I8F-MC-GPGS Clinical Pharmacology Protocol

A Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by an Autoinjector versus Prefilled Syringe in Healthy Subjects

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Protocol I8F-MC-GPGS
A Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by an Autoinjector versus Prefilled Syringe in Healthy Subjects

Tirzepatide (LY3298176)

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

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1. Protocol Synopsis

Title of Study:
A Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by an Autoinjector versus Prefilled Syringe in Healthy Subjects.

Rationale:
Study I8F-MC-GPGS (GPGS) will assess the pharmacokinetics (PK), safety and tolerability of a 5 mg subcutaneous (SC) dose of tirzepatide solution formulation administered via autoinjector (AI) (test) versus a prefilled syringe (PFS) (reference). The PFS is being used in one of the 5 Phase 3 studies implemented in the T2DM clinical programme, while the AI will be used in the remaining 4 Phase 3 studies. The AI device is planned as the eventual commercial product for use in the future. This study will provide tirzepatide PK comparability data when tirzepatide is administered via the AI (test) versus the PFS (reference) device.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To establish comparability between the autoinjector (AI; test) and the prefilled syringe (PFS; reference), as assessed by tirzepatide pharmacokinetics in healthy subjects.	Maximum drug concentration (C_{max}) and area under the concentration versus time curve from zero to infinity [AUC(0-∞)]
Secondary To compare the safety and tolerability of a single subcutaneous dose of tirzepatide administered by AI (test) versus PFS (reference).	Incidence of adverse events (AEs)

Summary of Study Design:

Study I8F-MC-GPGS is a single center, open-label, randomized, 2-period, 2-sequence, crossover study conducted in healthy subjects.

Treatment Arms and Planned Duration for an Individual Subject:
The study involves a comparison of:

- a single dose of 5 mg tirzepatide administered SC via AI
- a single dose of 5 mg tirzepatide administered SC via PFS

The study duration for individual subjects, inclusive of screening is expected to be approximately 14 weeks, divided as follows:

- Screening: up to 27 days prior to Day -1
- Treatment Periods 1 and 2: Day 1 to Day 36, including single dosing with tirzepatide on Day 1 of each period
- Washout: there will be a washout of at least 35 days between tirzepatide doses

- Follow-up: Period 2, Day 36 (±1) will be considered as the final follow-up visit

Number of Subjects:
Up to 48 subjects may be enrolled to ensure that approximately 36 subjects with evaluable results complete the study.

Statistical Analysis:

The primary PK parameters for analysis will be C_{max} and AUC(0-∞).

Two one-sided equivalence tests (TOST) will be applied to the ratios of each of C_{max} and AUC using the AI as the test sample and the PFS as the reference. Test limits of the ratios to establish comparability are 0.8 and 1.25.

Pharmacokinetic parameters will be evaluated to estimate the relative bioavailability. Log-transformed C_{max} and AUC(0-∞) will be evaluated in a linear mixed-effects model with fixed effects for device, sequence, period, and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians and 90% CIs from the Wilcoxon test will be calculated.

Planned PK parameters will also be summarized with descriptive statistics.

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

Safety parameters that will be assessed include adverse events, safety lab parameters (including amylase, lipase, and blood glucose), and vital signs. The parameters will be listed and summarized using standard descriptive statistics, where appropriate.

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.

Incidence of erythema, induration, pain, itching, and edema will be listed and summarized.

Additional analyses may be performed, if appropriate.

2. Schedule of Activities

Study Schedule Protocol I8F-MC-GPGS

	Screening	Periods 1 and 2 Study Days – at least 35 days washout between Day 1 doses												EDc	Comments
Procedure	D-28 to D-2	D-1b	D1b	D2	D3	D4	D5	D6	D7	D8	D15	D21	D36 (±1)b		
Informed Consent	X														
Subject Admission to CRU		X													
Tirzepatide Dosing			0 hour												Study drug will be administered after an overnight fast of at least 8 hours.
Subject Discharge from CRU						X									Subjects' CRU stay may be extended at the investigator's discretion for safety monitoring.
Outpatient Visit							X	X	X	X	X	X	X	X	
Medical History and Demographics	X														
Physical Examination /Medical Assessment	X		Predose			X							X	X	Physical examination at screening. Thereafter, targeted reviews and medical assessments as appropriate.
Weight	X		Predose										X	X	
Height	X														
Temperature	X		Predose												
Safety 12-lead ECGa	X		Predose	X		X				X			X	X	Single safety ECG will be collected. ECGs must be recorded before collecting any blood samples at each timepoint. Subjects must be supine for approximately 5 to 10 minutes before ECG collection, and remain supine but awake during ECG collection.
Supine Vital Signs (hours)	X		Predose, 12	24	48	72				X	X	X	X	X	Additional time points may be added, if warranted and agreed upon between Lilly and the investigator.
Clinical Laboratory Tests	X		Predose			X				X	X	X	X	X	See Appendix 2 for details. Day 1 predose sample is for baseline only.
Pregnancy Test	X	X											X	X	Female subjects only. Serum pregnancy test will be performed at screening and urine pregnancy tests at subsequent visits.
FSH test, if applicable	X														Female subjects considered to be postmenopausal only. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.
AEs/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacogenetic Samplea			Predose												Single sample in Period 1 only.

	Screening	Periods 1 and 2 Study Days – at least 35 days washout between Day 1 doses												ED[c]	Comments
Procedure	D-28 to D-2	D-1[b]	D1[b]	D2	D3	D4	D5	D6	D7	D8	D15	D21	D36 (±1)[b]		
Immunogenicity[a]			Predose								X		X	X	Where applicable, collection times should match with PK sampling time points. In the event of immediate or non-immediate drug hypersensitivity reactions, unscheduled samples will be collected as detailed in Section 9.4.6. Subjects with TE ADA at follow-up/ED will undergo additional follow-up as detailed in Section 9.7.
Blood glucose monitoring (hours)[a]			Predose, 12	24, 36	48	72									Performed using a bedside glucose monitor. Additional unscheduled measurements may be taken at the discretion of the investigator where clinically indicated.
PK Sampling (hours)[a]			Predose, 8, 12	24, 36	48	72	96	120	144	168	336	480	X	X	Up to a 10% deviation from the nominal collection time is permissible as long as actual sampling time is recorded.

Abbreviations: ADA = antidrug antibodies; AE = adverse event; CRU = clinical research unit; D or 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). Unless otherwise indicated, predose procedure may be performed any time prior to dosing.

If multiple procedures take place at the same time point, the following order of the procedures should be used: ECGs, vital signs, PK sample (record of actual PK sampling time is the priority), clinical laboratory sample, immunogenicity, blood glucose and pharmacogenetic sample.

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

b Period 2, Day -1 procedures (pregnancy tests) and some Period 2, Predose procedures (physical examinations, medical assessments, and clinical laboratory assessments) may be omitted if Period 1, D36 (±1) procedure dates occur within 4 days of Period 2 dosing. Period 2, Day 36 (±1) will also be considered as the final follow-up visit.

c Within 7 to 14 days upon confirmation of early discontinuation.

3. Introduction

3.1. Study Rationale

Tirzepatide (LY3298176) is being developed for the treatment of type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise. In addition, it is being developed as a therapy for the indications of chronic weight management and nonalcoholic steatohepatitis (NASH). It is administered once weekly by SC injection.

Study I8F-MC-GPGS (GPGS) will assess the pharmacokinetics (PK), safety and tolerability of a 5 mg subcutaneous (SC) dose of tirzepatide solution formulation administered using autoinjector or AI (test) versus prefilled syringe or PFS (reference).

The PFS device is being used in first of the 5 planned Phase 3 studies in the T2DM clinical program of tirzepatide. The following 4 Phase 3 T2DM studies will use the AI device. Additionally, the AI device is intended as the eventual commercial product for future use in patients.

3.2. Background

The available preclinical and clinical data indicate that co-stimulation of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors may enhance insulin secretion, improve insulin sensitivity, and reduce body weight beyond the effect of selective GLP-1R stimulation (Frias et al. 2018; Coskun et al. 2018).

Tirzepatide, a dual agonist of GIP and GLP-1, 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.

In a Phase 1 study (Coskun et al. 2018) that included single and multiple ascending dose (SAD, MAD) parts, tirzepatide has been administered as single SC doses up to 8 mg in healthy subjects. In the MAD part, higher doses up to 10 mg were attained in healthy subjects via dose escalation. Doses up to 15 mg were achieved in patients with T2DM via dose escalation. In this study, gastrointestinal (GI) adverse events (AEs) (nausea, vomiting, diarrhea, abdominal distension) and decreased appetite were the most frequently reported events by both healthy subjects and also by patients with T2DM and were dose related. Most AEs were mild in severity, a few were moderate, and none were reported as severe. During the single ascending dose study, the high incidence of GI AEs, notably vomiting, were considered to be dose limiting at the 8-mg dose; therefore, the 5-mg dose was considered the maximum tolerated dose. 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. Once-weekly doses of 1, 5, 10, and 15 mg have been further investigated in a Phase 2 study (Frias et al, 2018). An additional dose level of 12 mg and alternate dose escalation schemes were investigated in a 12-week Phase 2 study.

Doses above 5 mg of tirzepatide were attained via step-wise dose escalation. Results from the two Phase 2 studies demonstrated that tirzepatide at doses between 5 and 15 mg provided clinically meaningful efficacy in both glucose- and body weight-lowering. Gastrointestinal-related AEs (nausea, diarrhea, vomiting) were the most frequently reported AEs in Phase 2 studies. The majority of the treatment emergent adverse events (TEAEs) were mild or moderate in severity. There were no other clinically relevant safety observations in the Phase 1 and 2 studies.

Tirzepatide terminal half-life was estimated to be approximately 5 days, thus supporting a once-weekly (QW) dosing regimen, with maximum observed drug concentration (C_{max}) occurring 24 to 72 hours postdose.

Overall, the safety and tolerability, and PK/PD profiles of tirzepatide support further development of tirzepatide in patients with T2DM. Further details can be found in the Investigator's Brochure (IB).

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, gastrointestinal (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 weekly doses, when escalated up to 15 mg. Based on this information, the 2 × single 5-mg doses to be administered in Study GPGS are reasonably anticipated to be tolerable in this group of healthy subjects.

There is no anticipated therapeutic benefit in these healthy 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 IB.

4. Objectives and Endpoints

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

Table GPGS.1. Objectives and Endpoints

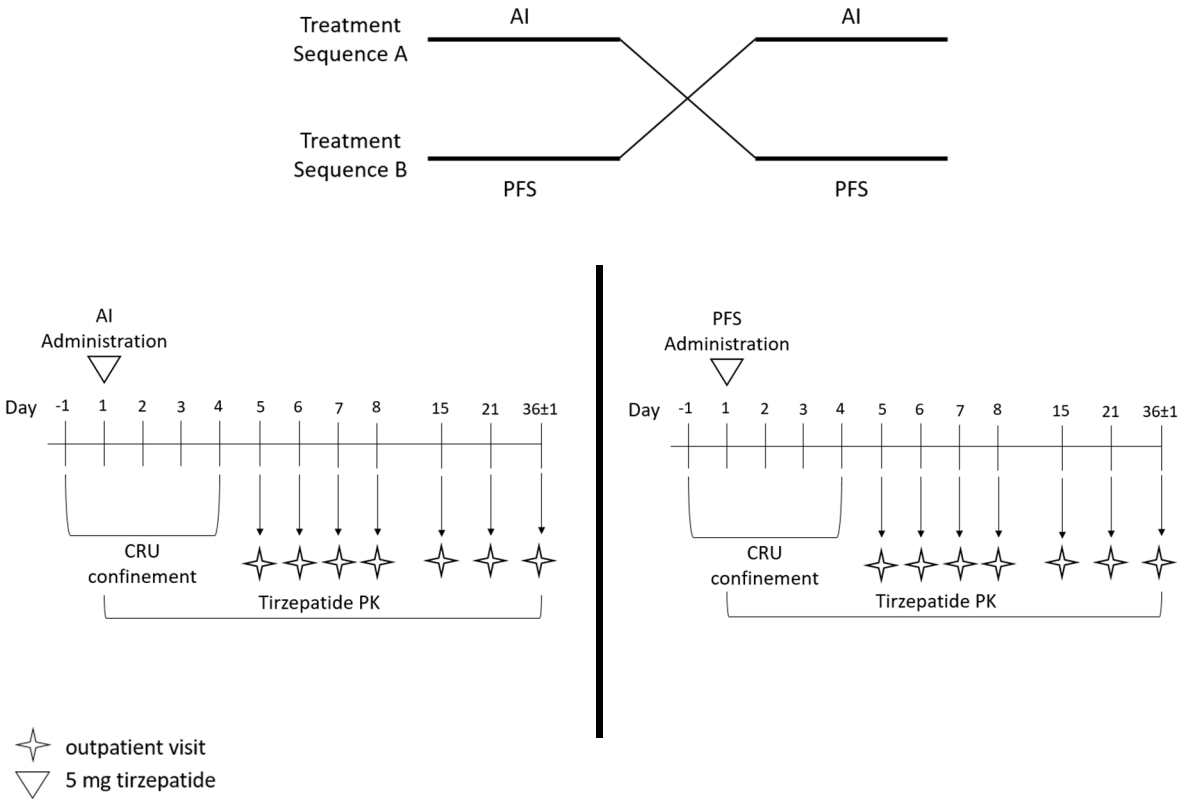
Objectives	Endpoints
Primary To establish comparability between the autoinjector (AI; test) and the prefilled syringe (PFS; reference), as assessed by tirzepatide pharmacokinetics in healthy subjects.	Maximum drug concentration (C_{max}) and area under the concentration versus time curve from zero to infinity [AUC(0-∞)]
Secondary To compare the safety and tolerability of a single subcutaneous dose of tirzepatide administered by AI (test) versus PFS (reference).	Incidence of AEs

5. Study Design

5.1. Overall Design

This study is a single center, open-label, randomized, 2-period, 2-sequence, crossover study conducted in healthy subjects.

The study design is as follows:



Abbreviation: AI = autoinjector; CRU = clinical research unit; PFS = prefilled syringe; PK = pharmacokinetics.

Site staff will administer all injections. All injections will be administered in the abdomen whilst the subject is in a sitting or reclining position. Injections will be given in the lower abdominal quadrant. Study injections should be given by a limited number of individuals for consistency.

There will be a washout of at least 35 days between tirzepatide doses. Subjects will be randomized to 1 of the 2 treatment sequences shown above. It is intended that the same number of subjects will be randomized into each treatment sequence.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to 48 subjects may be enrolled so that approximately 36 evaluable subjects complete the study. A subject who discontinued before completing study activities may be replaced at the discretion of the investigator in consultation with the sponsor in order to meet the study objectives.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

A population of healthy subjects was selected since this will permit an objective assessment of PK between the 2 devices.

A healthy subject population will allow assessments of the PK, safety, and tolerability of tirzepatide with a reduced likelihood of physiologic variability. Also, healthy subjects are usually devoid of other confounding factors, such as concomitant medications.

This study will be open-label as the study primary endpoint PK measures are objective rather than subjective.

In order to minimize any potential period-effect and to allow each subject to act as their own control, a randomized, 2-sequence, crossover design has been selected. A washout period of at least 35 days between doses is considered sufficient to minimize any carryover of tirzepatide concentrations from the first period into the second period.

5.5. Justification for Dose

Data from Phase 1 study GPGA has shown that a 5 mg dose of tirzepatide was well tolerated by healthy subjects and patients with T2DM, and is also planned as one of the doses to be investigated in Phase 3 studies. Doses higher than 5 mg were achieved via escalation since a 5 mg dose was considered the MTD when administered as a single dose.

6. Study Population

Eligibility of subjects for the study will be largely based on the results of screening and/or Day -1 medical history, physical examination, vital signs, clinical laboratory tests and electrocardiogram (ECG).

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

Screening may occur up to 28 days prior to enrollment. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

If the investigator decides not to administer the dose to a subject or not to enroll a subject on a particular day, the subject's visit may be rescheduled and any assessments or procedures performed up to that point may be repeated to confirm their eligibility.

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

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or Day -1:

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

[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 90 days after dosing. A full list of permitted highly effective and effective methods of contraception is presented in Appendix 6.

- 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 90 days 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 21 years and 70 years of age, inclusive, at the time of screening.

[3] have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, and a minimum body weight of 45 kg.

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

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

[6] are willing to receive study treatment by SC injections.

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

[8] have blood pressure, pulse rate, and an ECG reading that are considered to be within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator limits as determined by the investigator.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or Day -1:

[9] 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.

[10] are Lilly employees or are employees of a third-party organization involved with the study.

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

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

[13] have previously completed or withdrawn from this study or any other study investigating tirzepatide, and have previously received the IP.

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

[15] have any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study.

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

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

[18] regularly use known drugs of abuse

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

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

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

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

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

[24] have donated blood of more than 450 mL or more in the last 3 months, have participated in a clinical study that required a similar blood volume be drawn in the last 3 months, or have had any blood donation within the last month prior to screening.

[25] have an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), OR are unwilling to stop alcohol consumption during study visits/time in the CRU
(1 unit of alcohol = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

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

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

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

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

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

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

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

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 any SC dose of tirzepatide, and when clinical laboratory test samples are taken (see Schedule of Activities). A meal will be offered to study subjects at around 2 hours postdose. During inpatient stays, subjects may not consume any food other than that provided by the CRU. Water may be consumed freely.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed from 24 hours prior to each dose and whilst resident at the CRU, or completion of all study procedures. No nicotine use will be permitted while in the CRU. While not resident in the CRU, subjects must consume no more than 10 cigarettes or the equivalent per day.

Subjects will be allowed to maintain the regular caffeine consumption throughout the study period (except during specific fasting time periods).

6.3.3. Activity

No strenuous physical activity will be allowed for 48 hours prior to dosing until discharge from the CRU, and 24 hours prior to each outpatient visit.

6.3.4. Screen Failures

Screening tests such as clinical laboratory tests and vital signs/ECGs may be repeated at the discretion of the investigator. As this is a healthy volunteer only study, individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. Treatment

7.1. Treatment Administered

Each subject will receive 2 doses of tirzepatide administered via 2 different devices. Each dose of IP will comprise 1 SC injection of 5 mg tirzepatide into the abdomen. All doses will be administered by clinical site staff.

The study involves a comparison of:

- a single dose of 5 mg tirzepatide administered SC via AI (Test)
- a single dose of 5 mg tirzepatide administered SC via PFS (Reference)

Prior to injection, the investigator or designee will clean the subject's skin. During each of the 2 study periods, the injection will be administered to the lower abdominal quadrant, approximately 5 cm from the umbilicus (ie, left lower quadrant and right lower quadrant). Detailed instructions for use will be provided by the sponsor.

A limited number of clinical site staff will perform SC administration for consistency reasons.

Table GPGS.2 shows the treatment regimens.

Table GPGS.2. Treatments Administered

Treatment Name	Test Treatment	Reference Treatment
Dosage Formulation	solution for injection	solution for injection
Dose	5 mg tirzepatide / 0.5 mL	5 mg tirzepatide / 0.5 mL
Route of Administration	SC injection	SC injection
Delivery Method	autoinjector	prefilled syringe

Abbreviations: SC = subcutaneous.

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling

Tirzepatide will be supplied by the sponsor or its designee in accordance with current good manufacturing practice, labeled according to the country's regulatory requirements.

Each syringe of tirzepatide is designed to deliver 5 mg of tirzepatide. The following products will be supplied by Lilly, with study-specific labels, for use in the study:

- tirzepatide in 5 mg single-dose, pre-assembled, investigational AIs (Test)
- tirzepatide in 5 mg single-dose, disposable manual PFS (Reference)

7.1.2. Medical Devices

The investigator or designee will ensure that the instructions have been followed properly; maintaining accurate records of study devices, dispensing, and collection. The used or unused AI and PFS may be destroyed by a qualified vendor.

7.2. Method of Treatment Assignment

Subjects will be randomly assigned to 1 of 2 possible treatment sequences using a computer-generated allocation code.

7.2.1. Selection and Timing of Doses

The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

This study is open-label.

7.4. Dose Modification

Dose modification is not permitted in this study.

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 IP received and that any discrepancies are reported and resolved before use of the study treatment.

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

The investigator is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

In general, concomitant medication should be avoided; however, paracetamol (1g, maximum 3g/24 hours) may be administered at the discretion of the investigator for treatment of headaches etc. If the need for concomitant medication (other than paracetamol) arises, inclusion or continuation of the subject may be at the discretion of the investigator, preferably after consultation with a Lilly Clinical Pharmacologist (CP) or CRP or designee. Any medication used during the course of the study must be documented.

7.8. Treatment After the End of the Study

Not applicable.

8. Discontinuation Criteria

Subjects discontinuing from the study and treatment prematurely for any reason should complete AE and other follow-up procedures per Schedule of Activities (Section 2) of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the IP for abnormal liver tests **should be considered** by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- ALT or AST (aspartate aminotransferase) >5 × ULN
- ALT or AST >3 × ULN sustained for more than 2 weeks or
- ALT or AST >3 × ULN and TBL >2 × ULN or international normalized ratio >1.5 or
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3 × ULN
- ALP >2.5 × ULN and TBL >2 × ULN
- ALP >2.5 × ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

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

8.2. Discontinuation from the Study

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

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

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

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

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

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 on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU 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.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

After the informed consent form (ICF) is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions, including clinically significant

signs and symptoms. 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 the AI or PFS, the IP, and/or a study procedure, taking into account concomitant treatment or pathologies.

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

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

If a subject's IP 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
- when a condition related to the AI or the PFS, the IP, and/or study procedure necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned

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.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (and 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 AI or PFS, the IP and/or study procedure, the investigator must promptly notify Lilly.

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

For the purposes of this study, an overdose of tirzepatide is considered any dose higher than the dose assigned through randomization.

There is no specific antidote for tirzepatide. In the event of an overdose, the subject should receive appropriate supportive care and any AEs should be documented.

Refer to the IB.

9.4. Safety

9.4.1. Laboratory Tests

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

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

9.4.2.1. Hyperglycemia and Hypoglycemia Reporting

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

If the fasting plasma glucose during Periods 1 and 2, 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 glucose continues to exceed the acceptable level, treatment with an appropriate antidiabetic agent may be initiated by the investigator.

Hypoglycemia episodes will be recorded on specific eCRF pages. Hypoglycemia will be treated appropriately by the investigator and additional monitoring of plasma 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 regarding SAE reporting).

9.4.3. Vital Signs

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

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

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

9.4.4. Electrocardiograms

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

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the IP, should be reported to Lilly, or its designee.

For each subject, a single12-lead digital electrocardiogram (ECG) will be collected according to the Schedule of Activities. Electrocardiograms must be recorded before collecting any blood samples at individual timepoints. 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 adverse event.

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

- trends in safety data
- laboratory analytes including glucose, amylase, and lipase
- serious and nonserious AEs, including AEs of interest.

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

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, TBL, conjugated bilirubin, gamma-glutamyl transferase (GGT), and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of 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 time (24-hour clock time) of each sampling will be recorded.

Failure or being late (ie, outside stipulated time allowances) to perform obtain samples due to legitimate clinical issues (eg, equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will have to notify the sponsor in writing via a file note.

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 IP 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

Not applicable.

9.7. 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 tirzepatide. Additional samples may be collected if there is a possibility that an AE is immunologically mediated (see Section 9.4.6). All samples for immunogenicity testing should have a time-matched sample for PK analysis where relevant. Detailed instructions for the sample collections and handling 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 antidrug antibodies (ADA) in the presence of tirzepatide at a laboratory approved by the sponsor. Antibodies may be further evaluated for their ability to neutralize the activity of tirzepatide on GIP and GLP-1 receptors. Positive tirzepatide ADA samples may also be tested for cross-reactivity against native GIP and GLP-1, and, if positive, may then be tested for neutralizing antibodies against native GIP and/or GLP-1.

All subjects will have an ADA sample measured at early discontinuation or at Period 2, Day 36. A risk-based approach will be used to monitor subjects who develop treatment-emergent ADA (TE ADA), defined in Section 10.3.3 (Evaluation of Immunogenicity).

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

Subjects who have clinically significant TE ADA at early discontinuation or at the safety follow-up should be followed with ADA testing every 3 months until the ADA titers have returned to the baseline ADA titer (defined as ADA titer within 2-fold of baseline) or for up to 1 year, whichever is less. A PK sample may be collected at the follow-up immunogenicity assessment(s), if warranted and agreed upon by the investigator and sponsor.

Every effort 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 ERBs, 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.

9.8. 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 ERBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of 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.

9.9. Biomarkers

Not applicable.

9.10. 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 approximately 48 subjects may be enrolled so that at least 36 evaluable subjects complete the study. With 36 subjects, we expect the two one-sided tests (TOST) for equivalence applied to the lognormal mean ratio to have a power of 98%. This assumes a nominal expected mean ratio of 1.05 (autoinjector over prefilled syringe), a coefficient of variation of 19.6%, and significance level of 0.05 of each one-sided test when testing against an upper limit of 1.25 and lower limit of 0.80. The source of the choice of coefficient of variation is from the final results of study I8F-MC-GPGE.

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, or other demographic characteristics will be recorded and may be used in the PK and safety analyses as quantitative of classification variables.

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least one dose of the IP 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.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IP, study device, and protocol procedure AEs, and study device deficiencies/complaints will be listed, and if the frequency of events allows, data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with IP as perceived by the investigator. Symptoms reported to occur prior to 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 IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include adverse events, safety lab parameters (including amylase, lipase, and blood glucose), and vital signs. The parameters will be listed and summarized using standard descriptive statistics, where appropriate.

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.

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 PK parameters for analysis will be C_{max} and AUC(0-∞). Other noncompartmental parameters, such as time to C_{max} (t_{max}), AUC(0-t_{last}), half-life associated with the terminal rate constant in noncompartmental analysis (t1/2), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Two one-sided equivalence tests (TOST) will be applied to the ratios of each of C_{max} and AUC using the AI as the test sample and the PFS as the reference. Test limits of the ratios to establish comparability are 0.8 and 1.25.

Pharmacokinetic parameters will be evaluated to estimate the relative bioavailability. Log-transformed C_{max} and AUC(0-∞) will be evaluated in a linear mixed-effects model with fixed effects for device, sequence, period, and a random effect for subject within sequence. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI. Other parameters may be analyzed in this way as needed.

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians and 90% CIs from the Wilcoxon test will be calculated.

Planned PK parameters will also be summarized with descriptive statistics.

10.3.3. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting 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. The frequency of neutralizing antibodies if performed, will be tabulated in TE ADA+ subjects. If cross-reactivity with to native GLP-1 and GIP or neutralizing antibodies against native GLP-1 and GIP assays are performed, the frequency of each will be reported.

10.3.4. Data Review During the Study

This section is not applicable for this study.

10.3.5. Interim Analyses

No interim analyses are planned for this study. If an 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.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a subject 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.
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some ethical review boards [ERBs]).
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist
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.
enroll	The act of assigning a subject to a treatment sequence. Subjects who are enrolled in the study are those who have been assigned to a treatment sequence.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IND	Investigational New Drug: An application to the FDA to allow testing of a new drug in humans.

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.
Investigational product (IP)	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.
IV	intravenous
MTD	maximum tolerated dose
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
randomize	The process of assigning subjects to an experimental group on a random basis
PK/PD	pharmacokinetic/pharmacodynamic
SAE	serious adverse event
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
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment

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	Glucose (fasting)
Leukocytes (WBC)	Blood urea
	Total protein
Absolute counts of:	Albumin
Neutrophils	Total bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Aspartate aminotransferase
Eosinophils	Alanine aminotransferase
Basophils	Creatinine
Platelets	Amylase
	Lipase
	Triglyceride[c]
Urinalysis[a]	
Specific gravity	Hepatitis B surface antigen[c]
pH	Hepatitis C antibody[c]
Protein	HIV or HIV antibody[c]
Glucose	FSH[d]
Ketones	Pregnancy test[d]
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Leukocytes (WBC)	
Microscopic examination of sediment[b]	

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

[a] Performed by local laboratory. Results will be validated by the laboratory at the time of initial testing.

[b] Test only if dipstick result is abnormal (ie, positive for blood, protein, or nitrites) if clinically indicated, per investigator discretion.

[c] Performed by local laboratory at screening only. Tests may be waived if they have been performed within 6 months before screening with reports available for review.

[d] For women only. Serum pregnancy test will be performed at screening and urine pregnancy tests at subsequent visits. For women who are considered to be postmenopausal, a blood sample for follicle stimulating hormone should be drawn at screening to confirm postmenopausal status as defined in inclusion criterion [1b]; women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.

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. 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 IP.
- 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 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 ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

This study will be conducted in accordance with 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 investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his 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 site, 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 ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; 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, immunogenicity, pharmacokinetics, blood glucose, and bioanalytical assays) during the study.

Protocol I8F-MC-GPGS Sampling Summary

Purpose	Blood Volume per Sample (mL)	Estimated Number of Blood Samples	Total Volume (mL)
Screening tests (local laboratory)[a]	20	1	20
Clinical laboratory tests (local laboratory)[a] • Study visits (2 periods)	10	6 × 2 periods = 12	120
Pharmacokinetics (central or referral laboratory)[b] • Study visits (2 periods)	3	14 × 2 periods (+3 unscheduled) = 31	93
Immunogenicity (central or referral laboratory) • Study visits (2 periods)	10	3 × 2 periods (+3 unscheduled) = 9	90
Blood glucose[a]	0.3	6 (+5 discard for cannula patency +3 unscheduled) x 2 periods = 28	8.4
Pharmacogenetics (stored sample)	10	1	10
Total			341.4
Total for clinical purposes rounded up to nearest 10 mL			350

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

[b] Up to 3 additional unscheduled samples may be drawn based on emerging data.

Appendix 6. Classification of Contraceptive Methods

Highly Effective (Less Than 1% Failure Rate) 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

* The use of male and female condoms as a double-barrier method is not considered acceptable.

Appendix 7. Pancreatic Monitoring

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

To enhance understanding of the natural variability of pancreatic enzymes in the T2DM population and, 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 and/or lipase values ≥3 × ULN at any visit, even in asymptomatic subjects (see figure below). Lipase and amylase values may also be obtained at any time during the clinical trials for any subject suspected of having symptoms suggestive of exenatide pancreatitis (such as severe GI signs and/or symptoms), at the investigator's discretion.

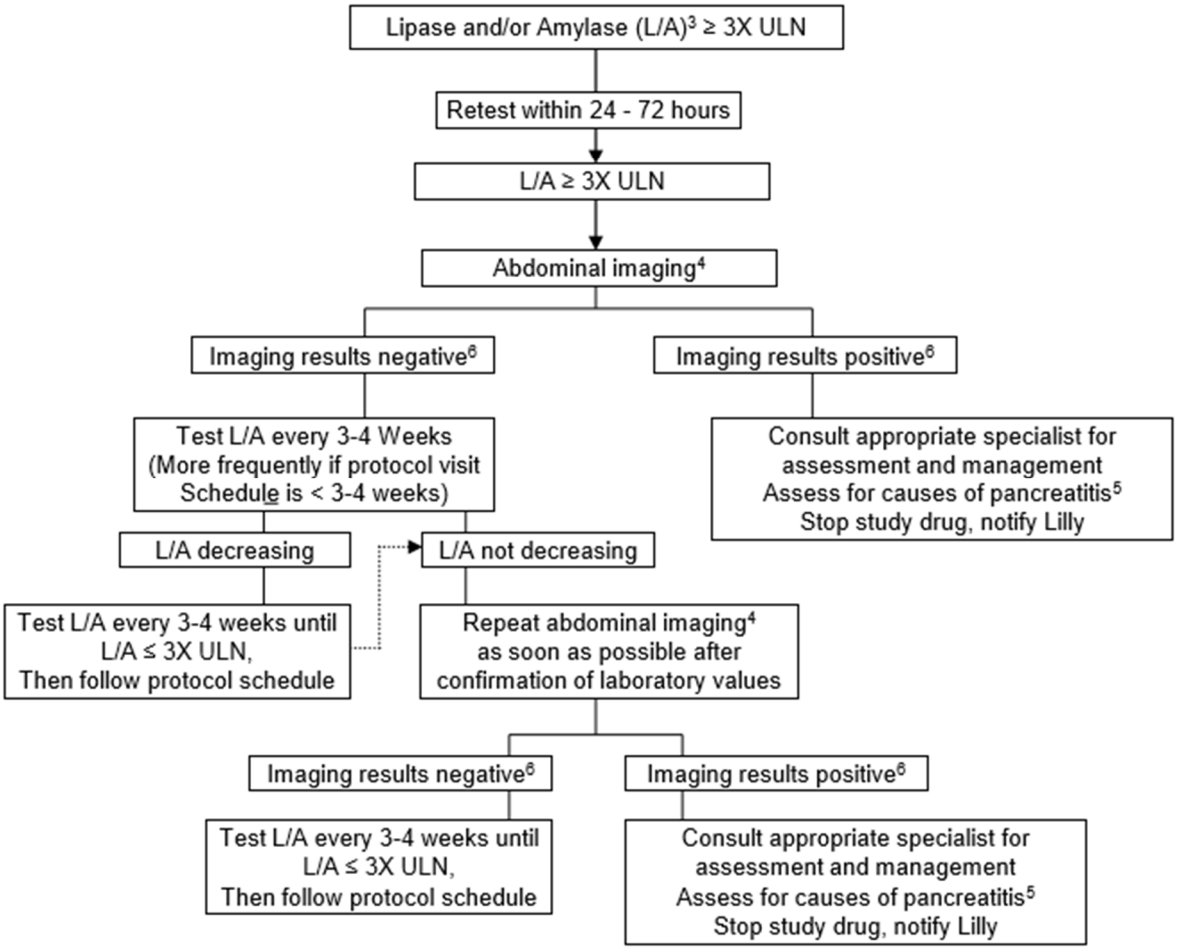
Acute pancreatitis is an AE defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase ≥3 × ULN
- characteristic findings of acute pancreatitis on CT 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
   (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.

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