Protocol I8F-MC-GPIN (b)

A Study to Evaluate Tirzepatide Concentrations in Breastmilk Following Administration of Single Dose of Tirzepatide by Subcutaneous Injection in Healthy Lactating Females

NCT05978713

Approval Date: 15 SEP 2023

Title Page

Protocol Title:

A Study to Evaluate Tirzepatide Concentrations in Breastmilk Following Administration of Single Dose of Tirzepatide by Subcutaneous Injection in Healthy Lactating Females

Protocol Number: I8F-MC-GPIN

Amendment Number: I8F-MC-GPIN (b)

Compound: Tirzepatide

Brief Title:

A Study to Measure Tirzepatide Levels in Breastmilk of Healthy Lactating Females

Study Phase: 1

Acronym: GPIN

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number

IND: 128801

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

Document ID: VV-CLIN-075154

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol amendment (a)	*24-Jul-2023*
Original Protocol	*17-May-2023*

Amendment [b]

This amendment is considered to be non-substantial.

Overall Rationale for the Amendment:

The protocol is being amended to address FDA recommendations on contraceptive guidance.

Section # and Name	Description of Change	Brief Rationale
10.4.2 Contraception Guidance	Removed wording “less than 1% failure rate” describing “highly effective contraception.”	Updated based on FDA feedback

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Study to Evaluate Tirzepatide Concentrations in Breastmilk Following Administration of Single Dose of Tirzepatide by Subcutaneous Injection in Healthy Lactating Females

Brief Title: A Study to Measure Tirzepatide Levels in Breastmilk of Healthy Lactating Females

Regulatory Agency Identifier Number: IND: 128801

Rationale:

Tirzepatide (MOUNJARO™; LY3298176) is a glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist approved as an adjunct to diet and exercise for improving glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The disposition of tirzepatide for adult patients has been characterized but data is lacking on whether tirzepatide is excreted in breastmilk. There is a need to understand tirzepatide concentrations in breastmilk to better inform healthcare practitioners in managing women of childbearing potential who may be potential users of tirzepatide.

Study I8F-MC-GPIN (GPIN) is a postmarketing lactation study that will primarily assess the pharmacokinetics (PK) of tirzepatide in breastmilk following administration of a single CCI dose of tirzepatide via the subcutaneous (SC) route in healthy lactating females. Additionally, plasma PK of tirzepatide will also be assessed.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate tirzepatide pharmacokinetics (PK) in breastmilk of healthy lactating females	• Area under the tirzepatide concentration-time curve in breastmilk from time 0 extrapolated to infinity $AUC_{(0-\infty)}$
Secondary	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Abbreviations: $AUC_{(0-tlast)}$ = area under the concentration versus time curve from time zero to the last observable concentration; C_{max} = maximum observed drug concentration; t_{max} = time to maximum observed drug concentration.

Overall Design

Brief Summary:

This is a postmarketing, open-label, single-treatment arm, single-dose, lactation study, assessing PK of tirzepatide in breastmilk and plasma in healthy lactating females.

Potential participants will be screened to assess their eligibility to enter the study within 27 days prior to Day -1. Participants will be admitted to the clinical research unit (CRU) on Day -1 to establish baseline measurements.

Participants will receive a single subcutaneous tirzepatide CCI dose on Day 1 following overnight fasting of approximately 8 hours. Breastmilk and plasma samples will be collected. Participants will be permitted to leave the CRU on Day 5 following completion of study procedures. During inpatient stays, the infant is allowed to be in the CRU with the study participant during supervised visitation hours. On Days 6, 8, 15±1, and 22±1, participants may either return to the CRU for outpatient visits or have these visits be performed remotely by home health nurses as deemed appropriate by the study investigator. On Day 29±1, the participants will return to the CRU for the final follow-up visit.

Safety will be assessed by vital signs, electrocardiograms (ECGs), safety laboratory tests, and the recording of adverse events (AEs). Breastfeeding must be discontinued prior to the administration of tirzepatide and for the duration of the study.

Study Population:

Healthy lactating females.

Number of Participants:

Approximately 14 healthy lactating females will be enrolled so that about 8 females complete the study.

Intervention Groups and Duration:

Participants will receive a single SC tirzepatide CCI dose on Day 1.

The study duration for individual participants, inclusive of screening is expected to be approximately 8 weeks, as detailed here:

- Screening: up to 27 days prior to Day -1
- Inpatient Treatment Period: Day -1 to Day 5 (may be extended if necessary for safety reasons based on the Investigator's discretion)
    - Single dose of study intervention
- Outpatient follow-up period Days 6, 8, 15±1, and 22±1 with the final follow-up visit on Day 29±1.

Ethical Considerations of Benefit/Risk:

There is no anticipated therapeutic benefit for participants in this study.

As of 26 September 2022, tirzepatide 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 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.

No clinically significant safety or tolerability concerns have been identified during clinical investigation of tirzepatide up to the single dose of 5 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 (Coskun et al. 2018). Based on this information, the single dose of CCI tirzepatide to be administered in this study is anticipated to be tolerable in healthy lactating females.

Tirzepatide is a peptide molecule that is administered subcutaneously. Its excretion into the breastmilk is expected to be low. Even if it is ingested orally by a breastfed infant, it is unlikely that the tirzepatide peptide will be absorbed intact, since it will be digested in the gastrointestinal tract. Despite this, breastfeeding to infant will be discontinued and prohibited for the duration of the study to avoid exposing the infant to tirzepatide.

The participation in the study requires interruption of breastfeeding for a total of 29 days after the administration of a single dose of tirzepatide. Interruption of breastfeeding or lactation gap for such a period of time may lead to difficulty or even failure in achieving satisfactory relactation. This risk is expected to be partially mitigated by providing adequate relactation support and education to the study participants who wish to resume breastfeeding after the completion of the study. Thereby, a lactation consultant will be readily available at the CRU as a resource to support potential efforts to achieve relactation if required or requested by the participant.

Data Monitoring Committee: No

1.2. Schema

1.3. Schedule of Activities (SoA)

Procedure	Screening	Treatment and Safety Monitoring										FU/ED[a]	Comments
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**15±1**	**22±1**	**29±1**	
Informed consent	X												
Admission to CRU		X											Enrollment will occur on Day -1
Discharge from CRU							X						May be extended at the investigator's clinical discretion for safety monitoring
Outpatient visits to CRU	X							X	X	X	X	X	Days 6, 8, 15±1, and 22±1 may be performed remotely by home health nurses
Review and confirm inclusion/exclusion criteria	X												
Medical history and demographics	X												
Physical exam/Medical assessment	X	X				X			X			X	Screening: Full physical examination All other timepoints: symptom-driven
Height, weight, and BMI	X	X							X			X	Height required only at screening
Temperature	X		P										
Safety 12-lead ECG	X		P			X						X	
Vital signs	X		P			X			X			X	

Clinical laboratory tests – local laboratory	X		P						X			X	See Appendix 2 (Section 10.2) for details. Predose measures are for baseline purpose only and results need not be reviewed prior to tirzepatide dosing
Ethanol breath test and urine drug screen testing	X	X											Per CRU local requirements
Pregnancy test	X	X										X	Screening: Serum pregnancy test. All other timepoints: urine pregnancy test
AEs/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Tirzepatide dosing			0										Actual tirzepatide dosing will be arbitrarily considered as time 0 hour
CCI													
Tirzepatide plasma PK samples (h)			P, 12	24	48	72	96		168	X		X	Predose sample should be collected within 2 hours prior to dosing (time 0)
Glucose safety monitoring (h)			P, 12	24, 36	48	72							Performed using a glucometer using fingerprick capillary blood. Additional unscheduled

													measurements may be taken at the clinical discretion of the investigator

Abbreviations: AE = adverse event; BMI = body mass index; CRU = clinical research unit; D = Day; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; h = hours; P = predose; PK = pharmacokinetics.

Note: CRU should schedule procedures as appropriate. However, if multiple procedures take place at the same time point, the following order of the procedure should be considered in terms of prioritization: ECGs, vital signs, PK breastmilk samples, PK plasma samples, clinical laboratory samples, and glucose samples. Unless otherwise specified, predose samples and procedure may be collected or performed any time up to 24 hours prior to dosing.

[a] Final follow-up will occur 28 days ± 1 day after tirzepatide dose. Early discontinuation visit should take place within 14 days upon confirmation of early discontinuation. Tirzepatide breastmilk and plasma PK samples need not be collected if the participant discontinues prior to receiving a dose of tirzepatide.

[b] Optional breastmilk PK sample. Breastmilk PK sample may be collected based on participant's need to pump during this interval.

2. Introduction

2.1. Study Rationale

Tirzepatide (MOUNJARO™; LY3298176) is a glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist (RA) approved as an adjunct to diet and exercise for improving glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The disposition of tirzepatide for adult patients has been characterized but data is lacking on whether tirzepatide is excreted in breastmilk. There is a need to understand tirzepatide concentrations in breastmilk to better inform healthcare practitioners in managing women of childbearing potential who may be potential users of tirzepatide.

Study I8F-MC-GPIN (GPIN) is a postmarketing lactation study that will primarily assess the pharmacokinetics (PK) of tirzepatide in breastmilk following administration of a single CCI dose of tirzepatide via the subcutaneous (SC) route in healthy lactating females. Additionally, plasma PK of tirzepatide will also be assessed.

2.2. Background

Tirzepatide is a GIP and GLP-1 RA. It is a 39 amino acid synthetic modified 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 once-weekly by SC injection in a single-use prefilled pen.

Tirzepatide has a chemical structure and pharmacologic profile that is distinct from GLP1 RAs due to the additional effects on GIP receptor (GIPR), 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 of reaching higher efficacy in target tissues such as the insulin-producing pancreatic β-cells that express both GIPR and glucagon-like peptide 1 before reaching its therapeutic limitation, which supports its use as a treatment for T2DM.

Tirzepatide may attain additional efficacy by recruiting metabolically active tissues not targeted by classical GLP-1 analogs (for example, adipose tissue as indicated by the observation of increased energy utilization and resulting body weight loss) (Coskun et al. 2018; Frias et al. 2018). Weight loss data support the ongoing investigation of chronic weight management, non-alcoholic fatty liver disease, heart failure with preserved ejection fraction, obstructive sleep apnea, and chronic kidney disease as additional potential indications.

2.3. Benefit/Risk Assessment

There is no anticipated therapeutic benefit for participants in this study.

As of 26 September 2022, tirzepatide 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 RA 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.

No clinically significant safety or tolerability concerns have been identified during clinical investigation of tirzepatide up to the single dose of 5 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 (Coskun et al. 2018). Based on this information, the single dose of CCI tirzepatide to be administered in this study is anticipated to be tolerable in healthy lactating females.

Tirzepatide is a peptide molecule that is administered subcutaneously. Its excretion into the breastmilk is expected to be low. Even if it is ingested orally by a breastfed infant, it is unlikely that the tirzepatide peptide will be absorbed intact since it will be digested in the GI tract. Despite this, breastfeeding to the infant will be discontinued and prohibited for the duration of the study to avoid exposing the infant to tirzepatide.

The participation in the study requires interruption of breastfeeding for a total of 29 days after the administration of a single dose of tirzepatide. Interruption of breastfeeding or lactation gap for such a period of time may lead to difficulty or even failure in achieving satisfactory relactation. This risk is expected to be partially mitigated by providing adequate relactation support and education to the study participants who wish to resume breastfeeding after the completion of the study. Thereby, a lactation consultant will be readily available at the clinical research unit (CRU) as a resource to support potential efforts to achieve relactation if required or requested by the participant.

More information about the known and expected risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of tirzepatide can be found in the package insert of MOUNJARO or in the tirzepatide Investigator's Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate tirzepatide pharmacokinetics (PK) in breastmilk of healthy lactating females	• Area under the tirzepatide concentration-time curve in breastmilk from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
Secondary	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

Abbreviations: $AUC_{(0\text{-tlast})}$ = area under the concentration versus time curve from time zero to the last observable concentration; C_{max} = maximum observed drug concentration; t_{max} = time to maximum observed drug concentration.

4. Study Design

4.1. Overall Design

This is a postmarketing, single-site, open-label, single-treatment arm, single-dose, lactation study, assessing PK of tirzepatide in breastmilk and plasma in healthy lactating women.

Approximately 14 healthy lactating females will be enrolled so that about 8 females complete the study.

Participants will receive a single dose of tirzepatide CCI delivered by subcutaneous injection.

The study duration for individual participants, inclusive of screening, is expected to be approximately 8 weeks.

Screening

Screening may occur up to 27 days prior to Day -1. During the screening visit, participants will undergo screening tests as mentioned in Schedule of Activities (SoA; Section 1.3). Participants who are not enrolled within 28 days of screening may be subject to an additional medical assessment, clinical measurements or both, to confirm their eligibility. In such instances, at a minimum, the following screening tests and procedures should be repeated:

- weight
- vital signs
- safety 12-lead electrocardiogram (ECG)
- clinical laboratory tests, and
- pregnancy test.

Inpatient Treatment Period

Participants will be admitted to the CRU on Day -1 to establish baseline measurements.

Participants will receive a single SC tirzepatide CCI dose on Day 1 following overnight fasting of approximately 8 hours. Participants will remain in the CRU until Day 5 following the completion of study procedures. During inpatient stays, the infant is allowed to be in the CRU with the study participant during supervised visitation hours. The inpatient stay for the participant may be extended at the clinical discretion of the investigator (for example, necessary for the participant's clinical wellbeing and management and monitoring of AEs).

Breastmilk and plasma samples for tirzepatide PK will be collected. Breastmilk volume will be measured across the study duration as indicated in the SoA. Safety will be assessed by physical examination, medical assessments or both, vital signs, ECGs, safety laboratory tests, glucose safety monitoring, and the recording of AEs. Breastfeeding must be discontinued prior to the administration of tirzepatide and for the duration of the study. All costs associated with formula feeding and breast pumps required during the study will be covered by the study sponsor.

Outpatient Follow-up Period

On Days 6, 8, 15±1, and 22±1, participants may either return to the CRU for outpatient visits or have these visits be performed remotely by home health nurses as deemed appropriate by the study investigator. On Day 29±1, the participants will return to the CRU for the final follow-up visit.

4.2. Scientific Rationale for Study Design

This study will be a single-arm open-label as the study's primary endpoint PK measures are objective rather than subjective.

The dose justification for tirzepatide is provided in Section 4.3.

The rationale for the sample size is provided in Section 9.5.

4.3. Justification for Dose

No clinically significant safety or tolerability concerns have been identified during clinical investigation of tirzepatide up to the single dose of 5 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 single dose of CCI tirzepatide to be administered in this study is reasonably anticipated to be tolerable in this group of adult females.

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 (Section 1.3) for the last participant in the study.

5. Study Population

The eligibility of participants for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and 12-lead 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. Participants must be greater than or equal to 18 years of age inclusive at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy females as determined by medical evaluation including medical history, physical examination, and laboratory tests.
3. Female participants who delivered normal-term infant (at least 37 weeks gestation) and are at least 6 weeks postpartum at the time of screening.
4. Female participant who has well-established lactation and is breastfeeding her infant (1 supplemental bottle of formula per day is acceptable). Note: Breastfeeding must be discontinued prior to the administration of tirzepatide on Day 1 and not resumed for the remaining duration of the study until a follow-up visit (or for total of 29 days after tirzepatide dosing for participants who discontinue early).
5. Participants who have clinical laboratory test results, blood pressure, pulse rate, and an ECG reading that are considered to be within the normal reference range for the population or CRU 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

6. Body mass index within the range of 18.5 to 40.0 kg/m^2, inclusive.

Sex and Contraceptive/Barrier Requirements

7. Females only.

   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 Appendix 4 (Section 10.4).

Informed Consent

8. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusion Criteria

9. Have venous access sufficient to allow for blood sampling as per the protocol.
10. Having a breastfed infant who is able to feed from a bottle and use formula while breastfeeding is prohibited.
11. Agree to abstain from breastfeeding their infant from the dose of tirzepatide on Day 1 to the follow-up visit, or for a total of 29 days after tirzepatide dosing for participants who discontinue early, to avoid potentially exposing their infant to tirzepatide.
12. Willing and able to commit to the inpatient stays and procedures per study requirements.

5.2. Exclusion Criteria

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

Medical Conditions

13. 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 tirzepatide, or of interfering with the interpretation of data.
14. Have a history or presence of pancreatitis, elevation in serum amylase or lipase (>1.5 fold the ULN), clinically significant GI disorders (for example, 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. 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. A history of uncomplicated acute appendicitis and appendectomy is acceptable as well.
15. Have evidence of significant active neuropsychiatric disease, as determined by the investigator.
16. Have a history of multiple or clinically significant drug allergies or severe posttreatment hypersensitivity reactions.
17. Have a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
18. Have a history of malignancy within 5 years prior to screening.
19. Show evidence of human immunodeficiency virus infection, positive human immunodeficiency virus antibodies, or both.
20. Have evidence of hepatitis C, are positive for hepatitis C antibodies, or both.
21. Have evidence of hepatitis B, are positive for hepatitis B surface antigen, or both.
22. Have confirmed type 1 or type 2 diabetes mellitus.
23. Have a history of inadequate lactation (for multiparous females who have previously breastfed).

24. Have a history of breast augmentation procedures judged to have a clinical impact on breastmilk expression (such as breast reduction surgery and some breast implants) or current evidence of acute or chronic conditions affecting breasts and potentially interfering with breast milk collection.

Prior/Concomitant Therapy

25. Regularly use known drugs of abuse or show positive findings on drug screen.
26. Have received treatment with a drug that has not received regulatory approval for any indication within 30 days or 5 half-lives (whichever is longer) of screening. Other concomitant medications (including over-the-counter and prescription medications) may be considered on a case-by-case basis by the investigator preferably in consultation with the clinical pharmacologist (CP).

Prior/Concurrent Clinical Study Experience

27. Have previously completed or withdrawn from this study.
28. 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.
29. Any exposure to tirzepatide within the prior 3 months of screening or history of allergies to tirzepatide, other GLP 1 analogs, or related compounds.

Diagnostic Assessments

30. Have glycated hemoglobin (HbA1c) greater than or equal to 6.5% at screening.

Other Exclusion Criteria

31. Unable or unwilling to adhere to smoking and alcohol restrictions during CRU admission and visits.
32. Are CRU personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
33. Are Lilly employees or are employees of a third-party organization involved with the study.
34. Have an average weekly alcohol intake that exceeds 14 units per week,
    OR
    are unwilling to stop alcohol consumption during study visits and time in the CRU (number of units = [total volume of drink (mL) x ABV (%)]/1000. ABV = alcohol by volume).
35. 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

The participant will be required to fast overnight for at least 8 hours when clinical laboratory test samples are taken. A meal will be offered to study participants after about 2 hours post tirzepatide dose. During inpatient stays, the participant may not consume any food other than that provided by the CRU, although water may 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 in the CRU.

Alcohol intake during outpatient periods should not exceed 2 units per day.

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

Participants will be allowed to maintain 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 tirzepatide dose administration until discharge from the CRU.

5.4. Screen Failures

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

Screening tests such as clinical laboratory tests and vital signs, ECGs may be repeated at the discretion of the investigator. Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened. Participants numbers, enrollment numbers are assigned after medical assessments have been completed to ensure only eligible participants enter the study.

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 or used by a study participant according to the study protocol.

6.1. Study Intervention Administered

Each participant will receive 1 dose of tirzepatide administered as a single SC injection of CCI tirzepatide into the abdomen. Tirzepatide will be administered by CRU personnel to the lower abdominal quadrants, approximately 5 cm from the umbilicus.

This table lists the interventions used in this study.

Intervention Name	Tirzepatide*
Dosage Formulation	Autoinjector
Dosage Strength and Volume	CCI
Route of Administration	Subcutaneous
Dosing Instructions	Inject subcutaneously into lower abdominal quadrant, approximately 5 cm from the umbilicus

*Supplied as MOUNJARO.

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.

Tirzepatide will be provided as autoinjectors containing CCI solution and provided in individual cartons to be dispensed.

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

The investigator or designee is responsible for

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

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

CRU staff will administer the injection. Instructions for autoinjector administration will be provided by the sponsor. Only a limited number of individuals will perform SC administration for consistency reasons. The actual time of dosing will be recorded in the participant's electronic case report form (eCRF).

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all tirzepatide 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 (that is, 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.

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 that the dose is 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 intended for this study (CCI single dose).

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

Refer to the package insert of MOUNJARO or the tirzepatide Investigator's Brochure 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, or SAE and laboratory abnormalities as medically appropriate until 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 eCRF.

6.8. Prior and Concomitant Therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest 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 CP should be contacted if there are any questions regarding concomitant or prior therapy.

Participants should generally abstain from taking over-the-counter or prescription medication, and/or herbal supplements (except for vitamin/mineral supplements, hormonal contraception 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 per day from all acetaminophen- or paracetamol-containing medicinal products. Other concomitant medications (including over-the-counter and prescription medications) may be considered on a case-by-case basis by the investigator preferably in consultation with the CP.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of the study as a whole is handled as part of Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

Not applicable as this is a single-dose study.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon. A participant may withdraw from the study

- at any time at the participant's 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, and
- 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 the 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.

Note: Breastfeeding must be discontinued prior to the administration of tirzepatide on Day 1 and not resumed for the remaining duration of the study until a follow-up visit or for a total of 29 days after tirzepatide dosing for participants who discontinue early.

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 the destruction of any samples taken and not tested, and the investigator must document this in the CRU 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 CRU. CRU 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.

CRU personnel or an independent third party will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get an IP. Public sources may be searched for vital status information. If the 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 (Section 1.3).
- The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the eCRF.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence.
- 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.

Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.

Section 10.2.1 of Appendix 2 provides a summary of the maximum number and volume of blood samples, for all sampling, during the study.

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

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

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

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, as well as a breast exam. 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 the investigator's clinical discretion.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).

- Blood pressure and pulse rate should be measured after at least 3 minutes of seated rest.
- If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes.
- If the participant feels unable to stand, supine vital signs only will be recorded.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

8.2.3. Electrocardiograms

- For each participant, a single 12-lead ECG will be obtained at the CRU as outlined in the SoA (see Section 1.3).
- ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the dose of tirzepatide should be reported to Lilly or its designee, as an AE via eCRF.
- ECGs may be obtained at additional times when deemed clinically necessary. All ECGs recorded should be stored at the CRU.
- ECGs will be interpreted by a qualified physician (the investigator or qualified designee) as soon after the time of ECG collection as possible, and ideally, while the participant is still present, to determine whether the participant meets entry criteria at the relevant visits and for immediate participant management, should any clinically relevant findings be identified.
- If a clinically significant finding is identified 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 their 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 (see Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (see Section 1.3) 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 which 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 or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor should be notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. Pregnancy Testing

In this study, a serum pregnancy test will be performed at screening and urine pregnancy tests at subsequent visits as indicated in the SoA (Section 1.3)

8.2.6. 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 6, Section 10.6) for the monitoring of pancreatic events whenever lipase and/or amylase is confirmed to be ≥3x ULN at any visit postdose, even if the participant is asymptomatic.

8.2.7. Glucose Monitoring

For safety purposes, blood glucose measurements will be performed using a glucometer with fingerprick capillary blood 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.

8.2.7.1. 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 the 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 severe 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, were semiconscious or unconscious, or experienced coma with or without seizures; 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.

8.2.8. Injection-Site Reactions

Symptoms and signs of a local injection-site reaction (ISR) may include erythema, induration, pain, pruritus, and edema.

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

8.2.9. 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, and
- 30 (±3) days following the event.

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

8.2.10. 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/scientist will periodically review

- trends in safety data
- laboratory analytes, and
- AEs.

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

8.2.10.1. Hepatic Safety

See Appendix 5, Section 10.5 for the full list of hepatic evaluation tests.

Close Hepatic Monitoring

Laboratory tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin level (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)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated CP or CRP/scientist. At a minimum, this evaluation should include a physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel history, history of concomitant medications (including over-the-counter medications), 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)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

[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 a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalization ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis.

Based on the participant's history and initial results, further testing should be considered, in consultation with the Lilly-designated CP or CRP/scientist, including

- 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
- liver biopsy.

Additional Hepatic Data Collection (hepatic safety eCRF) in Study Participants Who Have Abnormal Liver Test Results During the Study

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

1. Elevation of serum ALT level 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. Elevated TBL level 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 level 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 tirzepatide due to a hepatic event.

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

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

The definitions of the following events can be found in Appendix 3 (Section 10.3):

- 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 on events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

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 each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed 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 Appendix 3 (Section 10.3).

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

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

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 informed consent form (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 informed consent form (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	After the start of study intervention	90 days plus 5 half-lives	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

		after the last dose			
Product Complaints					
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	

Abbreviations: AE = adverse event; CRF = case report form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

* Serious adverse events should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of Pregnancy Information

Female participants who become pregnant

- The investigator will collect pregnancy information on any 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 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.
- 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.

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
- arrhythmias and cardiac conductive disorders
- hypersensitivity events
- severe ISRs, and
- severe GI AEs.

8.4. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), breastmilk will be collected to determine tirzepatide concentration and amount excreted from lactation. Venous blood samples of approximately 3 mL each will also be collected to determine the plasma concentrations of tirzepatide. A maximum of 3 unscheduled samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of breastmilk samples will be provided by the sponsor. The actual date and time (24-hour clock time) and time intervals of each sampling will be recorded.

8.4.1. Bioanalysis

Breastmilk and plasma samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of tirzepatide in breastmilk and plasma will be assayed using validated liquid chromatography tandem mass spectrometry methods.

Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism, protein binding, or bioanalytical method cross-validation.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable.

8.9. 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

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

9.1. Statistical Hypotheses

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analyses Sets

Pharmacokinetic analyses will be conducted on data from all participants who have received tirzepatide and have evaluable PK. Safety summaries will be conducted for all participants who have received tirzepatide, whether or not they completed all protocol requirements.

9.3. Statistical Analyses

9.3.1. General Considerations

PK parameter estimates for tirzepatide in breastmilk and plasma will be calculated by standard noncompartmental methods of analysis and summarized using standard descriptive statistics. See Appendix 7 (Section 10.7) for details of the PK analysis plan.

9.3.2. Primary Endpoint(s) Analysis

The primary PK parameter for analysis will be area under the tirzepatide concentration-time curve in breastmilk from time 0 extrapolated to infinity ($AUC_{[0-\infty]}$). Summary of tirzepatide area under the concentration-time curve in breastmilk, $AUC_{(0-\infty)}$, and a 95% confidence interval for the geometric mean will be provided.

9.3.3. Secondary Endpoint Analysis

Summaries of CCI [redacted] will be provided. Additional parameters may be estimated as deemed necessary.

9.3.4. Safety Analyses

Safety summaries will be conducted for all participants who have received tirzepatide, whether or not they completed all protocol requirements.

9.3.4.1. Clinical Evaluation of Safety

All treatment-emergent adverse events (TEAEs) will be listed and, if the frequency of events allows, TEAEs will be summarized using descriptive methodology. The incidence of TEAEs will be presented by severity and by association with tirzepatide as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new

or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary. The number of IP-related SAEs will be reported.

9.3.4.2. Statistical Evaluation of Safety

Safety parameters that will be summarized include incidence of TEAEs, safety lab parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data. Physical examinations and ECGs will be performed for safety monitoring purposes and will not be presented.

9.3.4.3. Injection-Site Reactions

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

9.3.5. Other Analyses

Not applicable.

9.4. Interim Analysis

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP, CRP, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

9.5. Sample Size Determination

Approximately [redacted] participants will be enrolled so that about [redacted] participants provide evaluable PK data. Since inter-participant variability of primary PK parameter in breastmilk is unknown, sample size is not chosen to achieve a specific precision in estimation of the primary endpoint.

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 (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an Institutional Review Boards (IRB)/Independent Ethics Committees (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 (CFR), 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 sub-investigators 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 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.
- 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 study due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by 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 data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, study 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 electronic CRFs unless transmitted to the sponsor or designee electronically (for example, 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. Source data may include laboratory tests, medical records, and clinical notes.
- 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.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- 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 (for example, 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 (CTA) 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, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the CRU. The study may be audited by 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 (EDC) 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 EDC 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 cross-reference to 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 table below 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 (fasting)[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Glucose
Leukocytes (WBC)	Blood urea nitrogen
Platelets	Total protein
Absolute counts of:	Albumin
Neutrophils	Total bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Aspartate aminotransferase
Eosinophils	Alanine aminotransferase
Basophils	Creatinine
	Amylase
	Lipase
Urinalysis[a]	
Specific gravity	Hepatitis B surface antigen[b]
pH	Hepatitis C antibody[b]
Protein	HIV or HIV antibody[b]
Glucose	Pregnancy test[c]
Ketones	Ethanol breath test and urine drug screen testing[d]
Bilirubin	Hemoglobin A1C[b]
Urobilinogen	
Blood	
Nitrite	
Microscopic examination of sediment[e]	

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

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

[b] Performed by local laboratory at screening only.

[c] Pregnancy test: Serum pregnancy test will be performed at screening and urine pregnancy test will be performed at Day -1 and at the safety follow-up, see Schedule of Activities in Section 1.3.

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

[e] Test only if urinalysis result is abnormal (i.e., 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. Number of samples in parenthesis assumes 3 additional unscheduled samples which may be taken for safety purpose.

Protocol GPIN Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a,b]	25	1	25
Clinical laboratory tests[a,b]	12	3	36
Pharmacokinetics[c]	3	9 (+3)	36
Capillary plasma glucose[a,d]	Negligible	6 (+3)	1
Total			98
Total for clinical purposes (rounded up to the nearest 10 mL)			100

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

[b] Performed in a local laboratory.

[c] Performed at a central or referral laboratory approved by the sponsor.

[d] Performed at bedside using a glucometer – rounded to 1 mL.

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.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing 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 IMP, including signs, symptoms, or clinical sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

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 (for example, 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 pre-existing 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 one 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 pre-existing 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 (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
  - Abnormal pregnancy outcomes (for example, 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 one 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.

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 (for example, hospital progress notes, laboratory reports, and diagnostics 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 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 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 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 one of the following categories:

- Mild: A type of adverse event 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 adverse event 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 adverse event 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 a 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 one 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 Investigator’s Brochure and/or Product Information, for marketed products 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 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 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 one 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 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.

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 a SAE is essential so that legal obligations and ethical responsibilities towards 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, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or state other documents 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 may participate in this study.

WOCBPs 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 contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and for at least 30 days after the last dose of the study intervention.

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	• 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 by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• barrier method with use of a spermicide ○ male 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 • lactational amenorrhea • diaphragm with spermicide or cervical sponges

	• female condom with spermicide

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

See protocol Section 8.2.10.1 for guidance on appropriate test selection.

Testing by an investigator-designated local laboratory should be performed for all applicable and available 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	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Hepatic Coagulation Panel	Copper
Prothrombin time, INR (PT-INR)	Ethyl alcohol (EtOH)
Hepatitis A virus (HAV) testing:	Haptoglobin
HAV total antibody	Immunoglobulin IgA (quantitative)
HAV IgM antibody	Immunoglobulin IgG (quantitative)
Hepatitis B virus (HBV) testing:	Immunoglobulin IgM (quantitative)
Hepatitis B surface antigen (HBsAg)	Phosphatidylethanol (PEth)
Hepatitis B surface antibody (anti-HBs)	**Urine Chemistry**
Hepatitis B core total antibody (anti-HBc)	Drug screen
Hepatitis B core IgM antibody	Ethyl glucuronide (EtG)
HBV DNA[b]	**Other Serology**
Hepatitis C virus (HCV) testing:	Anti-nuclear antibody (ANA)
HCV antibody	Anti-smooth muscle antibody (ASMA)[a]
HCV RNA[b]	Anti-actin antibody[c]
Hepatitis D virus (HDV) testing:	Epstein-Barr virus (EBV) testing:
HDV antibody	EBV antibody
Hepatitis E virus (HEV) testing:	EBV DNA[b]
HEV IgG antibody	Cytomegalovirus (CMV) testing:
HEV IgM antibody	CMV antibody
HEV RNA[b]	CMV DNA[b]
Microbiology	Herpes simplex virus (HSV) testing:
Culture:	HSV (Type 1 and 2) antibody
Blood	HSV (Type 1 and 2) DNA[b]
Urine	Liver kidney microsomal type 1 (LKM-1) antibody

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

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

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

10.6. Appendix 6: 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 (i.e., 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, 2017b). 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.

10.7. Appendix 7: Pharmacokinetic Analysis Plan

PK Software and Version

- Phoenix Version 8.1 or higher will be used for noncompartmental analyses.

Rules for Handling Measurement Values in PK Analysis

- Actual times will be used for the calculation of individual plasma PK parameters.
- The actual start times of each breastmilk collection will be used for the calculation of individual breastmilk PK parameters.
- Concentrations below the quantification limit occurring before the first quantifiable concentration in an individual profile will be treated as missing.
- Atypical data will be reviewed for possible outliers according to the criteria outlined in the standard operating procedure (SOP) "Treatment of Outliers During PK Analysis."
- Sample times deviating >10% from the scheduled sample time will be excluded from the mean concentration-time plots.

Analysis Methods

- Standard noncompartmental PK methods will be used to calculate relevant PK parameters according to the SOP for Non-Compartmental PK Analysis Methods and Reporting.
- Mean concentration profiles will be evaluated graphically for plasma and breastmilk. Mean concentrations will be calculated as described in the SOP for Non-Compartmental PK Analysis Methods and Reporting. If a specific sample is collected >10% outside of the scheduled time, the concentration in that sample will not be included in the mean calculation.

PK Data Reported

- $AUC_{(0-\infty)}$, CCI [redacted] breastmilk will be summarized with geometric mean and 95% confidence interval for the geometric mean.
- Milk-to-plasma ratio will be estimated as $AUC_{(0-\infty)}$, breastmilk / $AUC_{(0-\infty)}$,plasma.
- Steady-state breastmilk exposure $AUC_{(tau,ss)}$ would be considered to approximate $AUC_{(0-inf)}$,breastmilk after a single dose.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [a]: 24 July 2023

This amendment is considered to be non-substantial.

Overall Rationale for the Amendment:

The protocol is being amended to address FDA recommendations on contraceptive and barrier guidance.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Added CCI optional breastmilk PK sample	To permit collection of breastmilk based on participant's need to pump during this interval and to ensure that all breastmilk is captured during the CCI post dose.
10.4.2 Contraception Guidance	"diaphragms with spermicide or cervical sponges" and "female condom with spermicide" were removed from the effective forms of contraception list and added to the ineffective forms of contraception list	Updated based on FDA feedback

10.9. Appendix 8: 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
$AUC_{(0\text{-}last)}$	AUC from time 0 to the last measurable concentration after the first dose
$AUC_{(0\text{-}\infty)}$	AUC from time 0 to infinity
CFR	Code of Federal Regulations
C_{max}	maximum observed drug concentration
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all 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
eCRF	electronic case report form
ECG	electrocardiogram
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
GIP	glucose-dependent insulinotropic peptide
GIPR	GIP receptor
GLP-1	glucagon-like peptide 1
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IP	investigational product
IRB	Institutional Review Boards
ISR	injection-site reaction
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."
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 one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five 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 (for example, 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
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
PC	product complaint
PK	pharmacokinetic(s)
RA	receptor agonist
SAE	serious adverse event
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.
SC	subcutaneous
SoA	schedule of activities
SOP	standard operating procedure
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
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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