendix 6. Pancreatic Monitoring

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

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

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

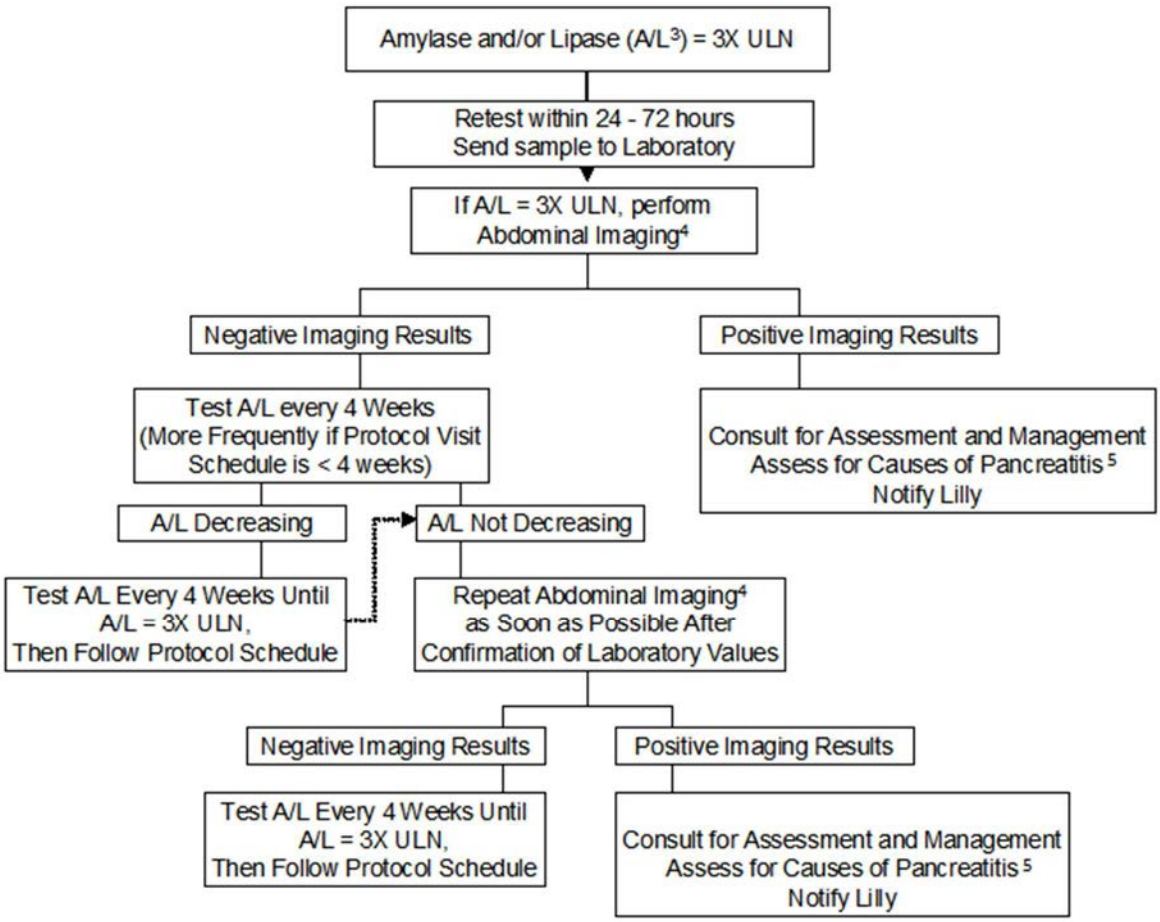
Acute pancreatitis is an adverse event defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

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

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

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

Follow this algorithm when the value(s) for serum amylase and/or lipase are ≥3× upper limit of normal.



1. Symptomatic – related 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 subject has symptoms of acute pancreatitis:
   (a) Discontinue subject
   (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 algorithm criteria.
4. Abdominal imaging is most valuable when performed at the time of elevated enzymes. If, in the opinion of the investigator, it is safe for the subject to receive contrast, and 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 trigycerides). Record all concomitant medications

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

Appendix 7. Permitted Concomitant Medication

Common medications prescribed to patients with renal impairment

Other drugs not listed in this table may be authorized for use during the study at the discretion of the investigator in consultation with the Lilly clinical pharmacologist or clinical research physician.

Therapeutic Category	Medication
Vitamin D compounds	Doxercalciferol
Anemia / iron deficiency	Erythropoietin, intravenous or oral iron
Antihypertensives	Beta blockers, ACE inhibitors, controlled release calcium channel blockers, angiotensin II receptor agonists
Hypolipidemics	HMG-CoA reductase inhibitors (Atorvastatin, Simvastatin, Pravastatin, Fluvastatin)
Antihyperuricemics	Allopurinol
Vasodilators	Nitrates
Diuretics	Furosemide, Hydrochlorothiazide, Spironolactone
Phosphate binding agents	Calcium acetate, calcium carbonate, Sevelamer

Appendix 8. Calculation of Estimated Glomerular Filtration Rate

Calculation of estimated glomerular filtration rate (eGFR) from serum creatinine (S_{cr}) assayed using an isotope dilution mass spectrometry method and using the Modification of Diet in Renal Disease abbreviated equation (Levey et al. 2006). The equation does not require weight or height variables because the results are reported normalized to an accepted average adult body surface area of 1.73 m^2. The equation has been validated extensively in Caucasian and African American populations between the ages of 18 and 70 with impaired kidney function (eGFR <60 mL/min/1.73 m^2) and has shown good performance for patients with all common causes of kidney disease.

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

Appendix 9. Protocol Amendment I8F-MC-GPGG(b) Summary Pharmacokinetics of LY3298176 Following Administration to Subjects with Impaired Renal Function

Overview

Protocol I8F-MC-GPGG, Pharmacokinetics of LY3298176 Following Administration to Subjects with Impaired Renal Function, has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Based on early recruiting experience with subjects with severe renal impairment, the protocol was amended to facilitate enrollment of subjects in Group 4.
    - Severe renal impairment classification is revised to include subjects with eGFR <30 mL/min/1.73m^2 and not requiring dialysis, as defined in the EMEA guideline (EMEA CHMP 2016).
    - Subjects with T2DM are now allowed to use insulin, outside of metformin.

Revised Protocol Sections

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

1. Protocol Synopsis

Summary of Study Design:

Study I8F-MC-GPGG is a Phase 1, multicenter, nonrandomized, open-label, parallel-design study in subjects with mild, moderate, or severe renal impairment, or end-stage renal disease (ESRD), and control subjects with normal renal function. Renal function will provide the basis for assignment to treatment group.

- Group 1: control subjects with normal renal function (estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73m^2)
- Group 2: subjects with mild renal impairment (eGFR between 60 and 89 mL/min/1.73m^2)
- Group 3: subjects with moderate renal impairment (eGFR between 30 and 59 mL/min/1.73m^2)
- Group 4: subjects with severe renal impairment (eGFR ~~between 15 and 29~~<30 mL/min/1.73m^2 and not requiring dialysis)
- Group 5: subjects with ESRD (have received ~~hemo~~dialysis for at least 3 months).

5.1. Overall Design

Table GPGG.2. Subject Groups based on Renal Impairment Status

	Classification	eGFR (mL/min/1.73m^2)
Group 1	Control (normal renal function)	≥90
Group 2	Mild renal impairment	60-89
Group 3	Moderate renal impairment	30-59
Group 4	Severe renal impairment	~~15-29~~<30 and not requiring dialysis
Group 5	End-stage renal disease	Requiring dialysis

Abbreviations: eGFR = estimated glomerular filtration rate (as determined by the Modification of Diet in Renal Disease abbreviated equation).

5.4. Scientific Rationale for Study Design

A comprehensive range of renal impairment is necessary to fully characterize the impact of renal impairment on the PK of LY3298176. Subjects undergoing ~~hemo~~dialysis (Group 5) will be included to determine the effect of dialysis on drug removal.

6.1.3. Additional Inclusion Criteria for Subjects with Mild to Severe Renal Impairment or ESRD

[10] Males or females with stable mild to severe renal impairment, assessed by eGFR or with ESRD (having received ~~hemo~~dialysis for at least 3 months).

6.1.4. Additional Inclusion Criteria for Subjects with T2DM and Renal Impairment or ESRD

[13] Have T2DM ~~controlled~~treated with diet or exercise alone or with stable doses of ~~on~~ metformin and/or insulins for at least 8 weeks.

[15] Have a hemoglobin A1c (HbA1c) ≥~~7.0~~6.0% and ≤11.0% at the screening visit.

6.2.3. Additional Exclusion Criteria for Subjects with T2DM and Renal Impairment or ESRD

[46] Have taken any glucose-lowering medications other than metformin and/or insulins (refer to Inclusion Criterion [13])~~, including insulin,~~ in the past 3 months before screening. In general, stable dosages of metformin and insulins will be continued; however, a washout period or dose modifications may be necessary to allow for optimal blood glucose monitoring throughout the dosing period at the discretion of the investigator.

7.7. Concomitant Therapy

Stable single oral doses of metformin and/or stable doses of insulins (for at least 8 weeks) are allowed for subjects with T2DM. Refer to Exclusion Criterion [46] in Section 6.2.3.~~Additional concomitant medications for treatment of T2DM, other than metformin, are not permitted during the study.~~

Table GPGG.3. Renal Function Classification for Primary Analyses

Group	Classification	eGFR (mL/min/1.73 m^2)[a]	CLcr (mL/min)[b]
1	Control (normal renal function)	≥90	≥90
2	Mild renal impairment	60-89	60-89
3	Moderate renal impairment	30-59	30-59
4	Severe renal impairment	~~15-29~~<30, not requiring dialysis	~~15-29~~<30, not requiring dialysis
5	End-stage renal disease	Requiring dialysis	Requiring dialysis

Abbreviations: CLcr = creatinine clearance; eGFR = estimated glomerular filtration rate.

[a] Per enrollment classification; eGFR will be calculated using the Modification of Diet in Renal Disease abbreviated equation.

[b] CLcr will be calculated using the Cockcroft-Gault formula (Cockcroft and Gault 1976).

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