Protocol I8F-MC-GPGQ(a)

A Single Dose Pharmacokinetic Study of Tirzepatide in Subjects With Varying Degrees of Hepatic Impairment

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Tirzepatide (LY3298176)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
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1. Protocol Synopsis

Title of Study:
A Single Dose Pharmacokinetic Study of Tirzepatide in Subjects with Varying Degrees of Hepatic Impairment

Rationale:
Tirzepatide (LY3298176) is a dual agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors being developed for the treatment of type 2 diabetes mellitus. As the patient population for tirzepatide may include patients with hepatic impairment, it is important to ascertain whether tirzepatide can be safely prescribed to this population without dose adjustment, once marketed. The fatty acid component of tirzepatide is expected to bind to albumin; however, albumin concentration in hepatic impaired subjects can be lower than that seen in control subjects. Therefore, this study will evaluate the pharmacokinetics (PK) of tirzepatide in subjects with hepatic impairment compared to healthy control subjects to investigate the impact of hepatic impairment, if any, on the PK of tirzepatide.

Objectives/Endpoints:

Objectives	Endpoints
Primary To evaluate the PK of a single SC dose of tirzepatide in subjects with mild, moderate, and severe hepatic impairment compared to control subjects with normal hepatic function.	AUC(0-∞) and C_{max}
Secondary To evaluate the safety and tolerability of a single SC dose of tirzepatide in subjects with mild, moderate, and severe hepatic impairment compared to control subjects with normal hepatic function.	Incidence of AEs

Abbreviations: AE = adverse event; AUC(0-∞) = area under the drug concentration-time curve from zero to infinity; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SC = subcutaneous.

Summary of Study Design:
Study I8F-MC-GPGQ will be a multicenter, parallel, single-dose, open-label, single-period study of tirzepatide in subjects with normal hepatic function and subjects with mild, moderate, and severe hepatic impairment. Subjects enrolled in Group 1 (normal hepatic function) will be matched by weight (±10 kg), age (±10 years), and sex to subjects with hepatic impairment, as far as practically possible.

Subjects will undergo a screening examination within 28 days prior to enrollment, check in to the clinical research unit (CRU) on Day -1, and receive a single subcutaneous dose of 5 mg tirzepatide on Day 1, following an overnight fast of at least 8 hours. Subjects will 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. Each subject will be required to return to the CRU for a follow-up visit and final PK blood sample collection at least 28 days postdose.

Treatment Arms and Planned Duration for an Individual Subject:
Subjects will be enrolled within the following groups:

Group 1: at least 6 subjects and up to 12 subjects with normal hepatic function (Control).

Group 2: at least 6 subjects with mild hepatic impairment (Child Pugh [CP] A).

Group 3: at least 6 subjects with moderate hepatic impairment (CP B).

Group 4: up to 6 subjects with severe hepatic impairment (CP C).

Efforts will be made to achieve 6 completers with severe hepatic impairment (Group 4); however, acknowledging the difficulty in recruiting this subject population, 2 to 3 subjects with severe hepatic impairment may be an acceptable target.

Subjects with normal hepatic function cannot be matched to more than 1 hepatically-impaired subject within an impairment group; however, subjects with normal hepatic function may be matched to 1 subject from more than 1 hepatic impairment group, therefore requiring fewer subjects to be enrolled to Group 1 (minimum of 6). Subjects may be replaced at the discretion of the investigator in discussion with the sponsor.

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 8 weeks.

Number of Subjects:
Up to 30 subjects may be enrolled to achieve the target minimum number of completers in each of the 4 study groups.

Statistical Analysis:
Pharmacokinetic: Blood samples will be collected for the measurement of tirzepatide concentrations, using validated liquid chromatography tandem mass spectrometry methods. Pharmacokinetic parameter estimates for tirzepatide will be calculated by standard noncompartmental methods of analysis. The primary parameters analyzed will be maximum observed drug concentration (C_{max}) and area under the drug concentration-time curve from zero to infinity (AUC[0-∞]). Other noncompartmental parameters may be reported as appropriate.

The primary PK analysis is the evaluation of log-transformed AUC(0-∞) and C_{max} using an analysis of covariance (ANCOVA) model with hepatic function group as a fixed factor and body weight as a covariate. The geometric least squares means for each group, geometric least squares mean ratios between each hepatic impairment level versus the control group, and the corresponding 90% confidence intervals will be estimated from the ANCOVA model. In the event of dose adjustment based on the interim analyses results, dose normalized PK parameters may be used in the above model. The analysis of t_{max} will be based on a nonparametric method. Medians and differences in medians for hepatic function groups and the p-value from a Wilcoxon rank sum test will be presented.

The relationship between the PK parameters and Child-Pugh Classification parameters (serum albumin concentration, total bilirubin concentration, and prothrombin time) will be assessed graphically. The PK parameters AUC(0-∞), C_{max}, and apparent clearance will be plotted against each Child-Pugh Classification parameter separately.

Additional PK parameters may be analyzed if deemed appropriate following a review of the data.

Safety: All investigational product and protocol procedure adverse events will be listed and, if the frequency of events allows, safety data will be summarized using descriptive methodology.

2. Schedule of Activities

Study Schedule Protocol I8F-MC-GPGQ

	Screening	Study Days							Follow-up or ED[c]	Comments
Procedure	D-29 to D-2	D-1	D1	D2	D3	D4	D5	D8	D15	
Informed Consent	X									
Subject Admission to CRU		X								
Tirzepatide Administration			X (0 hour)							Study drug will be administered after an overnight fast of at least 8 hours.
Subject Discharge from CRU							X			Subjects may be required to stay longer in the CRU at the investigator's discretion for safety monitoring.
Outpatient Visit	X							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)[a]	X	X	Predose, 12	24	48	72	96	X	X	X	Additional time points may be added, if warranted and agreed upon between Lilly and the investigator.
Clinical Laboratory Tests[b]	X	X			X		X	X	X	X	See Appendix 2 for details. Day -1 samples may be collected between Day -4 to Day -1, provided that the results are reviewed prior to actual dosing on Day 1.
Child-Pugh Classification	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	
Pharmacogenetic Sample			Predose								Single sample for pharmacogenetic analysis.

	Screening	Study Days							Follow-up or ED[c]	Comments
Procedure	D-29 to D-2	D-1	D1	D2	D3	D4	D5	D8	D15	
Immunogenicity (hours)			Predose						X	X	Where applicable, collection times should match with PK sampling time points. 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 (± 3) days following the event. Subjects with TE ADA at follow-up/ED will undergo additional follow-up. See Section 9.6.1 for details.
Blood Glucose Monitoring (hours)			Predose, 8, 12	24, 36	48	72	96	X	X	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	The exact time of sampling must be recorded.

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

Note: All sampling times are given relative to dosing (Time 0 hour) with tirzepatide (predose or hours postdose).

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, PK sample (record of actual PK sampling time is the priority), immunogenicity, blood glucose and pharmacogenetic sample.

[a] Specified times are approximate and actual times will be recorded. Actual time should not exceed 1 hour prior to dosing for the predose assessment.

[b] Screening sample and any unscheduled samples for immediate safety assessments may be performed by the local laboratory affiliated with the sites. All other scheduled clinical safety laboratory samples will be assayed by a central laboratory for study reporting purpose.

[c] At least 28 days postdose or within 7 to 14 days upon confirmation of early discontinuation.

3. Introduction

3.1. Study Rationale

Tirzepatide (LY3298176) is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors being developed for the treatment of type 2 diabetes mellitus (T2DM). As the patient population for tirzepatide may include patients with hepatic impairment, it is important to ascertain whether tirzepatide can be safely prescribed to this population without dose adjustment, once marketed. Tirzepatide is a synthetic peptide conjugated to a C20 fatty di-acid moiety and is presumed to be degraded into component amino acids by protein catabolism pathways. It is not expected to be biotransformed by drug metabolizing enzymes. However, the fatty acid component is expected to bind to albumin, thereby leading to a prolonged half-life, which supports a once weekly dosing regimen. Albumin concentration in hepatic impaired subjects can be lower than that seen in control subjects.

The liver plays a central role in glucose metabolism. Almost all patients with cirrhosis are insulin-resistant, 60% to 80% are glucose intolerant, and about 20% develop diabetes [Honda F et al 2018]. The main feature of blood glucose dynamics in patients with chronic liver disease (CLD) is marked blood glucose fluctuations, such as postprandial hyperglycemia and hypoglycemia. To address this issue, regular blood glucose monitoring has been included in the Schedule of Activities. Additionally, Study I8F-MC-GPGQ (GPGQ) will evaluate the pharmacokinetics (PK) of tirzepatide in subjects with hepatic impairment compared to healthy control subjects to investigate the impact of hepatic impairment, if any, on the PK profile of tirzepatide.

3.2. Background

Tirzepatide is being developed as a therapy to improve glycemic control in adults with T2DM as an adjunct to diet and exercise. Tirzepatide has agonist activity at both the GIP and GLP-1 receptors. As a dual agonist, tirzepatide combines the signaling of each receptor for improved glycemic control. By virtue of being a dual agonist incretin mimetic, tirzepatide has the potential of reaching higher efficacy in target tissues such as the insulin-producing pancreatic ß-cells that express both GIP receptors and GLP-1 receptors before reaching its therapeutic limitation. Tirzepatide may attain additional efficacy by recruiting metabolically active tissues not targeted by classical GLP-1 analogs (for example, adipose tissue as indicated by the observation of increased energy utilization and resulting body weight loss).

Tirzepatide is a 39-amino acid synthetic peptide. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that prolongs the duration of action. It has a chemical structure and pharmacologic profile that is distinct from the GLP-1 receptor agonists due to the addition of GIP, which is unique among the marketed incretin mimetics. It is administered once weekly by subcutaneous (SC) injection.

Results from 4 tirzepatide clinical trials that have completed dosing are available, including two Phase 1 studies, Study I8F-MC-GPGA (Study GPGA) and Study I8F-JE-GPGC (Study GPGC),

and two Phase 2 studies, Study I8F-MC-GPGB (Study GPGB) and Study I8F-MC-GPGF (Study GPGF).

Study GPGA was a combination single-ascending dose (SAD) and a multiple ascending-dose (MAD) study in healthy subjects (Part A and B) and a multi-dose study in patients with T2DM (Part C). The study investigated the safety, tolerability, PK, and pharmacodynamics (PD) of tirzepatide administered as SC injections. Weekly doses of tirzepatide ranged from 0.25 mg to 8 mg in the SAD. Maximum tolerated dose in healthy subjects following single-dose administration was 5 mg. In the 4-week MAD part of the study, doses up to 10 mg in healthy subjects or 15 mg in patients with T2DM were attained via a dose escalation approach. A dose of 15 mg tirzepatide attained by fast dose escalation over 4 weeks (5/5/10/15 mg), while considered to be safe, was associated with high incidence of gastrointestinal (GI) events. Terminal half-life was estimated to be approximately 5 days, thus supporting a once weekly dosing regimen, with maximum observed drug concentration (C_{max}) occurring between 24 to 72 hours postdose, and steady-state tirzepatide exposures expected to be attained within 4 weeks of once weekly dosing. Study GPGC was a MAD study to investigate the safety, tolerability, PK, and PD in Japanese patients with T2DM. Overall, tirzepatide PK parameters in Japanese patients with T2DM appeared comparable to corresponding parameters from non-Japanese patients with T2DM observed in Study GPGA.

Gastrointestinal adverse events (AEs) (nausea, vomiting, diarrhea, abdominal distension) and decreased appetite were the most frequently reported events by both healthy subjects and patients with T2DM and were dose related in the two Phase 1 studies. A dose-dependent increase in heart rate was detected for both healthy subjects and patients with T2DM who received tirzepatide, similar to what was observed with selective GLP-1 receptor agonists. A few subjects experienced transient elevations in lipase and/or amylase levels, but these episodes were not associated with any relevant clinical outcomes. There were no other clinically relevant safety observations in the Phase 1 studies.

Phase 2 studies evaluated the efficacy, tolerability, and safety of 5 doses of tirzepatide (1 mg, 5 mg, 10 mg, 12 mg and 15 mg) in patients with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy up to 26 weeks. Results demonstrated that tirzepatide in doses between 5 mg and 15 mg provides a clinically meaningful glucose-lowering and body weight-lowering efficacy. Similar to data from Study GPGA, most of the AEs associated with tirzepatide were GI-related, consisting mainly of nausea, vomiting, and diarrhea and were dose-dependent. In addition, patients treated with tirzepatide reported AEs of decreased appetite more frequently than patients who received 1.5-mg dose of dulaglutide, a selective GLP-1 receptor agonists.

An integrated clinical and PK/PD assessment of the GI tolerability AEs, and the impact of dose escalation regimens in the Phase 2 trials, suggested that dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks would permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

Overall, the safety and tolerability, and PK/PD profiles of tirzepatide support further development of tirzepatide in patients with T2DM.

3.3. Benefit/Risk Assessment

Risks of tirzepatide have been consistent with risks associated with other GLP-1 receptor agonists currently marketed. Potential risks include, but are not limited to, GI effects, acute pancreatitis, increases in heart rate, and hypoglycemic events (GLP-1 receptor agonist class effect).

No clinically significant safety or tolerability concerns have been identified during clinical investigation of tirzepatide up to the highest single-dose level of 8 mg or multiple doses, when titrated up to 15 mg. Based on this information, a single 5-mg dose to be administered in Study GPGQ is reasonably anticipated to be tolerable in subjects with hepatic impairment and in control healthy subjects.

Subjects will reside in the clinical research unit (CRU) under close monitoring for 5 days, with the option of remaining inpatient for longer if deemed necessary by the investigator for additional safety monitoring; the subject's discharge from the CRU will be per investigator discretion after medical assessments for safety. An interim analysis for safety, tolerability, and PK data is planned to determine whether any dose adjustment is needed (see Section 10.3.5).

There is no anticipated therapeutic benefit for the subjects.

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

4. Objectives and Endpoints

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

Table GPGQ.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the PK of a single SC dose of tirzepatide in subjects with mild, moderate, and severe hepatic impairment compared to control subjects with normal hepatic function.	AUC(0-∞) and C_{max}
Secondary To evaluate the safety and tolerability of a single SC dose of tirzepatide in subjects with mild, moderate, and severe hepatic impairment compared to control subjects with normal hepatic function.	Incidence of AEs
Exploratory To evaluate the formation of ADA to tirzepatide after a single 5-mg SC dose administered to subjects with mild, moderate, or severe hepatic impairment compared to control subjects with normal hepatic function.	Presence of ADA to tirzepatide

Abbreviations: ADA = antidrug antibodies; AE = adverse event; AUC(0-∞) = area under the drug concentration-time curve from zero to infinity; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SC = subcutaneous.

5. Study Design

5.1. Overall Design

This will be a multicenter, parallel, single-dose, open-label, single-period study of tirzepatide in subjects with normal hepatic function and subjects with mild, moderate, and severe hepatic impairment. Subjects who have a concomitant T2DM diagnosis will not be specifically excluded.

Subjects will be enrolled within the following groups:

- Group 1: at least 6 subjects and up to 12 subjects with normal hepatic function (Control).
- Group 2: at least 6 subjects with mild hepatic impairment (Child Pugh [CP] A).
- Group 3: at least 6 subjects with moderate hepatic impairment (CP B).
- Group 4: up to 6 subjects with severe hepatic impairment (CP C).

Efforts will be made to achieve 6 completers with severe hepatic impairment (Group 4); however, acknowledging the difficulty in recruiting this subject population, 2 to 3 subjects with severe hepatic impairment may be an acceptable target.

The Child-Pugh classification is described in Section 5.1.1.

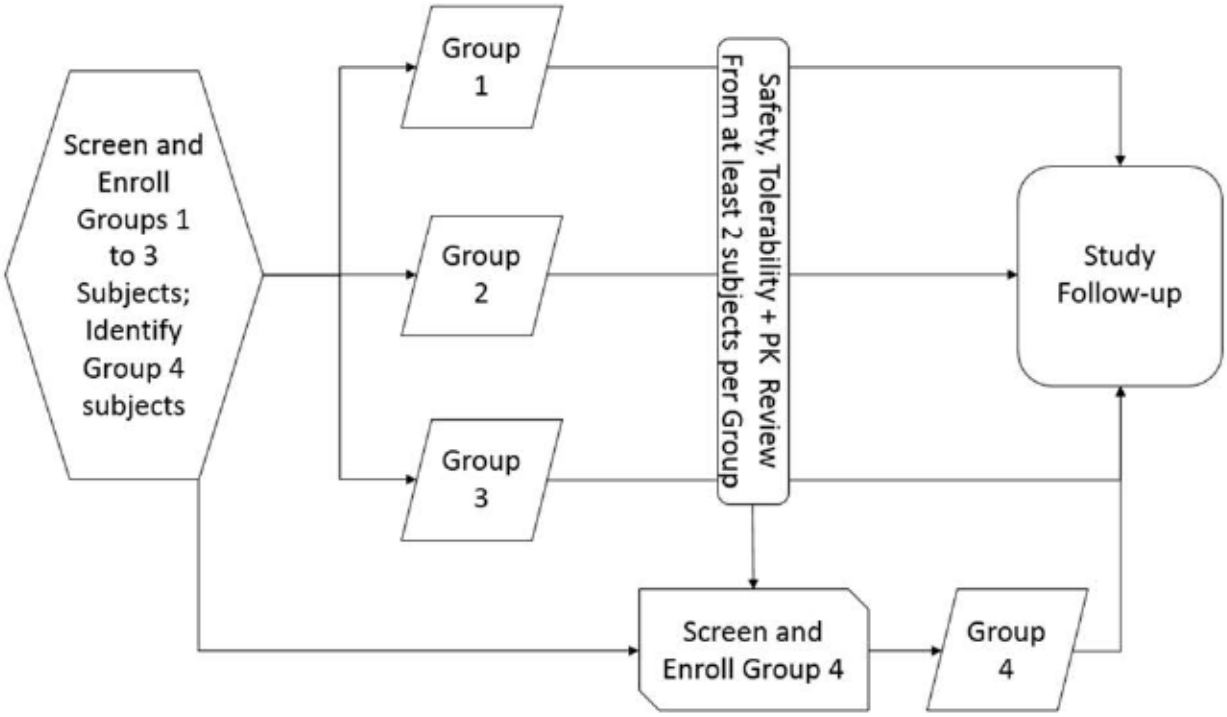
Subjects enrolled in Group 1 (normal hepatic function) will be matched by weight (±10 kg), age (±10 years), and sex to subjects in Groups 2 through 4, as far as practically possible. Subjects with normal hepatic function cannot be matched to more than 1 hepatically-impaired subject within an impairment group; however, subjects with normal hepatic function may be matched to 1 subject from more than 1 hepatic impairment group, therefore requiring fewer subjects to be enrolled to Group 1 (minimum of 6). Subjects who withdraw before completing all study procedures may be replaced at the discretion of the investigator in discussion with the sponsor.

Subjects will undergo a screening examination within 28 days prior to enrollment, check in to the CRU on Day -1, and receive a single SC dose of 5 mg tirzepatide on Day 1, following an overnight fast of at least 8 hours. Subjects will 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. Each subject will be required to return to the CRU for a follow-up visit and final PK blood sample collection at least 28 days postdose.

Pharmacokinetic blood sampling and safety assessments, including vital sign measurement, physical examination, clinical laboratory tests, electrocardiograms (ECGs), and AE recording, will be performed according to the Schedule of Activities (Section 2).

Subjects with normal hepatic function and with mild and moderate hepatic impairment (Groups 1 to 3) can be dosed concurrently (Figure GPGQ.1). Dosing of the first subject in Group 4 (severe hepatic impairment) may proceed only after satisfactory review of safety, tolerability, and PK data from at least 2 subjects in Group 2 (mild hepatic impairment), at least 2 subjects in Group 3 (moderate hepatic impairment), and at least 2 subjects in Group 1 (appropriate matched-control

subjects with normal hepatic function). Based on continuous review of safety and tolerability data, the dose of tirzepatide may be reduced to 2.5 mg for the remainder of subjects in Groups 2 and 3 (mild and moderate impairment) and all subjects in Group 4 (severe impairment), as well as for control subjects in Group 1.



Note: dosing of the first subject with severe hepatic impairment (Group 4) may proceed only after satisfactory review of safety, tolerability and PK data from at least 2 subjects with mild hepatic impairment (Group 2), and at least 2 subjects with moderate hepatic impairment (Group 3), and at least 2 subjects in Group 1 (appropriate matched-control subjects with normal hepatic function).

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

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be approximately 8 weeks.

5.1.1. Child-Pugh Classification

Hepatic impairment is classified using the Child-Pugh system. The classification parameters will be collected at screening to determine the Child-Pugh class for each subject prior to tirzepatide dose administration (Table GPGQ.2).

Table GPGQ.2. Child-Pugh Classification

Parameter	1 point	2 points	3 points
Serum Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total Bilirubin (mg/dL)	<2	2 to 3	>3
Prothrombin Time (sec. prolonged) or	<4	4 to 6	>6
Prothrombin Time INR	<1.7	1.7 to 2.3	>2.3
Ascites [a]	Absent	Slight	Moderate
Hepatic Encephalopathy [b]	None	1 or 2 Or current treatment with lactulose or neomycin or other antibiotics	3 or 4 Or continued encephalopathy while receiving treatment with lactulose and/or neomycin or other antibiotics

Child-Pugh A (mild): 5 or 6 points; Child-Pugh B (moderate): 7 to 9 points; Child-Pugh C (severe): 10 to 15 points. Adapted from Child and Turcotte (1964) and Pugh et al. (1973).

Abbreviations: INR = international normalized ratio.

[a] Absent: no detectable ascites.
Slight: no distension; ascites are only detectable by ultrasound examination.
Moderate: ascites causing moderate symmetrical distension of the abdomen.

[b] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity.

5.2. Number of Subjects

Up to 30 subjects may be enrolled to achieve the target minimum number of completers in each of the 4 study groups.

Group 1: at least 6 subjects and up to12 subjects with normal hepatic function (Control).

Group 2: at least 6 subjects with mild hepatic impairment (CP A).

Group 3: at least 6 subjects with moderate hepatic impairment (CP B).

Group 4: up to 6 subjects with severe hepatic impairment (CP C).

Matching subjects with normal hepatic function will be enrolled on up to a one-to-one basis; however, subjects with normal hepatic function may be matched to 1 subject from more than 1 hepatic impairment group, therefore requiring fewer subjects to be enrolled to Group 1 (minimum of 6).

Efforts will be made to include a reasonable number of subjects with severe hepatic impairment, acknowledging that recruitment of CP C subjects is difficult. The sponsor may elect to complete fewer than 6 subjects (2 to 3 subjects) in Group 4 if the investigative sites cannot recruit sufficient numbers for this group. Subjects may be replaced at the discretion of the investigator in discussion with the sponsor.

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

This study has been designed in accordance with the Food and Drug Administration (FDA) regulatory guidance for the study of PK in subjects with impaired hepatic function (FDA 2003).

This study will be open-label as the study endpoints are objective rather than subjective.

Those with hepatic impairment will be categorized based on the Child-Pugh classification system (Section 5.1.1; Child and Turcotte 1964; Pugh et al. 1973) for hepatic impairment (Class A, B, or C) as recommended by the FDA and international guidance documents. As suggested in the guidance, the control group should be as similar as possible to the hepatically-impaired group, apart from hepatic function. For this reason, subjects enrolled in the control group (Group 1) will have normal hepatic function and will be matched by weight (±10 kg), age (±10 years), and sex to subjects in Groups 2 through 4, where possible.

5.5. Justification for Dose

Subcutaneous injection is the intended clinical route of administration. 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. Doses higher than 5 mg were achieved via titration and a 5-mg dose was considered the maximum tolerated dose when administered as a single dose.

If the interim analysis shows that safety and tolerability measures manifest at a higher than expected rate, or if the PK appears to be influenced by hepatic impairment and the exposure in subjects with impairment is notably higher than expected, a dose reduction to 2.5 mg may be administered in the remainder of subjects in Groups 2 and 3 (mild and moderate impairment) and all subjects in Group 4 (severe impairment), as well as for control subjects in Group 1 (see Section 10.3.5).

6. Study Population

The criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria or is inadvertently enrolled, that subject should be discontinued from the study and Lilly or its designee must be contacted. Eligibility of subjects for study enrollment will be based on the results of a screening medical history, physical examination, clinical laboratory tests, and ECGs. The nature of any conditions present at the time of the physical examination and any pre-existing conditions will be documented.

Child-Pugh classification of hepatic impairment will be based on the screening data and confirmed prior to dosing (Day -1). Screening for all subjects may occur up to 28 days prior to dosing of tirzepatide.

In Group 4 (severe hepatic impairment) hepatic function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and alkaline phosphatase [ALP]) and prothrombin time international normalized ratio must be repeated within 24 hours prior to dosing of tirzepatide as an additional safety measure.

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' hepatic function (Inclusion Criteria [7] through [12]) and diabetic status (Inclusion Criteria [13] through [16]).

6.1.1. Inclusion Criteria for All Subjects

[1] male and female subjects may participate in this study

[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 for at least 3 months after dosing.

- 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, postovulation 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.

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 for at least 3 months after dosing.

[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 body mass index (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 Institutional Review Board (IRB) governing the site

6.1.2. Additional Inclusion Criteria for Control Subjects (Group 1)

[7] healthy males or females as determined by medical history, physical examination, and other screening procedures, with clinically normal hepatic function 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 blood pressure (BP) and pulse rate, as determined by the investigator

6.1.3. Additional Inclusion Criteria for Subjects with Mild to Severe Hepatic Impairment (Groups 2 to 4)

[10] are individuals with hepatic impairment classified as Child-Pugh score A, B, or C (mild, moderate, or severe impairment) (Section 5.1.1; Child and Turcotte 1964; Pugh et al. 1973), who are considered acceptable for participation in this study by the investigator. Subjects must have a diagnosis of chronic hepatic impairment (>6 months) per physician diagnosis and standard of care practice, with no clinically significant changes within 90 days prior to study drug administration. Subjects may have mild stable baseline medical conditions for which neither the condition nor treatments received would negatively impact the health of the subject or study conduct.

[11] clinical laboratory test results with deviations that are judged by the investigator to be compatible with the hepatic impairment of the subject, or of no additional clinical significance for this study

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

[13] no significant history of spontaneous or ethanol induced hypoglycemia

6.1.4. Additional Inclusion Criteria for Subjects with both T2DM and Hepatic Impairment

[14] have T2DM controlled with diet or exercise alone or on stable doses of metformin for at least 8 weeks

[15] 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

[16] have a hemoglobin A1c ≥6.0% and ≤11.0% at the screening visit

[17] 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 [18] through [44] apply; additional subgroupings of exclusion criteria below are specific to the subjects' hepatic function (Exclusion Criteria [45] through [56]) and diabetic status (Exclusion Criteria [57] through [60]).

6.2.1. Exclusion Criteria for All Subjects Unless Otherwise Specified

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

[19] are Lilly employees, or employees of third-party organizations involved with the study that require exclusion of their employees

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

[21] have known allergies to tirzepatide or related compounds

[22] 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)

[23] have previously completed or withdrawn from this study or any other study investigating tirzepatide, and have previously received the investigational product

[24] persons who have a current, functioning organ transplant

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

[26] febrile illness within 3 days prior to dosing

[27] 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

[28] have estimated creatinine clearance (CLcr) <50 mL/min (using the 4 factor modification of diet in renal disease [MDRD-4]) at screening. Exceptions to this may be allowed on a case-by-case basis after discussion and agreement between the investigator and the sponsor or designated medical representative (no estimated CLcr <30 mL/min will be approved).

[29] have a significant history of or presence of cardiovascular (eg, myocardial infarction, cerebrovascular accident, etc. within the past 6 months), respiratory, hepatic (applies to Group 1 control subjects 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

[30] show evidence of significant active neuropsychiatric disease

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

[32] have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase and/or lipase >1.5 × the upper limit of normal (ULN) 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 dipeptidyl peptidase-IV inhibitors. Subjects with dyslipidemia and subjects who had cholecystolithiasis treatment (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.

[33] have serum AST or ALT >2× ULN or total bilirubin >1.5× ULN (applies to Group 1 control subjects only)

[34] have a serum triglyceride ≥5 mmol/L (442.5 mg/dL) at screening (applies to Group 1 control subjects only)

[35] show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies

[36] show evidence of hepatitis C and/or positive hepatitis C antibody (applies to Group 1 control subjects only)

[37] show evidence of hepatitis B and/or positive hepatitis B surface antigen (applies to Group 1 control subjects only)

[38] are women with a positive pregnancy test or women who are lactating

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

[40] intend to use:

a. over-the-counter medication within 7 days prior to dosing (except for hepatic impairment and T2DM subjects on stable doses)

b. prescription medication (other than those listed in Section 7.7 and Appendix 9) within 14 days prior to dosing

c. herbal preparations within the 14 days prior to screening

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

[41] have donated more than 450 mL blood, including plasma and platelets, within 1 month prior to Check-in

[42] 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), or are unwilling to stop alcohol consumption from 48 hours prior to Check-in on Day -1 and the follow-up visit, and while resident in the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[43] are currently heavy users of nicotine (>10/cigarettes/day) or cannot comply with the restrictions of the study site during confined periods or abstain for 1 hour prior to dosing and 4 hours following dosing

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

6.2.2. Additional Exclusion Criteria for Subjects with Mild to Severe Hepatic Impairment (Groups 2 to 4)

[45] are anticipating organ transplant within 6 months

[46] presence of active portal shunt

[47] requires paracentesis more often than 2 times per month

[48] have evidence of spontaneous bacterial peritonitis within 6 months of dosing

[49] have had variceal bleeding within 3 months of Check-in to the CRU

[50] show presence of hepatocellular carcinoma

[51] show evidence of severe hyponatremia (sodium <120 mmol/L)

[52] hepatic encephalopathy of Grade 2 or higher

[53] have hemoglobin <8.5 g/dL

[54] have a platelet count $<30\times10^9$ cells/L

[55] have total bilirubin >15 mg/dL

[56] have ALT $\geq$ 6× ULN

6.2.3. Additional Exclusion Criteria for Subjects with T2DM and Hepatic Impairment

[57] have taken any glucose-lowering medications other than metformin (refer to Inclusion Criterion [13]), including insulin, in the past 3 months before screening

[58] 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 dosing should also be excluded.

[59] 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 hemoglobin A1c methodology

[60] 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 systemic 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 tirzepatide, 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 48 hours prior to Check-in on Day -1 and the follow-up visit, and while resident in the CRU. Any nicotine usage while inpatient will be restricted in accordance to the CRU's rules and operating procedure. 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

No strenuous physical activity will be allowed for 48 hours prior to dosing until discharge from the study or completion of all study procedures.

6.4. Screen Failures

Screening tests such as clinical laboratory tests and vital signs/ECGs may be repeated at the discretion of the investigator. Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened up to 2 times. The interval between re-screenings should be at least 1 week. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new subject screening number.

7. Treatment

7.1. Treatment Administered

Tirzepatide 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%. Dosing will occur after an overnight fast of at least 8 hours. Instructions for preparation and handling are summarized in Section 7.5.

Tirzepatide will be supplied as prefilled syringes (PFS) by Lilly or its representative in accordance with current good manufacturing practices and will be supplied with lot numbers. Each PFS will contain either 2.5 mg or 5 mg of tirzepatide for SC administration. Detailed instructions on the handling, storage, and SC administration of the tirzepatide PFS will be described in the separate Pharmacy Manual.

Whenever possible, investigational product administration should be carried out by the same personnel. The actual time of dosing will be recorded in the subject's electronic case report form (eCRF).

Table GPGQ.3. Treatments Administered

Treatment Name	Tirzepatide
Dosage Formulation	Prefilled syringe
Dosage strength	2.5 mg / 0.5 mL or 5 mg / 0.5 mL
Route of Administration	Subcutaneous
Dosing instructions	Single injection into abdomen on Day 1

The investigator or designee is responsible for:

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

7.1.1. Packaging and Labeling

Tirzepatide will be provided as PFS and provided in individual cartons to be dispensed.

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

7.2. Method of Treatment Assignment

All subjects will receive the same treatment; this study will not be subject to randomization.

7.2.1. Selection and Timing of Doses

Doses will be administered on the morning of Day 1, preceded by an overnight fast of at least 8 hours. A meal may be served approximately 2 hours postdose. See Section 6.3.1 for meal and dietary restrictions. The actual time of all dose administrations will be recorded in the subject's eCRF.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Interim review of safety/tolerability and PK data will be conducted during the course of this study (Section 10.3.5). If it appears that the PK are influenced by hepatic 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%.

No dose decision can occur without prior discussion and agreement between the investigator and the Lilly study team.

7.5. Preparation/Handling/Storage/Accountability

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

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

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

7.6. Treatment Compliance

The investigational product will be administered at the CRU, 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 hepatic impairment and T2DM. Subjects on stable concomitant medication(s) at the time of study entry should continue their regular, unchanged dose throughout the study.

Appendix 9 lists some of the common allowable treatment options for subjects with hepatic insufficiency.

Stable single oral doses of metformin (for at least 8 weeks) are allowed for subjects with T2DM. Additional concomitant medications for treatment of T2DM, other than metformin, are not permitted during the study.

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 eCRF.

No starting of new concomitant therapy, apart from occasional intake of vitamin/mineral supplements, allowable antiemetics, and acetaminophen, will be permitted for 14 days before the dosing of tirzepatide through the final post dosing 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 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 for this study.

8. Discontinuation Criteria

8.1. Discontinuation from the Study

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

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Subject Decision
    - the subject, or legal representative, requests to be withdrawn from the study.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist or 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 clinical pharmacologist or CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

8.2. 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 clinical 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.

The specifications in this protocol for the timings of safety and sample collections are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be recorded correctly in the eCRF. Failure or delays (ie, outside stipulated time allowances) in performing procedures or obtaining samples due to legitimate clinical issues (eg, equipment technical problems, venous access difficulty, or subject defaulting or turning up late for an agreed scheduled procedure) will not be considered as protocol deviations, but sites will still be required to notify the sponsor in writing via a file note.

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

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

After the ICF is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's pre-existing 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 investigational product, and/or study procedure and the AE.

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- 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 its designee, of any SAE as soon as practically possible.

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

Appendix 8 presents examples of AEs that are reasonably anticipated due to disease state and may not be considered related to tirzepatide.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and 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 investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of tirzepatide is considered any dose higher than the assigned dose. The treatment for an overdose of tirzepatide is supportive care.

Refer to the IB for tirzepatide.

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.

9.4.1.1. 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 7) 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.

9.4.2. 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.

9.4.2.1. 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, treatment with an appropriate antidiabetic agent may be initiated by the investigator. If hyperglycemia occurs during the follow-up period, the subject will remain in the study until completion of the planned follow-up.

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

Hypoglycemia will be described using the following definitions:

- **Documented Glucose Alert Level (Level 1), Plasma Glucose (PG) ≤70 mg/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. Plasma glucose 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).

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.

Hypoglycemic events will be recorded in the hypoglycemia module of the eCRF to allow for the collection of comprehensive safety information relating to these events. All episodes of severe hypoglycemia will additionally be reported as SAEs (see Section 9.2.1 for details).

9.4.3. Vital Signs

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

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

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.

9.4.4. Electrocardiograms

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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

If a clinically significant finding is identified (including, but not limited to, changes in QT/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.

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

9.4.5. Injection-site Reactions

Injection-site assessments for local tolerability will be conducted, when reported as:

- an AE from a subject, or
- a clinical observation from an investigator.

Reported injection-site reactions will be characterized within the following categories:

- edema
- erythema
- induration
- itching
- pain.

All injection-site reactions reported as AEs will be closely monitored until resolution. The report of a clinically significant AE of injection-site reaction may prompt notification of the sponsor, clinical photography, and referral for dermatologic evaluation and consideration of a skin biopsy and laboratory evaluations (ALT, AST, complete blood count with percent eosinophils, and additional immunogenicity testing).

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

9.4.6. Hypersensitivity Reactions

All hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs.

In the event of suspected drug hypersensitivity reactions (immediate or non-immediate) in subjects who experience moderate to severe injection reactions as assessed by the investigator, unscheduled blood samples will be collected for PK and antidrug antibody (ADA) analyses at the following time points:

- as close as possible to the onset of the event
- at the resolution of the event
- 30 (±3) days following the event.

Additionally, unscheduled serum samples for immune safety laboratory testing (including, but not limited to β tryptase, total IgE, complement and cytokine panel testing) should also be collected at approximately 60 to 120 minutes and 4 to 6 weeks after the onset of the event in these subjects.

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

9.4.7. Safety Monitoring

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

Lilly will review SAEs within timeframes 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 7) 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 Monitoring in Subjects with Treatment-emergent Abnormal Liver Tests

Abnormal liver tests in study participants with normal or near normal baseline ALT, AST, ALP, and total bilirubin (TBL; <1.5× ULN)

If a subject who was enrolled with baseline ALT, AST, ALP, TBL <1.5× ULN, experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, gamma-glutamyl transferase (GGT), and creatine kinase (CK) to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Elevated ALT/AST in subjects with baseline ALT/AST ≥1.5× ULN

If a subject, who was enrolled with baseline ALT/AST ≥1.5× ULN, experiences elevated ALT/AST ≥2× baseline (respectively), liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, GGT, and CK to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Elevated ALP in subjects with baseline ALP ≥1.5× ULN

If a subject, who was enrolled with baseline ALP ≥1.5× ULN, experiences elevated ALP ≥2× baseline, liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, GGT, and CK to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Elevated TBL in subjects with baseline TBL ≥1.5× ULN

If a subject, who was enrolled with baseline TBL ≥1.5× ULN, experiences elevated TBL ≥1.5× baseline, liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and CK to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with

the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

9.4.7.2. Additional Hepatic Data Collection (Hepatic Safety eCRF) in Subjects with Treatment-emergent Abnormal Liver Tests

Treatment-emergent abnormal liver tests in subjects with normal or near normal baseline ALT, AST, ALP, and TBL (<1.5× ULN)

In a subject, who was enrolled with baseline ALT, AST, ALP, and TBL < 1.5× ULN, additional hepatic 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 total bilirubin 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
- hepatic event considered to be a SAE

Elevated ALT/AST in subjects with baseline ALT/AST ≥ 1.5× ULN

In a subject, who was enrolled with baseline ALT/AST ≥1.5× ULN, elevated ALT/AST ≥3× baseline (respectively) on two or more consecutive tests should prompt additional hepatic safety data collection.

Abnormal ALP in subjects with baseline ALP ≥1.5× ULN

In a subject, who was enrolled with baseline ALP ≥1.5× ULN, elevated ALP ≥2× baseline on two or more consecutive tests should prompt additional hepatic safety data collection.

Abnormal TBL in subjects with baseline TBL ≥1.5× ULN

In a subject, who was enrolled with baseline TBL ≥1.5× ULN, elevated TBL ≥2× baseline on two or more consecutive tests should prompt additional hepatic safety data collection.

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 tirzepatide. A maximum of 3 unscheduled 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 tirzepatide will be assayed using a validated liquid chromatography tandem mass spectrometry method.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, or bioanalytical method cross-validation.

9.6. Pharmacodynamics

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 where relevant. In the event of drug hypersensitivity reactions (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible, at the resolution of the event, and 30 (± 3) 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. The minimum required dilution of the ADA assay is 1:10.

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
- 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 deviation.

Subjects followed for at least 1 year after dosing 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 IRB allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the tirzepatide. 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 tirzepatide 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 IRBs 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 tirzepatide or after tirzepatide 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

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

It is planned that up to 30 subjects may be enrolled. To support the planned analyses, at least 6 subjects in the mild and moderate hepatic impairment groups (Groups 2 and 3), at least 6 and up to 12 control subjects (Group 1) are expected to complete the study. Efforts will be made to achieve 6 completers with severe hepatic impairment (Group 4); however, acknowledging the difficulty in recruiting this subject population, 2 to 3 subjects with severe hepatic impairment may be an acceptable target.

This sample size is based on the FDA guidance (FDA 2003), which advises that at least 6 subjects in each study arm (group) are required to provide evaluable data. The sample size was not selected to satisfy an a priori statistical requirement.

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, BMI, race/sub-race, tobacco/nicotine habits, Child-Pugh score, or other demographic characteristics will be recorded and may be used in the PK and safety analyses as quantitative or classification variables.

10.3. Statistical Analyses

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

Pharmacokinetic analysis will be conducted on data from all subjects who were dosed and have evaluable data.

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

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

The incidence of symptoms will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment 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 investigational product-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 edema will be listed and summarized. 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 tirzepatide will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC(0-∞) of tirzepatide. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Additional analyses may be conducted as deemed appropriate.

10.3.2.2. Pharmacokinetic Statistical Inference

The primary PK analysis is the evaluation of log-transformed AUC(0-∞) and C_{max} using an analysis of covariance (ANCOVA) model with hepatic function group as fixed factor and body weight as covariate. The geometric least squares means for each group, geometric least squares mean ratios between each hepatic impairment level versus the control group, and the corresponding 90% confidence intervals will be estimated from the ANCOVA model. In the event of dose adjustment based on the interim analyses results, dose normalized PK parameters may be used in the above model.

The analysis of t_{max} will be based on a nonparametric method. Medians and differences in medians for hepatic function groups and the p-value from a Wilcoxon rank sum test will be presented.

The relationship between the PK parameters and Child-Pugh Classification parameters (serum albumin concentration, total bilirubin concentration, and prothrombin time) will be assessed graphically. The PK parameters AUC(0-∞), C_{max}, and apparent clearance will be plotted against

each Child-Pugh Classification parameter separately. An appropriate model may be fitted to the data.

Additional PK parameters may be analyzed if deemed appropriate following a review of the data.

10.3.3. Evaluation of Immunogenicity

The frequency and percentage of subjects with pre-existing ADA and with TE ADA+ to tirzepatide will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The minimum required dilution of the ADA assay is 1:10. For the TE ADA+ subjects 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.

10.3.4. 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.

10.3.5. Interim Analyses

One interim analysis is planned to occur during Study GPGQ. Two subjects each from Groups 2 and 3 (subjects with mild and moderate hepatic impairment, respectively) and at least 2 subjects in Group 1 (appropriate matched-control subjects with normal hepatic function) will be enrolled in parallel and dosed with 5 mg tirzepatide, followed by an interim analysis to evaluate safety, tolerability, and PK data. Based on this interim analysis, dosing will either continue at 5 mg or be reduced to 2.5 mg for the remainder of subjects in Groups 2 and 3 (mild and moderate impairment) and all subjects in Group 4 (severe impairment), as well as for control subjects in Group 1. 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.

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC(0-∞)	area under the drug concentration-time curve from zero to infinity
BMI	body mass index
BP	blood pressure
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CLcr	creatinine clearance
CLD	chronic liver disease
C_{max}	maximum observed 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	Child-Pugh

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
eCRF	electronic case report form
ECG	electrocardiogram
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.
IRB	Institutional Review Board
FDA	Food and Drug Administration
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulintropic polypeptide
GLP-1	glucagon-like peptide-1
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.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
MAD	multiple ascending dose
MDRD-4	the 4 factor modification of diet in renal disease
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PD	pharmacodynamic
PFS	prefilled syringe
PG	plasma glucose
PK	pharmacokinetic
SAE	serious adverse event
SAD	single ascending dose
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TE ADA	treatment-emergent antidrug antibody
t_{max}	time to maximum concentration
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[c]
	Alkaline phosphatase
Coagulation Panel[c]	Aspartate aminotransferase
aPTT, PT/INR	Alanine aminotransferase
	Creatinine
Urinalysis[a]:	Gamma-glutamyl transferase
Specific gravity	Amylase
pH	Lipase
Protein	
Glucose	Ethanol testing[e]
Ketones	Urine drug screen[e]
Bilirubin	Hepatitis B surface antigen[d]
Urobilinogen	Hepatitis C antibody[d]
Blood	HIV[d]
Nitrite	Pregnancy test[f]
Microscopic examination of sediment[b]	FSH[d,g]

Abbreviations: aPTT = activated partial thromboplastin time; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

a Performed by local laboratory at screening (and any unscheduled samples for immediate safety assessments) and by central laboratory at all other time points.

b If clinically indicated, per investigator's discretion.

c Performed at Screening and Day -1 with CP classification.

d Performed by local laboratory at screening only.

e 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.

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

g 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 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 IRB was properly constituted and convened as required by International Council for Harmonization (ICH) guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

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

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

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

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his 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 analyzable 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 eCRFs, 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 eCRF 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 IRBs 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 IRB 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 CRP.

Hepatic Monitoring Tests

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

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

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

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

Appendix 5. Blood Sampling Summary

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

Protocol I8F-MC-GPGQ Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	21	1	21
Clinical laboratory tests[a] • Hematology • Chemistry, including amylase and lipase • Coagulation panel	18	6	108
Pharmacokinetics	3	10 (+3)	39
Immunogenicity	10	3	30
Pharmacogenetics	10	1	10
Total		24	208
Total for clinical purposes rounded up to nearest 10 mL			210

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

Appendix 6. Classification of Contraceptive Methods

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence or in a same-sex relationship (if this is their preferred and usual lifestyle). Note: periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception
- Vasectomy – for men in clinical trials

Effective Methods of Contraception (must use combination of 2 methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Appendix 7. Pancreatic Monitoring

Glucagon-like peptide-1 agonists have been associated with a possible risk of acute pancreatitis. Epidemiologic studies have indicated that there is an increased incidence and prevalence of pancreatitis in persons with T2DM.

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

Additional monitoring will be requested for amylase or lipase values ≥3× the ULN at any visit, 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 GI signs and/or symptoms), at the investigator's discretion.

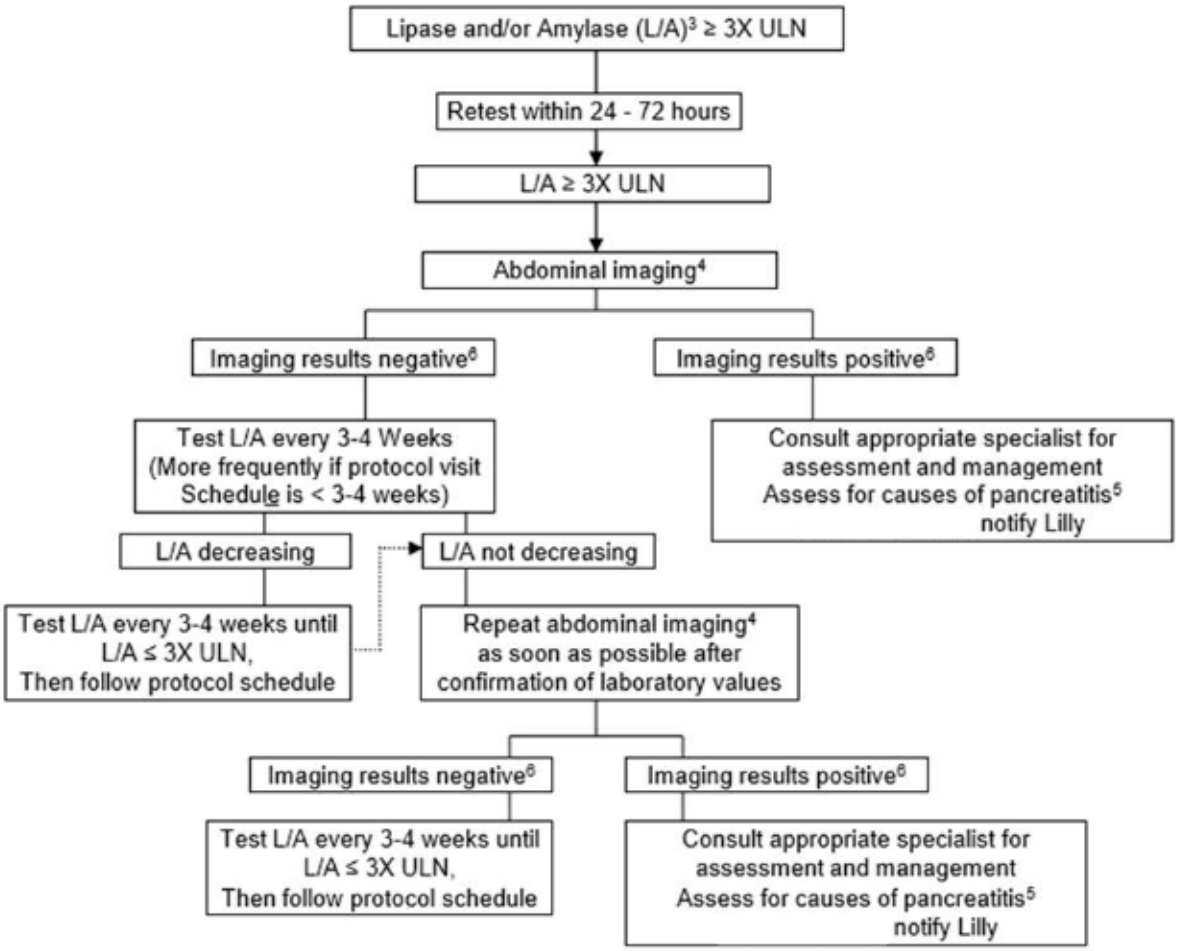
Acute pancreatitis is an AE defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

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

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

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

Follow this algorithm when the value(s) for serum lipase and/or amylase are ≥ 3X ULN.



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

2. If, at any time, in the opinion of the investigator, patient/subject has symptoms of acute pancreatitis irrespective of L/A results:
   (a) Consult appropriate specialist for assessment and management
   (b) Assess for causes of pancreatitis
   (c) Stop study drug (if applicable)
   (d) Notify Lilly

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

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

5. As minimum, test hepatic analytes, triglycerides, and calcium, and record all concomitant medications

6. Imaging results positive or negative for signs of acute pancreatitis

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

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

Appendix 8. Reasonably Anticipated Serious Adverse Events

Reasonably Anticipated Serious Adverse Events

Indication or Study Population: Type 2 Diabetes Mellitus

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

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

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

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

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

[a] Acute myocardial infarction, myocardial infarction, acute coronary syndrome.

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

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

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

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

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

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

Appendix 9. Permitted Medications for Subjects with Hepatic Impairment

Examples of permitted medications in subjects with hepatic impairment are presented in the table below, which serves as a guidance and is neither intended to be prescriptive nor exhaustive. Other drugs not listed in this table (such as antihypertensive agents) may be authorized during the study at the discretion of the sponsor and investigator.

Therapeutic Category Drugs	Drugs
Antibiotics	Ofloxacin Norfloxacin Neomycin
Pruritus Treatment	Ursodeoxycholic acid Cholestyramine
Nutritional supplementation	Vitamins A, D, E, K and Calcium
Diuretics	Furosemide Spironolactone Hydrochlorothiazide
Ammonium Detoxicant	Lactulose Neomycin Metronidazole Rifaximin
Immunosuppressive agents	Corticosteroids Interferon α2a Interferon α2b
Antivirals	Lamivudine Ribavirin Entecavir Ledipasvir/Sofosbuvir

Appendix 10. Protocol Amendment I8F-MC-GPGQ(a) Summary - A Single Dose Pharmacokinetic Study of Tirzepatide in Subjects with Varying Degrees of Hepatic Impairment

Overview

Protocol I8F-MC-GPGQ, A Single Dose Pharmacokinetic Study of Tirzepatide in Subjects with Varying Degrees of Hepatic Impairment, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Provide improved clarity on when additional hepatic monitoring tests, as described in Appendix 4, should be performed. There is a need to differentiate between the cut-off trigger for testing in subjects with normal liver function enzyme tests and patients with hepatic impairment with elevated baseline liver enzymes.
    - Amended Section 9.4.7.1.
    - Added Section 9.4.7.2.
- Added clarification to Exclusion Criterion [37] to apply only to Group 1 healthy controls.
- Added clarification to Exclusion Criterion [60] specifying systemic glucocorticoids.
- Minor editorial changes and formatting corrections were made but not necessarily detailed below.

Revised Protocol Sections

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

6.2.1. Exclusion Criteria for All Subjects Unless Otherwise Specified

[37] show evidence of hepatitis B and/or positive hepatitis B surface antigen (applies to Group 1 control subjects only)

6.2.3. Additional Exclusion Criteria for Subjects with T2DM and Hepatic Impairment

[60] 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 systemic glucocorticoid therapy within 30 days before screening

9.4.7.1. Hepatic Safety Monitoring in Subjects with Treatment-emergent Abnormal Liver Tests

~~If a study subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated total bilirubin ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, total bilirubin, gamma-glutamyl transferase, and creatinine phosphokinase 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 total bilirubin 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~~
- ~~hepatic event considered to be an SAE~~

Abnormal liver tests in study participants with normal or near normal baseline ALT, AST, ALP, and total bilirubin (TBL; <1.5× ULN)

If a subject who was enrolled with baseline ALT, AST, ALP, TBL <1.5× ULN, experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, gamma-glutamyl transferase (GGT), and creatine kinase (CK) to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with

the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Elevated ALT/AST in subjects with baseline ALT/AST ≥1.5× ULN

If a subject, who was enrolled with baseline ALT/AST >1.5× ULN, experiences elevated ALT/AST >2× baseline (respectively), liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, GGT, and CK to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Elevated ALP in subjects with baseline ALP ≥1.5× ULN

If a subject, who was enrolled with baseline ALP >1.5× ULN, experiences elevated ALP >2× baseline, liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, GGT, and CK to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Elevated TBL in subjects with baseline TBL ≥1.5× ULN

If a subject, who was enrolled with baseline TBL >1.5× ULN, experiences elevated TBL >1.5× baseline, liver tests (Appendix 4) should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, direct bilirubin, GGT, and CK to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

9.4.7.2 Additional Hepatic Data Collection (Hepatic Safety eCRF) in Subjects with Treatment-emergent Abnormal Liver Tests

Treatment-emergent abnormal liver tests in subjects with normal or near normal baseline ALT, AST, ALP, and TBL (<1.5× ULN)

In a subject, who was enrolled with baseline ALT, AST, ALP, and TBL < 1.5× ULN, additional hepatic 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 total bilirubin 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
- hepatic event considered to be a SAE

Elevated ALT/AST in subjects with baseline ALT/AST ≥ 1.5× ULN

In a subject, who was enrolled with baseline ALT/AST >1.5× ULN, elevated ALT/AST >3× baseline (respectively) on two or more consecutive tests should prompt additional hepatic safety data collection.

Abnormal ALP in subjects with baseline ALP ≥1.5× ULN

In a subject, who was enrolled with baseline ALP ≥1.5× ULN, elevated ALP ≥2× baseline on two or more consecutive tests should prompt additional hepatic safety data collection.

Abnormal TBL in subjects with baseline TBL ≥1.5× ULN

In a subject, who was enrolled with baseline TBL >1.5× ULN, elevated TBL >2× baseline on two or more consecutive tests should prompt additional hepatic safety data collection.

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