Protocol I8F-MC-GPIP (a)

A Bioequivalence Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by a Fixed-Dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

NCT05810597

Approval Date: 30-May-2023

Title Page

Protocol Title:

A Bioequivalence Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by a Fixed-Dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

Protocol Number: I8F-MC-GPIP

Amendment Number: I8F-MC-GPIP (a)

Compound: Tirzepatide (LY3298176)

Brief Title:

Bioequivalence Study to Compare the PK of Tirzepatide Administered by Fixed-dose Multi-use Prefilled Pen Versus Single-Use Prefilled Pen in Healthy Participants

Study Phase: 1

Acronym: GPIP

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND128801

Approval Date: Protocol Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-117711

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*21-Oct-2022*

Amendment [a]

Overall Rationale for the Amendment:

The protocol is being amended to address FDA recommendations on contraceptive and barrier guidance. This amendment is considered as non-substantial.

Section # and Name	Description of Change	Brief Rationale
10.4.2 Contraception Guidance	Revised to include 2 forms of effective methods of contraception where at least 1 form must be a highly effective method of contraception.	Based on FDA feedback
	Deleted "total abstinence" from the list of highly effective contraception.	Based on FDA feedback

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Bioequivalence Study to Compare the Pharmacokinetics of Tirzepatide Administered Subcutaneously by a Fixed-Dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

Brief Title: Bioequivalence Study to Compare the PK of Tirzepatide Administered by Fixed-Dose Multi-use Prefilled Pen Versus Single-Dose Pen in Healthy Participants

Regulatory Agency Identifier Number(s): IND128801

Rationale:

Study I8F-MC-GPIP (GPIP) will assess the pharmacokinetics (PK), safety, and tolerability of a 5-mg subcutaneous (SC) dose of tirzepatide solution formulation administered via fixed-dose multi-use prefilled pen (MUPFP) (test) versus a single-dose pen (SDP) (reference). The SDP autoinjector device is the currently approved commercial single-dose, single-use pen presentation of tirzepatide, while the MUPFP is being developed as an alternative multi-dose option. This study will provide PK bioequivalence data for tirzepatide when it is administered via the MUPFP versus the SDP device.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence between the MUPFP (test) and the SDP (reference), as assessed using tirzepatide PK in healthy participants	• C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$
Secondary	
• To evaluate the additional PK parameter • To evaluate the safety and tolerability of a single subcutaneous dose of tirzepatide administered through MUPFP (test) versus SDP (reference)	• tmax • Incidence of AEs

Abbreviations: AE = adverse event; $AUC_{(0-t)}$ = area under the concentration versus time curve from time zero to time t; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; MUPFP = multi-use prefilled pen; PK = pharmacokinetics; SDP = single-dose pen; t_{max} = time of maximum observed drug concentration.

Brief Summary of Study Design:

Study GPIP is a multicenter, open-label, randomized, 2-period, 2-sequence, crossover study conducted in healthy participants.

Study Population:

Healthy participants.

Number of Participants:

Approximately 65 participants will be enrolled so that at least 54 participants complete the study.

Intervention and Planned Duration for an Individual Participant:
The study involves a comparison of:

- a single dose of 5 mg tirzepatide administered SC via MUPFP
- a single dose of 5 mg tirzepatide administered SC via SDP

The study duration for individual participants, 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 dose administrations
- Follow-up: Period 2, Day 36 (±1) will be considered as the final follow-up visit

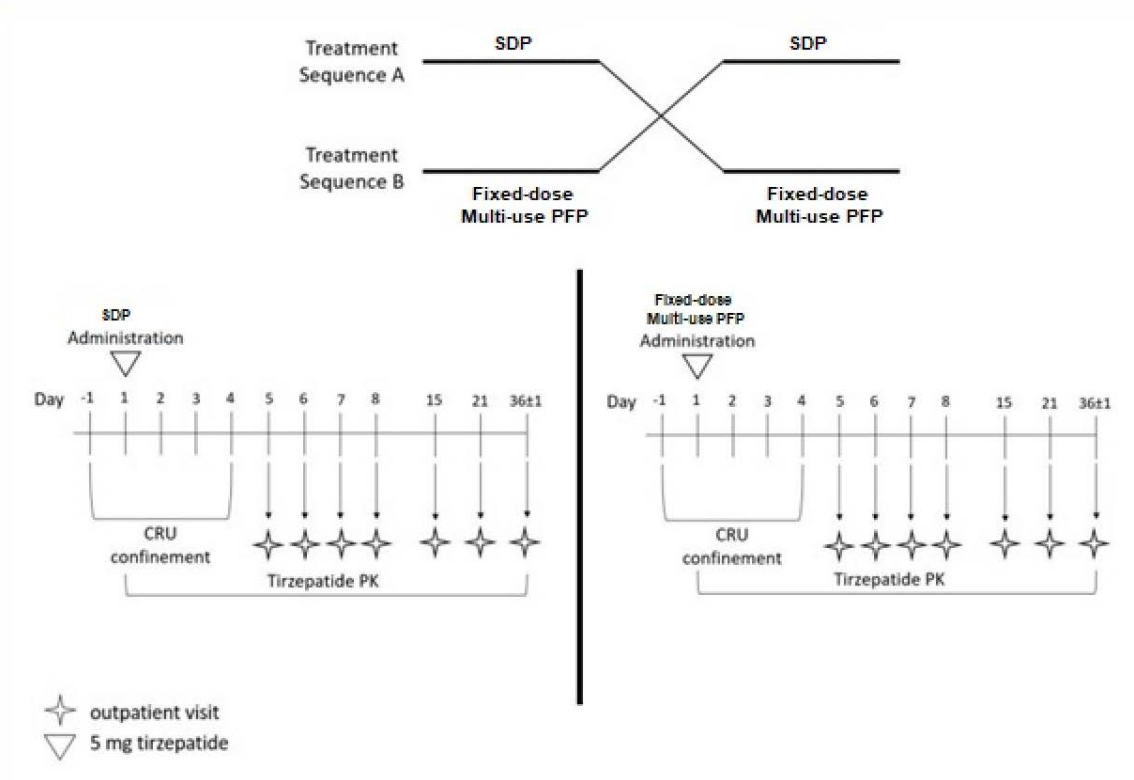
Ethical Considerations of Benefit/Risk:

As of 26 September 2022, tirzepatide (MOUNJARO™) was approved in the US, EU, and Japan as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Risks of tirzepatide have been consistent with risks associated with other glucagon-like peptide (GLP)-1 receptor agonists that are currently marketed. Potential risks include, but are not limited to, gastrointestinal effects, acute pancreatitis, increases in heart rate, and hypoglycemic events (GLP-1 receptor agonist class effect), which are all monitorable.

There is no anticipated therapeutic benefit in healthy participants.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: CRU = clinical research unit; PK = pharmacokinetics; PFP = prefilled pen, SDP =single dose pen

1.3. Schedule of Activities (SoA)

	Screening	Periods 1 and 2 Study Days – at least 35 days washout between Day 1 doses												ED[b]	Comments
Procedure	D -28 to D -2	D -1[a]	D1[a]	D2	D3	D4	D5	D6	D7	D8	D15	D21	D36 (±1)[a]		
Informed consent	X														
Participant admission to CRU		X													
Ethanol and urine drug screen testing	X	X													Per site CRU local requirements
Tirzepatide dosing			0 hour												Study drug will be administered after an overnight fast of at least 8 hours.
Participant discharge from CRU						X									Inpatient 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	Full physical examination at screening. Thereafter, assessments performed to include medical review and targeted, symptom-driven examination, as appropriate. Additional assessments may be performed at investigator's clinical discretion.
Weight	X		Predose										X	X	
Height	X														
Temperature	X		Predose												
Safety 12-lead ECG[c]	X					X								X	
Vital signs (hours)	X		Predose, 12	24	48	72				X	X	X	X	X	Additional unscheduled measures may be taken, at the clinical discretion of the investigator.
Clinical laboratory tests	X		Predose							X			X	X	See Appendix 2 for details. Day 1 predose sample is for baseline only and need not be reviewed prior to first dosing. Performed by local laboratory at screening and central laboratory for subsequent visits.
Pregnancy test	X		Predose										X	X	Female participants only. Serum pregnancy test will be performed at screening and urine pregnancy tests at subsequent visits.
FSH test, if applicable	X														Female participants 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	

	Screening	Periods 1 and 2 Study Days – at least 35 days washout between Day 1 doses												ED[b]	Comments
Procedure	D -28 to D -2	D -1[a]	D1[a]	D2	D3	D4	D5	D6	D7	D8	D15	D21	D36 (±1)[a]		
Pharmacogenetic sample[c]			Predose												Single sample in Period 1 only.
Blood glucose monitoring (hours)[c]			Predose, 12	24, 36	48	72									Performed using a bedside glucose monitor. Additional unscheduled measurements may be taken at the clinical discretion of the investigator.
PK sampling (hours)[c]			Predose, 8, 12	24, 36	48	72	96	120	144	168	336	480	X	X	

Abbreviations: AE = adverse event; CRU = clinical research unit; D or d = day; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; PK = pharmacokinetic(s).

a Period 2, Day -1 procedures (pregnancy tests) and some Period 2, predose procedures (physical examinations, medical assessments, ethanol and drug screening 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.

b Within 14 days upon confirmation of early discontinuation.

c Predose sample should be collected approximately 2 h prior to dose administration.

Note: All sampling and procedure 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, blood glucose and pharmacogenetic sample.

2. Introduction

2.1. Study Rationale

As of 26 September 2022, tirzepatide (MOUNJARO™) received regulatory approval in the US, EU, and Japan. Tirzepatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. In addition, it is being developed as a therapy for the indications of chronic weight management, nonalcoholic steatohepatitis, obstructive sleep apnea, and heart failure with preserved ejection fraction. It is administered QW through SC injection.

Study I8F-MC-GPIP (GPIP) will assess the PK, safety, and tolerability of a 5-mg SC dose of tirzepatide solution formulation administered using the MUPFP (test) versus the SDP (reference).

The SDP is the currently approved commercial presentation of tirzepatide. The fixed-dose MUPFP is being developed as an alternative option for future commercialization.

2.2. Background

Tirzepatide (LY3298176) is a GIP and GLP-1 RA. It is a 39 amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that prolongs the duration of action. It is administered QW through SC injection in a SDP.

Tirzepatide has a chemical structure and pharmacologic profile, ie, distinct from GLP-1 RAs due to the additional effects on GIP receptor, which is unique compared to the marketed incretin mimetics. As an agonist, tirzepatide combines the signaling of each receptor for improved glycemic control (Coskun et al. 2018). By virtue of being an agonist incretin mimetic, tirzepatide has the potential for reaching higher efficacy in target tissues such as the insulin-producing pancreatic β cells that express both GIP and GLP-1 receptors before reaching its therapeutic limitation, which supports its use as a treatment for T2DM.

A solution formulation of tirzepatide for injection in a SDP was developed for QW SC administration. This drug product formulation is composed of tirzepatide drug substance, sodium phosphate, sodium chloride, and water for injections.

The current commercial configuration is a single integral product with 0.5-mL sterile drug product solution contained in a 1-mL glass syringe with a plunger, which is assembled into a PFP (or autoinjector). The finished form is a SDP with a spring-driven design to administer the 0.5 mL. The 6 available strengths are 2.5, 5, 7.5, 10, 12.5, and 15 mg.

The MUPFP is configured to deliver multiple 0.6-mL doses of a single strength. The MUPFP uses a 3-mL cartridge that is preassembled into the device and is not replaceable. Six separate MUPFPs, 1 for each dose strength, are planned to match the approved SDP offering (2.5, 5, 7.5, 10, 12.5, and 15 mg). Each MUPFP will contain sufficient volume to deliver 4 doses covering 1 month of therapy.

2.3. Benefit/Risk Assessment

As of 26 September 2022, tirzepatide (MOUNJARO) was approved in the US, EU, and Japan as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Risks of tirzepatide have been consistent with risks associated with other GLP-1 RAs that are currently marketed. Potential risks include, but are not limited to, GI effects, acute pancreatitis, increases in heart rate, and hypoglycemic events (GLP-1 RA class effect), which are all monitorable.

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 up to 15 mg, attained by stepwise dose escalation. The maximum tolerated dose as a single dose of tirzepatide in healthy participants was determined to be 5 mg. Based on this information, the 2x single 5-mg doses to be administered in Study GPIP are reasonably anticipated to be tolerable in this group of healthy participants.

There is no anticipated therapeutic benefit in these healthy participants.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of tirzepatide are to be found in the package insert of tirzepatide.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the bioequivalence between the MUPFP (test) and the SDP (reference), as assessed using tirzepatide PK in healthy participants	• C_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$
Secondary	
• To evaluate the additional PK parameter • To evaluate the safety and tolerability of a single subcutaneous dose of tirzepatide administered through MUPFP (test) versus SDP (reference)	• tmax • Incidence of AEs

Abbreviations: AE = adverse event; $AUC_{(0-t)}$ = area under the concentration versus time curve from time zero to time t; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; MUPFP = multi-use prefilled pen; PK = pharmacokinetics; SDP = single-dose pen; t_{max} = time of maximum observed drug concentration.

4. Study Design

4.1. Overall Design

This is a multicenter, open-label, randomized, 2-period, 2-sequence, crossover study conducted in healthy participants.

The study will include 2 treatment arms. Approximately 65 participants may be enrolled so that at least 54 participants complete the study. Participants will be randomly assigned 1:1 to the 2 treatment sequences. It is intended that approximately the same number of participants will be randomly assigned into each treatment sequence. The treatment sequence are:

- a single dose of 5 mg tirzepatide administered SC via MUPFP followed by SDP; or
- a single dose of 5 mg tirzepatide administered SC via SDP followed by MUPFP.

The study duration for individual participants, inclusive of screening, is expected to be approximately 14 weeks.

4.1.1. Screening Period

Screening may occur up to 27 days prior to Day -1. During screening visit, participants will undergo screening tests as mentioned in Section 1.3. Participants 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. In such instances, at minimum, the following screening tests and procedures should be repeated: weight, vital signs, safety 12-lead ECG, clinical laboratory tests, and pregnancy test (females only).

4.1.2. Treatment Periods 1 and 2

- Each treatment period will last for 36 days.
- Participants will be randomly assigned to 1 of the 2 treatment arms (Section 1.2). On Day 1 of each treatment period, based on the randomization schedule, participants will receive either a single dose of 5 mg tirzepatide SC via MUPFP or a single dose of 5 mg tirzepatide SC via SDP.
- Study site personnel will administer all study drugs. Study drug should be administered by a limited number of individuals for consistency. All study drugs will be administered in the abdomen while the participant is in a sitting or reclining position. Study drug will be given in the lower abdominal quadrants.
- Participants will remain in the study site as inpatient from Day -1 to Day 4 or longer if required for management or monitoring of AE for safety and wellbeing of the participants, at the investigator's discretion.
- Participants will return to the study site for outpatient visits
    - daily from Day 5 to Day 8
    - weekly until Day 21 and
    - on Day 36

Study assessments will be performed in accordance with the SoA (Section 1.3).

4.1.3. Washout Period

There will be a washout of at least 35 days between tirzepatide doses.

4.1.4. Follow-Up Period

Day 36 (±1) of treatment Period 2 will be considered as the final follow-up visit.

4.2. Scientific Rationale for Study Design

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

A healthy participant population will allow assessments of the PK, safety, and tolerability of tirzepatide with a reduced likelihood of physiologic variability. Also, healthy participants 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.

To minimize any potential period-effect and to allow each participant 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 the risk of carry-over of tirzepatide concentrations from the first period into the second period, based on known understanding that the terminal half-life of tirzepatide is about 5 days (refer to IB).

4.3. Justification for Dose

It has been shown that a single 5-mg dose of tirzepatide was well tolerated by healthy participants and patients with T2DM.

The two 5-mg doses, separated by at least 35 days, planned to be administered in this study is expected to be tolerable in this group of healthy participants.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit or last scheduled procedure shown in the SoA for the last participant.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only unless otherwise specified, and not continuously throughout the study.

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 70 years of age, inclusive, at the time of screening.

Type of participant and disease characteristics

2. Participants who are overtly healthy as determined through medical history and physical examination.
3. Have clinical laboratory test results, blood pressure, pulse rate, and an ECG reading that are considered to be within normal reference range for the population or study site, or have results outside the normal reference range that are judged to be not clinically significant by the investigator at the time of screening.

Weight

4. Body mass index within the range 18.5 to 30.0 kg/m^2 (inclusive).

Sex and contraceptive/barrier requirements

5. Male, or female participants

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

Informed consent

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusion criteria

7. Have venous access sufficient to allow for blood sampling as per the protocol.
8. Are willing to receive study drug through SC injections.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

9. Have a significant history of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs, or of constituting a risk when taking the study drug, or of interfering with the interpretation of data.
10. Have evidence of significant active neuropsychiatric disease, as determined by the investigator.
11. Have a history or presence of pancreatitis, elevation in serum amylase or lipase (>1.5-fold the ULN), clinically significant GI disorders (eg, clinically significant esophageal reflux or gallbladder disease), or any GI disease or condition that impacts gastric emptying (e.g., history of gastric bypass surgery, pyloric stenosis) or could be aggravated by GLP analogs or dipeptidyl peptidase IV inhibitors. Participants with dyslipidemia and participants who had cholecystolithiasis and/or cholecystectomy in the past, with no further sequelae, may be included in the study, at the discretion of the investigator. History of uncomplicated acute appendicitis and appendectomy is acceptable as well.
12. Have a history of atopy or clinically significant multiple or severe drug allergies or severe posttreatment hypersensitivity reactions.
13. Have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2.
14. Have a history of malignancy within 5 years prior to screening.
15. Show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies.
16. Have evidence of hepatitis C and/or are positive for hepatitis C antibodies.
17. Have evidence of hepatitis B and/or are positive for hepatitis B surface antigen.

Prior/concomitant therapy

18. Regularly use known drugs of abuse or show positive findings on drug screen.
19. 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 RAs, dopamine antagonists, and opiates.

Prior/concurrent clinical study experience

20. Are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.
21. Have received treatment with a drug that has not received regulatory approval for any indication within 30 days of screening.

22. Have previously completed or withdrawn from this study.
23. Any exposure to tirzepatide within the prior 3 months, or history of allergies to tirzepatide, other GLP-1 analogs or related compounds.

Other exclusion criteria

24. Are study 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.
25. Are Lilly employees or are employees of a third-party organization involved with the study.
26. Smoke >10 cigarettes per day, or the equivalent, or are unable or unwilling to refrain from nicotine while resident in the study site.
27. Have donated blood of more than 450 mL or more in the past 3 months, have participated in a clinical study that required a similar blood volume be drawn in the past 3 months, or have had any blood donation within the last month prior to screening.
28. 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 and time in the study site (number of units = [total volume of drink (mL) x ABV (%)]/1000. ABV = alcohol by volume).

29. Are deemed unsuitable by the investigator for any other reason.

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

Participants will be required to fast overnight for at least 8 hours (see SoA, Section 1.3) before

- receiving any SC dose of tirzepatide, and
- clinical laboratory test samples are taken.

A meal will be offered to participants around 2 hours postdose. During inpatient stays, participants should not consume any food other than that provided by the study site. Water can be consumed freely.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Alcohol cannot be consumed

- from 24 hours before each CRU admission and outpatient visit, and
- while resident at the study site

Alcohol intake during outpatient periods should not exceed 3 units per day for males or 2 units per day for females.

No nicotine use will be permitted while in the study site. While not resident in the study site, participants should not consume more than 10 cigarettes or the equivalent per day.

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

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each dose administration until discharge from the study site. Participants will abstain from strenuous exercise for 24 hours prior to each outpatient visit.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study drug or enrolled in the study.

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

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Each participant 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 personnel.

The study involves a comparison of

- a single dose of 5 mg tirzepatide administered SC via MUPFP (test)
- a single dose of 5 mg tirzepatide administered SC via SDP (reference)

During each of the 2 study periods, the injection will be administered to the lower abdominal quadrants, approximately 5 cm from the umbilicus. Detailed instructions for use will be provided by the sponsor.

Whenever possible, study intervention administration should be carried by a limited number of clinical site personnel for consistency reasons.

The table below lists the interventions used in this clinical study.

Intervention Name	Tirzepatide 5 mg via MUPFP (Test)	Tirzepatide 5 mg via SDP (Reference)
Dosage Level(s)	5 mg tirzepatide / 0.6 mL	5 mg tirzepatide / 0.5 mL
Route of Administration	SC injection	SC injection
Delivery Method	Fixed-dose MUPFP	SDP

Abbreviations: MUPFP = multi-use prefilled pen; SC = subcutaneous; SDP = single-dose pen.

Packaging and labeling

Tirzepatide will be supplied by the sponsor or its designee in accordance with current good manufacturing practice. Study interventions will be labeled as appropriate for country 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 multi dose, pre-assembled, investigational MUPFPs (test), and
- tirzepatide in 5-mg single dose, pre-assembled SDP (reference)

6.1.1. Medical Devices

The investigator or designee will ensure that the instructions have been followed properly, maintenance of accurate records of study devices, dispensing, and collection. The used or unused MUPFPs and SDPs may be destroyed by a qualified vendor upon written approval by Lilly or designee.

All product complaints (including malfunction, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.
- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

This is an open-label study.

To minimize potential bias, assignment to treatment groups will be determined using a randomization table. On Day -1 of |Period 1, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to either starting treatment with tirzepatide MUPFP or SDP (1:1), according to the randomization schedule generated prior to the study by the sponsor's or designee's statistics department. Each participant will be dispensed study intervention labeled with his/her unique randomization number.

6.4. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.5. Dose Modification

Dose modification is not permitted in this study.

6.6. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.7. 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 for further details and recommendations.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- monitor the participant closely for any AE/SAE and laboratory abnormalities as medically appropriate until, eg, tirzepatide no longer has a clinical effect or can no longer be detected systemically, and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Prior and Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking 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.

If acetaminophen or paracetamol treatment is needed for pain management, the maximal allowed dose will be 3 g/day from all acetaminophen- or paracetamol-containing medicinal products. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for an early discontinuation visit and posttreatment follow-up, if applicable, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study, and
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons.

7.1.1. Hypersensitivity Reaction Criteria for Discontinuation

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

7.1.2. Hepatic Criteria for Discontinuation

Interrupting study drug based on liver test elevations in participants with normal or near-normal baseline liver test results

In study participants with normal or near-normal baseline liver test results (ALT, AST, ALP <1.5x ULN), the study drug should be **interrupted** and close hepatic monitoring is initiated (see Section 8.2.8.1) if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >5x ULN	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	

ALP >2.5x ULN and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation, July 2009, and other consensus guidelines, with minor modifications	

Interrupting study drug based on elevated liver tests in participants with abnormal baseline liver tests

In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5x ULN), the study drug should be **interrupted** if 1 or more of these conditions occur:

Elevation	**Exception**
ALT or AST >3x baseline	
ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5x baseline, when the source of increased ALP is the liver	
ALP >2x baseline and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation, July 2009, and other consensus guidelines, with minor modifications	

Resuming study drug after elevated liver test results

Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited nondrug etiology is identified. Otherwise, the study drug should be discontinued.

Participants who discontinue from study intervention due to the abnormal liver test results will undergo monitoring as described in Appendix 7 (Section 10.7).

7.2. Participant Discontinuation/Withdrawal from the Study

Participants discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 1.3 of this protocol.

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an IP, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and posttreatment follow-up, if applicable, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant 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 or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomly assigned, including those who did not get IP. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

Unless otherwise stated in the following subsections, 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.

8.2.1. Physical Examinations

- A complete physical examination will be performed at screening and will include, at a minimum, assessments of the cardiovascular, respiratory, GI, dermatological, and neurological systems. Height and weight will also be measured and recorded at screening.
- Subsequent brief physical examination will include medical review and targeted, symptom-driven examination, as appropriate. Additional assessments may be performed at investigator's clinical discretion.

8.2.2. Vital Signs

- For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3).
- Blood pressure and pulse rate should be measured after at least 3 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 at investigator's discretion.

8.2.3. Electrocardiograms

- For each participant, a single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) and stored at site.

- Participants must be supine for at least 5 minutes before ECG collection, and remain supine but awake during procedure.
- ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.
- 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 as an AE in the eCRF.
- ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.
- If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant 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.

8.2.4. Clinical Safety Laboratory Tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

- If laboratory values from nonprotocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then report the information as an AE.

Amylase and Lipase Measurements

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing and as specified in the SoA (Section 1.3). Additional measurements may be performed at the investigator's discretion. Further diagnostic assessments will be recommended as per the algorithm (refer to Appendix 8) for the monitoring of pancreatic events whenever lipase and/or amylase is confirmed to be ≥3x ULN at any visit postdose, even if the subject is asymptomatic.

8.2.5. Glucose Monitoring

For safety purposes, plasma glucose measurements will be performed using a bedside glucose monitor as specified in the SoA (Section 1.3). Additional blood glucose monitor measurements may also be taken during the study as deemed necessary by the investigator where clinically indicated.

8.2.5.1. Hypoglycemia Reporting

Participants will be trained to recognize the signs, symptoms, and management of hypoglycemia, and to inform the investigator as soon as possible about these events. Participants may, at investigator's discretion, be given a glucometer to assist in the evaluation of these symptoms.

All hypoglycemic events will be captured in the eCRF as specified below:

- All hypoglycemic episodes will be recorded on a specific eCRF and should not be recorded as AEs unless the event meets serious criteria.
- If a hypoglycemic event meets severe criteria (see definition below), it should be recorded as serious on the AE and SAE eCRFs, and reported to Lilly as an SAE.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the blood glucose values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2020 American Diabetes Association position statement on glycemic targets (ADA 2020) as below:

***Level 1 hypoglycemia*:**

Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L): Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

***Level 2 hypoglycemia*:**

Glucose <54 mg/dL (3.0 mmol/L): This is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

***Nocturnal hypoglycemia*:**
Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

8.2.6. Injection-Site Reactions

Symptoms and signs of a local ISR may include erythema, induration, pain, pruritus, and edema.

If an ISR is reported by a participant or assessed as clinically significant by site personnel, this shall be recorded as an AE and the ISR CRF will be used to capture additional information about this reaction, such as injection-site pain, degree and area of erythema, induration, pruritus, and edema.

8.2.7. 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 nonimmediate) in participants who experience moderate-to-severe injection reactions as assessed by the investigator, unscheduled blood samples will be collected for PK 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.

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.

8.2.8. 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 ≥3x ULN at any visit postdose even if the subject is asymptomatic.

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

8.2.8.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 7 [Section 10.7]), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver test results should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (eg, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over the counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms[a], or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper-quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (eg, ultrasound or CT scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver test results during the study

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
   - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevation of TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline

3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
   - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the 2 consecutive blood tests should be at least 2 days.

8.2.9. Pregnancy Testing

Pregnancy testing will be performed for all female participants at the time points detailed in the SoA (Section 1.3). Serum pregnancy testing will be used at screening. Urine pregnancy testing will be used at all other time points, as per SoA. See Section 8.3.2 for more detail.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs
- product complaints

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study.

Care will be taken not to introduce bias when detecting events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow up each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	The follow-up visit OR participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	90 days plus 5 half-lives after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Product Complaints (PCs)					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviation: N/A = not applicable.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive tirzepatide.
- After learning of a pregnancy in the female partner of a study participant, the investigator will
  - obtain a consent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

  The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process, and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and the participant's offspring.

8.3.3. Adverse Events of Special Interest

AEs of special interest for this program include:

- pancreatitis
- major adverse cardiovascular events
- deaths
- hypoglycemia (Level 2 and 3)
- thyroid malignancies and C-cell hyperplasia
- supraventricular arrhythmias and cardiac conductive disorders
- hypersensitivity events
- severe ISRs, and
- severe GI AEs

8.4. Pharmacokinetics

- Venous blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of tirzepatide as specified in the SoA (Section 1.3).
- A maximum of 3 unscheduled samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Failure or being late (outside stipulated time allowances) to 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.

8.4.1. 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 1 year 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.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants for pharmacogenetic analysis as specified in the SoA (Section 1.3), 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 ethical review boards 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.

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.

See Appendix 5 (Section 10.5) for information regarding genetic research and for details about sample retention and custody.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Health Economics OR Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

The primary objective of this study is to evaluate bioequivalence of the MUPFP (test) and the SDP (reference) with a 5-mg dose, as assessed using tirzepatide PK parameters C_{max}, AUC(0-tlast), and AUC(0-∞) in healthy participants.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analyses Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set / Population	Description
Enrolled	All randomly assigned participants.
Safety analysis set	All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.
PK analysis set	All randomly assigned participants who received at least 1 study intervention and have evaluable PK data.

9.3. Statistical Analyses

9.3.1. General Considerations

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

PK analyses will be conducted for the PK analysis set according to the actual tirzepatide formulation received. Safety analyses will be conducted for the safety analysis set.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety and population PK analysis purposes.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final clinical study report.

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

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

9.3.2. Primary Endpoints Analysis

PK parameter estimates for tirzepatide will be calculated using standard noncompartmental methods of analysis.

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

Other noncompartmental parameters, such as t_{max}, 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.

9.3.2.1. Pharmacokinetic Statistical Inference

Two 1-sided equivalence tests will be applied to the ratios of each of C_{max} and AUC using MUPFP as the test and SDP as the reference. Test limits of the ratios to establish bioequivalence are 0.8 and 1.25.

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

Planned PK parameters will also be summarized with descriptive statistics.

9.3.3. Secondary Endpoints Analysis

The t_{max} will be analyzed using Wilcoxon ranked sum test. Estimates of the median difference and 90% CIs will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

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. 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 Dictionary for Regulatory Authorities.

The number of IP-related SAEs will be reported.

If available, any incidence of erythema, induration, pain, pruritus, edema, bleeding, and bruising from injection site assessment will be listed.

9.3.4. Safety Analyses

Safety parameters that will be assessed include AEs, safety laboratory parameters, 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.

9.3.5. Other Analyses

If needed, details will be provided in the SAP.

9.4. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

Unblinding details are specified in the unblinding plan section of the SAP.

9.5. Sample Size Determination

Approximately 65 participants may be enrolled so that approximately 54 evaluable participants complete the study. A sample size of 54 participants will provide at least 95% power that the 90% confidence interval of the geometric mean ratio of C_{max} and AUC between the 2 devices will fall within the equivalence range of 0.8 to 1.25. This assumes a nominal expected mean ratio of 1.05 (test vs reference), a within-subject coefficient of variation of 24%.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
  - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or the potential participant's legally authorized representative and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (eg, through phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (eg, underpowered) or compromise the integrity of the overall analyses (eg, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

- The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture systems will be stored at third party (at third parties). The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study or site termination

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the following table will be performed by the local laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

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
Urinalysis[a]	
Specific gravity	Hepatitis B surface antigen[b]
pH	Hepatitis C antibody[b]
Protein	HIV or HIV antibody[b]
Glucose	FSH[c]
Ketones	Pregnancy test[d]
Bilirubin	Ethanol and urine drug screen testing[e]
Urobilinogen	
Blood	
Nitrite	
Leukocytes (WBC)	
Microscopic examination of sediment[f]	

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

[a] Performed by central laboratory except at screening which may be performed by a local laboratory. Results will be validated by the laboratory at the time of initial testing.

[b] Performed by local laboratory at screening only.

[c] FSH - Performed at screening only for females to confirm postmenopausal status.

[d] Pregnancy test - Serum pregnancy test will be performed at screening and urine pregnancy tests at subsequent visits. Women with confirmed nonchildbearing potential status can be exempted from further pregnancy tests during the study after screening.

[e] Performed locally at site during screening and admission on Day -1. Additional testing may be performed at the discretion of the investigator if warranted.

[f] Test only if dipstick result is abnormal (ie, positive for blood, protein, or nitrites)

10.2.1. 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-GPIP Sampling Summary

Purpose	Blood Volume per Sample (mL)	Estimated Number of Blood Samples	Total Volume (mL)
Screening tests (local laboratory)[a]	25	1	25
Clinical laboratory tests (central laboratory)[a] • Study visits (2 periods)	12	4 × 2 periods = 8	96
Pharmacokinetics (central or referral laboratory)[b] • Study visits (2 periods)	3	14 × 2 periods (+3 unscheduled) = 31	93
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			232.4
Total for clinical purposes rounded up to nearest 10 mL			240

[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.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE definition

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
- An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of investigational medicinal product, including signs, symptoms, or clinical sequelae.

Events <u>NOT</u> meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

- Results in death
- Is life-threatening
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
    - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Other situations:
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or

surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
    - Deficiencies in labeling information, and
    - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the

participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via SAE report

- Facsimile transmission of the SAE report is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE report within the designated reporting time frames.
- Contacts for SAE reporting can be found in SAE report.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Females are considered a woman of childbearing potential if they have • had at least 1 cycle of menses, or • Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner Staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner Staging.
Women not of childbearing potential (WNOCBP)	Females are considered women not of childbearing potential if they • have a congenital anomaly such as Mullerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, tubal ligation.
Postmenopausal state	The postmenopausal state should be defined as: 1. A woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. A woman aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND With a follicle-stimulating hormone >40 mIU/mL; or 3. A woman aged 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy * Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.
Reproductive toxicology studies	Embryofetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.4.2. Contraception Guidance

Contraception guidance for females

WOCBP and women not of childbearing potential may participate in this trial.

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

WOCBPs who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective methods of contraception where at least 1 form must be a highly effective method of contraception. These forms of contraception must be used for the duration of the study.

Contraception guidance for males

The following table describes contraception guidance for all men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 90 days
Contraception for men with partners of childbearing potential	• either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study, and for 90 days
Contraception for men in exclusively same-sex relationships, as their preferred and usual lifestyle	Are not required to use contraception

Examples of different forms of contraception

Examples of highly effective, effective, and ineffective methods of contraception can be found below.

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed through hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: Genetics

Use/analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to tirzepatide or T2DM and related diseases. They may also be used to develop tests/assays including diagnostic tests related to tirzepatide and T2DM. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to tirzepatide or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on tirzepatide or T2DM continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic evaluation testing

See Section 8.2.8.1 for guidance on appropriate test selection.

Testing by an investigator-designated local laboratory should be performed for all testing defined by this guidance.

The local laboratory must be qualified in accordance with applicable local regulations.

Hepatic Hematology Panel	**Hepatic Clinical Chemistry Panel**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Alkaline phosphatase isoenzymes
Platelets	Ceruloplasmin
Cell morphology (RBC and WBC)	Copper
Hepatic Coagulation Panel	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Hepatitis A virus (HAV) testing:	Immunoglobulin IgA (quantitative)
HAV total antibody[a]	Immunoglobulin IgG (quantitative)
HAV IgM antibody	Immunoglobulin IgM (quantitative)
Hepatitis B virus (HBV) testing:	Phosphatidylethanol (PEth)[a]
Hepatitis B surface antigen (HBsAg)	**Urine Chemistry**
Hepatitis B surface antibody (anti-HBs)	Drug screen
Hepatitis B core total antibody (anti-HBc)	Ethyl glucuronide (EtG)[a]
Hepatitis B core IgM antibody	**Other Serology**
HBV DNA[b]	Anti-nuclear antibody (ANA)
Hepatitis C virus (HCV) testing:	Anti-smooth muscle antibody (ASMA)[c]
HCV antibody	Anti-actin antibody[d]
HCV RNA[b]	Epstein-Barr virus (EBV) testing:
Hepatitis D virus (HDV) testing:	EBV antibody
HDV antibody	EBV DNA[b]
Hepatitis E virus (HEV) testing:	Cytomegalovirus (CMV) testing:
HEV IgG antibody	CMV antibody
HEV IgM antibody	CMV DNA[b]
HEV RNA[b]	Herpes simplex virus (HSV) testing:
Microbiology	HSV (Type 1 and 2) antibody
Culture:	HSV (Type 1 and 2) DNA[b]
Blood	Liver kidney microsomal type 1 (LKM-1) antibody
Urine	

[a] These tests are not done by local laboratory in Singapore.

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

[c] Not required if anti-actin antibody is tested.

[d] Not required if anti-smooth muscle antibody is tested.

10.8. Appendix 8: Pancreatic Monitoring

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with tirzepatide, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi et al. 2006):

- abdominal pain, characteristic of acute pancreatitis (ie, epigastric pain radiating to the back, often associated with nausea and vomiting)
- serum amylase (total, pancreatic, or both) and/or lipase ≥3x ULN
- characteristic findings of acute pancreatitis on CT scan or magnetic resonance imaging.

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal magnetic resonance imaging
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue use of the IPs.

Asymptomatic elevation of serum amylase and/or lipase levels

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck 2016; Steinberg et al. 2017a,b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or p-amylase ≥3x ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-tlast)	AUC from time 0 to the last measurable concentration after the first dose
AUC(0-∞)	AUC from time 0 to infinity
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 study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
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
CT	computed tomography
device deficiencies	equivalent to product complaint
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.

enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GIP	gastric inhibitory polypeptide
GLP	glucagon-like peptide
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalization ratio
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	institutional review board
ISR	injection-site reaction
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the 5 core rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (eg, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.

misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MUPFP	multi-use prefilled pen
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK/PD	pharmacokinetics/pharmacodynamics
QW	once weekly
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SoA	schedule of activities
screen	The act of determining if an individual meets minimum requirement to become part of a pool of potential candidates for participation in a clinical study.
SDP	single-dose pen
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
t_{max}	time to C_{max}
ULN	upper limit of normal
WOCBP	Women of childbearing potential

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