Protocol: J1X-MC-GZHI (Initial Version)

An Open-Label, Multiple-Dose Study to Investigate the Pharmacokinetics of LY3493269 Oral Formulations Administered in a Fed or Fasted State in Healthy Participants

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Title Page

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Protocol Number: J1X-MC-GZHI

Amendment Number: This is the initial protocol.

Compound: LY3493269

Brief Title: Pharmacokinetics of LY3493269 Oral Formulations in Healthy Participants

Study Phase: 1

Acronym: GZHI

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

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Medical Monitor Name and Contact Information will be provided separately

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

An Open-Label, Multiple-Dose Study to Investigate the Pharmacokinetics of LY3493269 Oral Formulations Administered in a Fed or Fasted State in Healthy Participants

Brief Title: Pharmacokinetics of LY3493269 Oral Formulations in Healthy Participants

Rationale:

LY3493269 is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1 receptor agonist being developed as a treatment for type 2 diabetes mellitus (T2DM). In addition to subcutaneous treatment, an oral formulation of LY3493269 is being developed for once-daily administration to improve patient convenience and therapy adherence. The aim of developing an oral formulation is to provide an effective oral incretin for patients with T2DM with inadequately managed blood glucose goals. This study of LY3493269, Study J1X-MC-GZHI (GZHI), will investigate the pharmacokinetics (PK) of LY3493269 administered as multiple once-daily oral doses in healthy participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate and compare the PK of up to 3 test capsule formulations with a reference tablet formulation of LY3493269 following 3 consecutive once-daily oral doses in healthy participants	• AUC and C_{max}
Secondary	
• To evaluate the PK of up to 2 LY3493269 formulations when administered in a fed condition following 3 consecutive once-daily oral doses in healthy participants	• AUC and C_{max}
• To assess the safety and tolerability of up to 3 test capsule formulations of LY3493269 with that of a reference tablet formulation following 3 once-daily oral doses in healthy participants	• TEAEs

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; TEAE = treatment-emergent adverse event.

Overall Design

Study GZHI is a Phase 1, single-center, open-label, multiple-dose study in 5 planned treatment groups targeting 10 healthy participants in each treatment group to complete. The study will be conducted in 2 parts (Part A and Part B).

Brief Summary:

The purpose of this study is to evaluate and compare the PK of up to 3 test capsule formulations with a reference tablet formulation of LY3493269 following 3 consecutive once-daily oral doses in healthy participants.

Study details include:

- The study duration will be up to 71 days.
- The treatment duration involves consecutive once-daily dosing up to 3 days.
- The visit frequency will be one inpatient stay (Day -1 through Day 5) and 5 outpatient visits.

Number of Participants:

Up to approximately 70 participants may be enrolled to ensure approximately 10 evaluable participants from each of the 5 planned treatment groups complete the study. Participants who are enrolled but not administered treatment prior to discontinuation may be replaced to ensure that the target number of participants complete the study.

Participants who discontinue early may be replaced after consultation with the investigator and sponsor. The replacement participant will be assigned to the same treatment as the discontinued participant.

Intervention Groups and Duration:

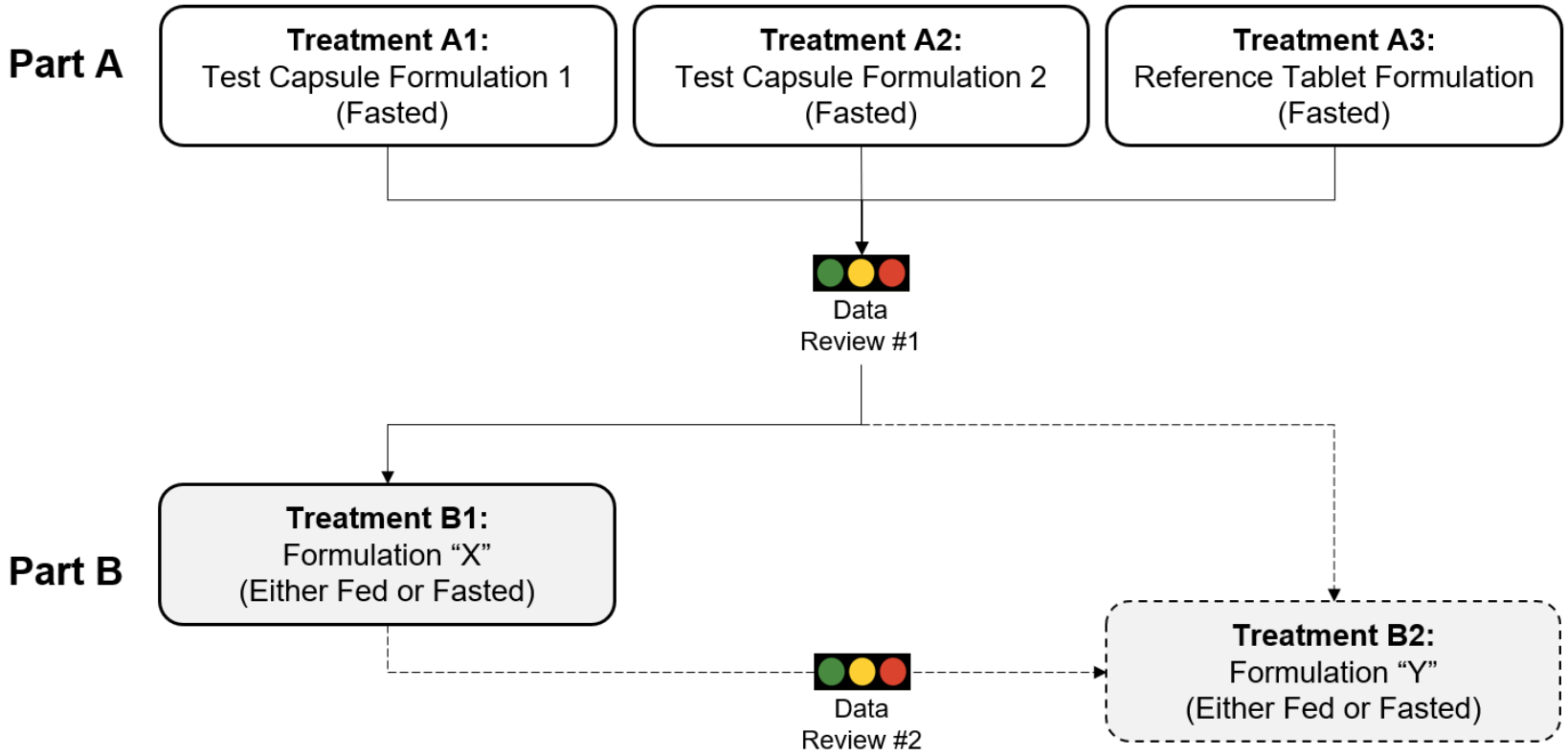
In each part of the study, eligible participants will be assigned to a study treatment (Test or Reference formulation) and will receive 3 once-daily doses of study intervention.

The maximum total duration of study participation for each participant may be up to 71 days, across the following study intervals:

- Screening, approximately 28 days
- Study period, approximately 15 days
- Follow up, approximately 28 days after the last dose of study intervention

Data Monitoring Committee: No

1.2. Schema



Formulations "X" and "Y" will be determined after review of interim data from Part A. If appropriate, Formulation "Y" may be determined after review of data from Treatment B1.

Figure GZHI.1.1 Illustration of Parts A and B for Protocol J1X-MC-GZHI.

1.3. Schedule of Activities (SoA)

Schedule of activities for Parts A and B

Study Activities	Scrn	Study Period (Parts A and B)									Follow-up			Comments/Notes
		CRU Inpatient Stay						Outpatient			Outpatient			
Days	-28 to -2	−1	1	2	3	4	5	6	8	15 ±1	29 ±3	43 ±3	ET	
Informed consent	X													
Medical history	X													
Physical examination	X													
Medical assessment			P	P	P		X	X	X	X	X	X	X	Medical review and symptom-directed physical examination, as appropriate.
Height and weight	X		P		X				X	X	X	X	X	Height at screening only.
Admit to CRU		X												
Discharge from CRU							X							At the investigator's discretion, participants may remain inpatient after Day 5.
Outpatient visit to CRU								X	X	X	X	X	X	
Administer study drug			X	X	X									Refer to Section 6.1 for details
AEs/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG – single (h)	X		P, 1, 4, 12	P, 1, 4, 12	P, 1, 4, 12					X	X	X	X	ECGs must be recorded approximately within 30 minutes before collection of any blood samples (applicable for study visits).
Vital signs: supine BP/PR (h)	X		P, 1, 4, 12	P, 1, 4, 12	P, 1, 4, 12	X	X	X	X	X	X	X	X	
Body temperature	X		P	P	P									
Clinical laboratory tests (fasted)	X		P				X		X	X	X	X	X	See Appendix 2 for details.
Point-of-care safety glucose samples (glucose analyzer)			Days 1 – 4: Pre-meals (breakfast, lunch, and dinner) and before bedtime				X	X						Day 5: Fasted sample collected before breakfast.

Study Activities	Scrn	Study Period (Parts A and B)									Follow-up			Comments/Notes
		CRU Inpatient Stay						Outpatient			Outpatient			
Days	-28 to -2	−1	1	2	3	4	5	6	8	15 ±1	29 ±3	43 ±3	ET	
LY3493269 PK sampling (h)			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 9, 10, 12, 14	P, 1, 2, 3, 4, 8, 14	P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 9, 10, 12, 14	X	X	X	X	X	X	X	X	Days 15, 29, 43, and ET: Samples collected anytime during visit.
SNAC (Reference Formulation) or C10 (Test Formulations) PK sampling (h)			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 9, 10, 12, 14	P, 1, 2, 3, 4, 8, 14	P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 9, 10, 12, 14	X	X							
Immunogenicity			P							X	X	X	X	Day 1: Samples are collected within 30 min of the predose PK samples.
Pharmacogenetic sample			X											Obtained any time on Day 1.
Nonpharmacogenetic biomarker stored samples – (fasted)			P		P		X		X	X	X			

Abbreviations: AE = adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination (applicable only to study participants who have received study intervention); P = predose; PK = pharmacokinetics; PR = pulse rate; Scrn = Screening Visit; SNAC = salcaprozate sodium; SoA = schedule of activities.

Notes:

1) Fasted samples or assessments should be collected or performed after a minimum 8-hour overnight fast. If multiple procedures take place at the same time point, ECGs and vital signs must be obtained prior to any blood sample collection.
2) For vital signs and ECGs
   - time points on Days 1 to 3 are relative to scheduled dosing at “0 h”. Assessments scheduled at “0” are conducted predose (P).
   - on Day 15, ECG should be measured within approximately 30 min prior to the scheduled PK sample.
   - on Day 15 and subsequent visits, vital signs should be measured within approximately 30 min prior to the scheduled PK sample.
3) PK and immunogenicity samples are not required at ET for participants who discontinue without receiving study intervention.
4) The following requirements are not applicable for urinalysis samples. Unless otherwise stated,

- predose study assessments and procedures should be performed within 3 hours prior to planned dosing,
- postdose assessments and procedures on Days 1, 2, and 3, up to and including 24 hours post-Day 3 dose should be performed within ±10% of the scheduled time, and
- postdose assessments and procedures on Days 4 to 8, scheduled after 24 hours post-Day 3 dose should be performed within ±3 hours of the scheduled time,
- windows for postdose assessments and procedures on Days 15 and later are indicated in the SoA.

2. Introduction

2.1. Study Rationale

LY3493269 is a dual GIP and GLP-1 RA being developed as a treatment for T2DM. In addition to SC treatment, an oral formulation of LY3493269 is being developed for once-daily administration to improve patient convenience and therapy adherence. The aim of developing an oral formulation is to provide an effective oral incretin for patients with T2DM with inadequately managed blood glucose goals. This study of LY3493269, Study J1X-MC-GZHI (GZHI), will evaluate and compare the PK of different test capsule formulations of LY3493269 administered as multiple once-daily oral doses in healthy participants with that of a reference tablet formulation.

2.2. Background

T2DM is characterized by impaired glycemic control due to insulin resistance and inadequate insulin secretion due to the pancreatic beta-cell failure. T2DM is frequently associated with comorbidities such as obesity, hypertension, and dyslipidemia resulting in increased risk of microvascular and macrovascular complications.

Synthesized and secreted in the proximal intestine, GIP is primarily regulated by nutrients, especially fats, and is responsible for the majority of the insulinotropic incretin effect in humans. In addition, distinct from GLP-1, GIP promotes glucagon secretion at low blood glucose levels to augment endogenous glucose production. It stimulates lipolysis and inhibits insulin-induced lipogenesis in human adipocytes.

GLP-1 is a well-characterized incretin hormone that potentiates insulin secretion and reduces glucagon secretion in a glucose-dependent manner after meal ingestion. GLP-1 exerts its insulinotropic action through distinct G protein-coupled receptors highly expressed on islet β cells and in some non-islet cells. For example, GLP-1 receptors are expressed throughout the brain, in regions that control

- glucose homeostasis
- gut motility
- food intake
- aversive signaling, and
- CV function (Campbell and Drucker 2013).

Currently, there are several approved GLP-1 RAs for the treatment of diabetes and obesity. The dosing of GLP-1 RAs in humans is limited by GI adverse effects, such as nausea and vomiting.

Available preclinical and clinical data indicate that co-stimulation of GIP and GLP-1 receptors may enhance insulin secretion, improve insulin sensitivity, and reduce body weight beyond the effect of selective GLP-1 receptor stimulation (Coskun et al. 2018; Frias et al. 2018).

The LY3493269 reference tablet formulation in Study GZHI will include the permeation enhancer SNAC, to enable oral absorption of the LY3493269 peptide, while the LY3493269 test capsule formulations will include sodium caprate (C10) as a permeation enhancer. CCI

CCI [redacted] As peptides are otherwise poorly absorbed orally due to low permeability, an enabling excipient such as SNAC or C10 in an oral tablet formulation is expected to transiently increase local permeability (Twarog et al. 2019) and result in increased oral bioavailability for therapeutic use.

2.3. Benefit/Risk Assessment

There is no anticipated therapeutic benefit for the participants in this trial.

The sponsor has evaluated the preclinical and clinical risks associated with LY3493269. Nonclinical safety of SC LY3493269 was evaluated in a CV safety pharmacology study in monkeys and 1-month repeat-dose toxicology studies in rats and monkeys. Important LY3493269-related findings in the rat and monkey included body weight loss and/or reduced body weight gain and decreased food consumption. Additional findings from the monkey studies included changes in CV parameters (such as increases in HR and BP). In the completed clinical studies where LY3493269 was administered SC (Studies GZHA and GZHC) or orally with C10 (Study GZHB) or SNAC (Study GZHF), similar findings were observed, which include

- nausea
- vomiting
- loss of appetite, and
- increased HR.

SNAC has generally regarded as safe status and is contained in FDA-approved medical food (Eligen®-Vitamin B12, Emisphere, Roseland, NJ, USA; Twarog et al. 2019). Rybelsus® tablet, which is approved by FDA, European Medicines Agency and Japan Pharmaceuticals and Medical Devices Agency, also contains SNAC (daily dose of 300 mg). In addition, in a first-in-human trial, up to 600 mg SNAC was evaluated with oral semaglutide with no safety concerns reported (Granhall et al. 2019).

C10 has a long history of use in humans and has food additive status in the US and EU with no daily limits on consumption (Twarog et al. 2019). In the completed nonclinical safety pharmacology and toxicology studies, LY3493269 orally co-administered with C10, produced increased HR, body weight loss and/or decreased body weight gain, and decreased food consumption, which are consistent with, or secondary to, incretin pharmacology. The effects on body weight were dose limiting and resulted in dosing suspension at the highest dose levels tested in monkeys. No adverse C10-related effects were observed up to 350 mg/kg in any of the toxicology studies/assessments.

In the completed nonclinical safety pharmacology and toxicology studies, LY3493269 orally co-administered with SNAC produced body weight loss and/or decreased body weight gain, and decreased food consumption, which are consistent with, or secondary to, incretin pharmacology. The effects on body weight were dose limiting and resulted in dosing suspension in monkeys. No adverse SNAC-related effects were observed up to 600 mg/kg in any of the toxicology studies/assessments. Refer to the IB for more information.

Based on the completed clinical Studies GZHA, GZHB, GZHC, and GZHF, potential risks for clinical trial participants receiving orally administered LY3493269 are similar to those for

participants receiving SC administered LY3493269 and include CV effects, GI disturbances, inappetence, skin burning sensation and related events, and weight loss.

All identified risks from the nonclinical and clinical studies are considered monitorable and manageable at the planned once-daily oral dose of 4 mg LY3493269. To further minimize any potential risk, participants will remain at the CRU for at least 5 days for safety and tolerability monitoring until discharge. Participants will be closely monitored with scheduled medical assessments, vital signs, and triplicate ECG measurements. The investigator will have the discretion to extend the participant inpatient stay for further safety monitoring.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3493269 may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate and compare the PK of up to 3 test capsule formulations with a reference tablet formulation of LY3493269 following 3 consecutive once-daily oral doses in healthy participants	• AUC and C_{max}
Secondary	
• To evaluate the PK of up to 2 LY3493269 formulations when administered in a fed condition following 3 consecutive once-daily oral doses in healthy participants • To assess the safety and tolerability of up to 3 test capsule formulations of LY3493269 with that of a reference tablet formulation following 3 once-daily oral doses in healthy participants	• AUC and C_{max} • TEAEs
Exploratory	
• To assess PK of SNAC and C10 following oral administration in healthy participants	• AUC and C_{max}

Abbreviations: AUC = area under the concentration versus time curve; C10 = sodium caprate; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SNAC = salcaprozate sodium; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

This is a 2-part, open-label study with a parallel design to be conducted in healthy participants.

The purpose of this study is to evaluate and compare the PK of up to 3 test capsule formulations with a reference tablet formulation of LY3493269 following 3 consecutive once-daily oral doses in healthy participants.

Study details include:

- The study duration will be up to 71 days.
- The treatment duration involves consecutive once-daily dosing up to 3 days.
- The visit frequency will be one inpatient stay (Day -1 through Day 5) and 5 outpatient visits.

In Parts A and B, eligible participants will receive 3 once-daily doses of study intervention.

The maximum total duration of study participation for each participant may be up to 71 days, across the following study intervals:

- Screening, approximately 28 days
- Study period, approximately 15 days, and
- Follow up, approximately 28 days after the last dose of study intervention.

The study shall target 10 participants completing each treatment – that is, these participants must complete Day 8 PK assessments after receiving all 3 consecutive daily doses of the study treatment.

Part A

Part A of the study is an initial characterization of 2 test capsule formulations, compared with a reference tablet formulation. Participants will be randomly assigned to receive 1 of the 3 possible treatments as follows:

- Treatment A1: Test capsule formulation 1
- Treatment A2: Test capsule formulation 2
- Treatment A3: Reference tablet formulation

Test formulations 1 and 2 and the reference formulation will be administered in the fasted state.

Part B

Part B of the study will investigate the test capsule formulations 1, 2, or 3 or the reference tablet formulation.

An initial review of safety and PK data from Part A will be conducted to determine the test or reference formulation(s) to be evaluated in Part B. Participants will be assigned to 1 of the 2 possible treatments as follows:

- Treatment B1: Test formulations 1, 2, or 3 (referred to as “X” from this point forward)
- Treatment B2: Test formulations 1, 2, or 3 or reference formulation (referred to as “Y” from this point forward).

The 3 test formulations will be administered in either the fasted or fed state depending on the review of safety and PK data from Part A. If the reference formulation is selected as Treatment B2, it will be administered in the fasted state.

Depending on the review results, the selected formulation(s) will be administered in either the fed or fasted state.

Treatments B1 and B2 may be initiated concurrently if the formulations "X" and "Y" and administration conditions are determined for both treatment groups after the first review. Otherwise, a second review of available PK data from Treatment B1 may be conducted prior to the initiation of Treatment B2.

4.2. Scientific Rationale for Study Design

The study is intended to estimate the relative oral bioavailability of various LY3493269 4-mg oral formulations with 280 mg C10 versus a LY3493269 4 mg with 300 mg SNAC oral formulation. A population of healthy participants is selected to assess the safety and tolerability of LY3493269 co-formulated with 280 mg C10 as a capsule for oral administration with an intended lower intestinal release mechanism. An LY3493269 tablet co-formulated with 300 mg SNAC will be used as the reference treatment. Using a healthy participant population mitigates possible confounding effects of comorbidities and concomitant medications. Therefore, Study GZHI provides an unbiased assessment of safety, tolerability, and PK of LY3493269 administered as oral doses.

A study design of once-daily oral dosing for 3 days will be employed to characterize oral PK behavior of LY3493269. The dosing duration of 3 days was selected after taking into consideration the following factors:

- low oral bioavailability expected from oral peptide formulations
- the exceptionally high inter- and intra-individual variabilities in oral bioavailability expected of oral peptide formulations
- the sensitivity of the bioanalytical assay, and
- once absorbed via the oral route of administration, LY3493269 systemic PK disposition should be similar regardless of route of administration, hence safety, tolerability, and PK data from past LY3493269 studies (GZHA, GZHB, GZHC, and GZHF) should be applicable to this study.

To predict the oral PK profiles for each treatment, extensive PK simulations were conducted. The PK profile following a single oral dose was deemed to be at risk of being highly variable and potentially returning lower than quantifiable concentrations at multiple time points. The simulation results did suggest that 3 days was adequate for a majority of PK profiles from participants in each treatment group to remain above the quantification limit of CCI to yield meaningful PK results. Therefore, PK exposures from a short dosing duration of 3 days from this study are not expected to reach steady state for the respective doses.

Strict oral administration conditions such as controlling the duration of fasting before and after dosing and water volume for oral administration of LY3493269 will be imposed. These are necessary to reduce any potential variability arising from oral administration conditions that may affect oral bioavailability of LY3493269.

Safety and tolerability assessments will be made, including incidence of nausea and/or vomiting, skin burning sensation, and other related events and evaluation of ECGs and vital signs conducted during the study (Section 8.2). The decisions to proceed from Part A to Part B and from Treatments B1 to B2, and the selection of LY3493269 formulations for Part B will be based primarily on safety and tolerability data (Sections 6.5.1) and all available PK data.

4.3. Justification for Dose

The proposed LY3493269 oral dose of 4 mg once daily is selected based on safety, tolerability, and PK data from oral administration of this same dose in combination with the permeation enhancers C10 and SNAC from Studies GZHB and GZHF. Based on past PK data, a 4-mg once-daily dose is likely still adequate to enable quantification of LY3493269 concentrations for PK analysis assuming oral bioavailability in the range of CCI as observed from Study GZHB when co-administered with the permeation enhancer C10. Oral bioavailability for LY3493269 was calculated to be CCI when co-administered with the SNAC permeation enhancer in Study GZHF. Should oral bioavailability reach preclinical values of CCI (relative to SC administration) in dogs or CCI (absolute oral bioavailability) observed in monkeys for the current co-formulation with C10, anticipated PK concentrations from the proposed 4-mg dose are not expected to exceed concentrations from the CCI dose tested in Study GZHF. When the highest preclinical relative oral availability of CCI in dogs is applied to simulate anticipated mean exposures of LY3493269 4 mg for this enteric formulation, C_{max} and AUC from time zero to 24 hours after the third daily oral dose are expected to be approximately 1.0x and 0.9x, respectively, of that for LY3493269 CCI + SNAC 600 mg SNAC. Exposures from the 4-mg dose are also expected to be well below exposures from the SC multiple-ascending dose study (Study GZHC). At this 4-mg dose, all of the expected safety findings (including skin burning sensation and related AEs) as evaluated in GZHF are monitorable.

SNAC has generally regarded as safe status and is contained in FDA-approved medical food (Eligen-Vitamin B12, Emisphere, Roseland, NJ, USA). Rybelsus tablet, which is approved by FDA, European Medicines Agency and Japan Pharmaceuticals and Medical Devices Agency, contains SNAC at 300 mg. The SNAC reference dose in this study has been administered in GZHF without SNAC-specific safety concerns.

While C10 has food additive status with no daily limits on consumption, up to 550 mg per day has been evaluated in an 8-week Phase 2 trial with oral insulin in patients with T2DM, with no safety concerns reported (Halberg et al. 2019). In the proposed study, C10 will be dosed at 280 mg, which is 1.7-fold below the top dose in Study GZHB. In Study GZHB, a top dose of 500 mg C10 was administered without C10-specific safety concerns.

All of the identified risks in Section 2.3 are considered to be reversible, monitorable, and manageable and will continue to be monitored closely in clinic.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all required phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

Any participant who does not satisfy this definition but who has completed all the key assessments may be considered a completer at the discretion of the sponsor.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Eligibility of participants for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

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

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

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. Parameters repeated for screening include clinical laboratory tests, body weight, ECGs, and vital signs.

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

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 21 to 65 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2. Participants who are overtly healthy as determined through medical evaluation including screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.
3. Have clinical laboratory test results within normal reference range for the population or CRU, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
4. Have venous access sufficient to allow blood sampling as per the protocol.
5. Are able and willing to consume the high-fat, high-calorie breakfast meal provided on dosing days (Part B only).
6. Are reliable and willing to make themselves available for the duration of the study and who will comply with the required study and dosing visits and abide by the clinical research site policy and procedure and study restrictions.

Weight

7. Body mass index within the range 19.0 to 40.0 kg/m^2 (inclusive), at screening.

Sex and contraceptive/barrier requirements

8. Males who agree to use highly effective/effective methods of contraception may participate in this trial. Please refer to Appendix 4 for definitions and additional guidance related to contraception.
9. Only women not of childbearing potential (WNOCBP) may participate in this trial

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 10.4.

Informed consent

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

5.2. Exclusion Criteria

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

Medical conditions

11. Have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).
12. Have a significant history of or current CV (for example, myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism, etc.), respiratory, renal, GI (including involving the liver, gallbladder or gallbladder surgery), endocrine, hematological (including history of thrombocytopenia), or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk while taking the IP; or of interfering with the interpretation of data.
13. Have a mean supine HR less than 45 bpm or greater than 100 bpm from 2 assessments at screening. If a repeat measurement (mean of 2 assessments) shows values within the range of 45 to 100 bpm, the participant may be included in the trial.
14. Have a mean supine systolic BP higher than 160 mmHg and a mean supine diastolic BP higher than 95 mmHg from 2 assessments at screening; therefore, if a repeat measurement (mean of 2 assessments) shows values within the range (systolic BP ≤160 mmHg and /or diastolic BP ≤95 mmHg), the participant can be included in the trial.
15. Have undergone any form of bariatric surgery.
16. Have a history of GI bleeding, or gastric or duodenal ulcers.
17. Have a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

18. Have a history of acute or chronic pancreatitis, or elevation in serum lipase and/or amylase levels greater than 1.5 times the ULN.
19. Have clinical signs or symptoms of liver disease, acute or chronic hepatitis.
20. Have evidence of significant active neuropsychiatric disease as determined by the investigator.

Prior/concomitant therapy

21. Have been treated with prescription drugs that promote weight loss within 3 months prior to screening. Examples include
    - Meridia® (sibutramine)
    - Sanorex® (mazindol)
    - Adipex-P® (phentermine)
    - BELVIQ® (lorcaserin)
    - Mysimba® (naltrexone/bupropion)
    - Saxenda® (liraglutide), or
    - similar other body weight loss medications including any over-the-counter medications or supplements (for example, alli®).
22. Have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy in the past year, or have received any glucocorticoid therapy within 1 month before screening (topical, intra-articular, and inhaled preparations such as steroid nasal spray are permitted in the study).

Prior/concurrent clinical study experience

23. 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.
24. Have participated within the past 30 days of screening in a clinical study involving an IP; at least 5 half-lives or 30 days, whichever is longer, should have passed.

Diagnostic assessments

25. Have an abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG (QT) data analysis, such as a QTcF >450 msec for males and >470 msec for females, short PR interval (<120 msec), or PR interval >220 msec, second- or third-degree atrioventricular block, intraventricular conduction delay with QRS >120 msec, right bundle branch block, left bundle branch block or Wolff-Parkinson-White syndrome.
26. Have serum AST or ALT >1.5x ULN or TBL >1.5x ULN.
27. Show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies.
28. Show evidence of hepatitis C and/or positive hepatitis C antibody.
29. Show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen.

Other exclusions

30. Are Site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling
31. Are Lilly employees.
32. Have previously completed or withdrawn from this study.
33. Have donated blood of more than 450 mL or have participated in a clinical study that required similar blood volume withdrawn within the past 3 calendar months.
34. Women who are lactating.
35. Women of childbearing potential
36. Have known allergies to LY3493269, related compounds, or any components of the formulation (including C10 or SNAC), or a history of significant atopy.
37. Regularly use known drugs of abuse.
38. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) or are unwilling to stop alcohol consumption as required during the study (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
39. Smoke >10 cigarettes per day or the equivalent or are unable or unwilling to refrain from nicotine during CRU admission.
40. Are unwilling to comply with the dietary restrictions required for this study.
41. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

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

All participants will observe an overnight fast of at least 8 hours prior to the scheduled dosing time and for each subsequent study day when clinical safety laboratory fasting samples are taken.

Further requirements on water and meal restrictions related to administration of study intervention are found in Section 6.1.

Throughout the inpatient period, apart from the high-fat, high-calorie meal served at dosing, and the standardized breakfast meal for Treatment B2 [dosing condition B2(b)], standard meals will be administered in the CRU. While not resident in the CRU, participants will be encouraged to follow their normal diet.

5.3.1.1. High-Fat, High-Calorie Breakfast

For Treatments B1 and B2, participants may receive study intervention in the fed state. A high-fat, high-calorie breakfast will be served to participants prior to dosing to achieve a fed state.

Participants will be encouraged to finish the meal, including milk or milk substitute. The amount of the meal consumed by the participant will be documented by the CRU.

The high-fat, high-calorie breakfast should consist of approximately 800 to 1000 calories. This meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrates, and fat, respectively. At least approximately 50% of the calories should be derived from fat. An example of a high-fat, high-calorie breakfast is as follows:

- two eggs fried in butter
- two strips of bacon
- two slices of toast with butter
- four ounces of hash brown potatoes, and
- 240 mL of whole milk or substitute.

Appropriate substitutions of meal components that match the fat- and calorie-content may be made to accommodate an individual participant's dietary restrictions or requirements.

Participants will receive each dose with approximately 240 mL of water.

5.3.1.2. Standardized Breakfast

Under dosing conditions in Treatment B2(b) as described in Table GZHI.6.1, a standardized breakfast will be served 30 minutes after dosing. This meal should consist of approximately 558 calories, composed of approximately 49% carbohydrate, 34% fat, and 17% protein.

Apart from the restrictions listed above and in Table GZHI.6.1, there are no other beverage restrictions. Water ad libitum is allowed only until 1 hour before dosing and following the 2-hour postdose fast.

Further requirements on water and timing of the high-fat, high-calorie breakfast and standardized breakfast meals are found in Section 6.1.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Participants are allowed to maintain their regular caffeine consumption throughout the study.

No alcohol will be allowed at least 24 hours before each CRU admission and each outpatient visit and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 3 units for males and 2 units for females (a unit is defined in Section 5.2, criterion [38]).

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

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity/exercise during the study, and to abstain from strenuous exercise for at least 24 hours before each blood collection for clinical laboratory tests.

When certain study procedures are in progress at the site, participants may be required to remain recumbent or sitting.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. However, participants who were eligible for inclusion in previous treatment groups, but were not randomly assigned for nonmedical reasons, may be reassessed. Additional medical assessments and clinical measurements include clinical laboratory tests, vital signs, and ECG to confirm their eligibility. This is applicable for both Parts A and B.

Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening. Abnormal screening laboratory tests may be repeated if the investigator considers that the abnormality is likely related to a sampling or handling issue, or to a technical error.

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

Not applicable in this study.

6. Study Interventions and Concomitant Therapy

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

6.1. Study Interventions Administered

The following table shows the planned study interventions in this study.

Intervention Name	LY3493269 Test Capsule formulation 1, 2, or 3	LY3493269 Reference Tablet formulation
Type	Drug	Drug
Dose Formulation	Capsule	Tablet
Unit Dose Strength	4 mg LY3493269 with 280 mg C10	4 mg LY3493269 with 300 mg SNAC
Dosage Level	Single 4-mg dose	Single 4-mg dose
Route of Administration	Oral	Oral
Use	Test formulation	Reference formulation
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement

Abbreviations: C10 = sodium caprate; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product; SNAC = salcaprozate sodium.

All participants in Part A will observe an overnight fast of at least 8 hours prior to the scheduled dosing time.

If dosing is to be done in the fed state, participants in Part B will observe an overnight fast of at least 8 hours prior to the administration of the high-fat, high-calorie breakfast. If dosing is to be done in the fasted state, participants will observe an overnight fast of at least 8 hours prior to the scheduled dosing time.

Water can be allowed as desired except as described in Table GZHI.6.1 and the following sections (dosing in the fasted or fed state). Any additional water required by the participant to complete the dose must be recorded in the CRF.

LY3493269, as Test Capsule formulations 1, 2, or 3, or the Reference tablet will be administered orally with CCI water in the morning of each dosing day in a sitting position.

Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Dosing in the fasted state

Participants will take each dose of LY3493269 on Days 1, 2, and 3 after the overnight fast. After each daily dose, participants must continue to fast for 2 hours or 30 mins, as described in Table GZHI.6.1. Water ad libitum is allowed only until 1 hour before dosing and following the 2-hour postdose fast.

Dosing in the fed state

For each participant, a high-fat, high-calorie breakfast meal shall be administered at the same time on each scheduled dosing day, to be consumed within 30 minutes.

Participants should be administered their assigned treatment 30 minutes after the start of the high-fat, high-calorie breakfast meal on each of the 3 dosing days. No food is allowed for at least 4 hours after the LY3493269 dose.

Table GZHI.6.1. Fasting or Fed Conditions and Water Consumption for Dosing

Treatment	Formulation	Dosing Conditions[a]	Overnight Fast?	Water for Dosing (Approximate Volumes)	Dosing vs. Meal Timing
A1	Test 1	Fasted	Yes	120 mL	Postdose fast duration: 2 hours
A2	Test 2	Fasted	Yes	120 mL	Postdose fast duration: 2 hours
A3	Reference	Fasted	Yes	120 mL	Postdose fast duration: 2 hours
B1	"X"	B1(a) Fasted[a]	Yes	120 mL	Postdose fast duration: 2 hours
		B1(b) Fasted[a]	Yes	240 mL	Postdose fast duration: 2 hours
		B1(c) Fed[a]	Yes	240 mL	Dosing is scheduled 30 minutes after the start of the high-fat, high-calorie breakfast meal
B2	"Y"	B2(a) Fed	Yes	240 mL	Dosing is scheduled 30 minutes after the start of the high-fat, high-calorie breakfast meal
		B2(b) Fasted[b]	Yes	120 mL	Standardized breakfast meal provided 30 minutes postdosing

Abbreviations: vs = versus; X = test formulation 1, 2, or 3; Y = test formulation 1, 2, or 3 or reference formulation.

[a] Dosing conditions for Treatment B1 will be dependent on which Test Formulation is selected:

- If Test Formulation 3 (not tested previously) is selected as Formulation "X", the dosing condition will be either B1(a), B1(b), or B1(c).
- If Test Formulation 1 or 2 is selected as Formulation "X", the dosing condition will be either B1(b) or B1(c).

[b] This condition applies only to a scenario that further evaluates the Reference tablet formulation as Treatment B2.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. 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.

3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Prior to the first dose, participants will be assigned a unique number (randomization number), which encodes the participant's assignment to 1 of the treatment arms of the study.

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the site personnel.

Study intervention will be administered under medical supervision by either the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. Study site staff shall confirm completion of dose administration by visual inspection of each participant's mouth. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.5. Dose Modification

No modification of the dosage is planned in this study.

6.5.1. Data Review during the Study

Part A

A review of available safety and PK data will be conducted to determine the test formulation(s) to be evaluated in Part B.

This review will include data from at least 8 participants who have completed 3 consecutive doses of the study intervention in each of the 3 planned treatment groups, and who have completed protocol assessments up to Day 8.

Part B

Emerging PK data from Part A will determine the formulations to be tested as Treatments B1 and B2, as well as the conditions (fed or fasted) under which the test or reference formulations are administered. If deemed appropriate, an interim review of PK data from Treatment B1 may be conducted prior to the initiation of Treatment B2. This review will include data from at least 8 participants who have completed 3 consecutive doses of the study intervention, and who have completed protocol assessments up to Day 8.

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

There is no planned/continued intervention after the end of the study.

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than daily dose assigned through randomization will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should

- contact the medical monitor immediately.
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically, and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Concomitant Therapy

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

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

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

Participants must abstain from taking prescription or nonprescription drugs (apart from vitamin/mineral supplements and thyroid replacement medication) within 7 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/acetaminophen, at doses not to exceed 3 g/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

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

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons
- an AE that is considered to be intolerable
- an abnormal safety laboratory test result, determined to be clinically significant by the investigator, or
- QTcF >500 msec and an increase from baseline in QTcF >60 msec, from at least 2 consecutive readings.

7.1.1. Liver Chemistry Stopping Criteria

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

In study participants with normal or near normal baseline liver tests (ALT, AST, ALP <1.5x ULN), the study drug should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.5.1) if 1 or more of these conditions occur:

Elevation	Exception
ALT or AST >5x ULN	
ALT or AST >3x ULN and either TBL >2x ULN or international normalized ratio (INR) >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.

ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications

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

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

Elevation	Exception
ALT or AST >3x baseline	
ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5x baseline, when the source of increased ALP is the liver	
ALP >2x baseline and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN.
ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications

Resuming study drug after elevated liver tests

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

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 own request
- at the request of the participant's designee (for example, parents or legal guardian)
- 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 treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

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

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

Complete physical examinations and symptom-directed physical examinations will be conducted at the visits specified in the SoA (Section 1.3). Symptom-directed physical examinations may also be conducted at other visits, as determined by the investigator, if a participant presents with complaints. A complete physical examination will include, at a minimum, assessments of the CV, respiratory, GI, and neurological systems.

Height and weight will also be measured and recorded as per SoA (Section 1.3).

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3) and as clinically indicated.

Vital sign measurements should be obtained before collection of blood samples (applicable for study visits).

BP and pulse rate should be measured after at least 5 minutes in a supine position.

Note: If white-coat hypertension is suspected at screening, the participant can be included in the trial if a repeated measurement (a mean of 2 measurements) shows values within the acceptable range.

If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 2 minutes. If the participant feels unable to stand, only supine vital signs 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.

Body temperature will be measured, as specified in the SoA (Section 1.3), and as clinically indicated.

8.2.3. Electrocardiograms

Single 12-lead ECGs will be obtained as specified in the SoA (Section 1.3). ECGs must be recorded approximately within 30 minutes before collecting any blood samples (applicable for study visits). Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary to assess participants' safety. Collection of additional ECGs at a particular time point is allowed to ensure high-quality records.

ECGs will be interpreted by a qualified physician, the investigator, or qualified designee at the site as soon after the time of ECG collection as possible. Ideally, the participant should be present

- to determine whether the participant meets entry criteria at the relevant visit(s), and
- for immediate participant management, should any clinically relevant findings be identified.

All single ECGs recorded should be stored at the investigational site. Single ECGs will not be transmitted to a central laboratory.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and applicable laboratory manual.

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

8.2.5. Safety Monitoring

The Lilly clinical pharmacologist or CRP will monitor safety data throughout the course of the study.

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

- trends in safety data
- laboratory analytes
- serious and non-SAEs including monitoring of GI events, hypoglycemia, and hypersensitivity reactions and reported and adjudicated pancreatitis

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (see Appendix 6; Section 10.6), including ALT, AST, ALP, TBL, creatine kinase, and direct bilirubin, should be repeated, with addition of gamma-glutamyl transferase, 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 participants 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 participants 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 test results should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel,

history of concomitant medications (including over the counter), herbal and dietary supplements, and 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 elevation:
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 participants 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 participants 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 physical examination and a thorough medical history, as outlined earlier, as well as tests for prothrombin time-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and

- blood phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a

- hepatologist or gastroenterologist consultation
- magnetic resonance cholangiopancreatography
- endoscopic retrograde cholangiopancreatography
- cardiac echocardiogram, or a
- liver biopsy.

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

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

1. Elevation of serum ALT levels to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    a. In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevation of TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    a. In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    a. In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

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

8.2.5.2. Pancreatic Safety (Elevated Lipase or Amylase)

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with LY3493269, 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 (that is, epigastric pain radiating to the back, often associated with nausea and vomiting), and
- 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 and lipase
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal magnetic resonance imaging, and

- 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 study intervention.

Asymptomatic elevation of serum amylase and/or lipase

Serial measures of pancreatic enzyme levels have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck 2016; Steinberg et al. 2017ab). 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.

8.2.5.3. Hypoglycemia

Participants will be trained by site personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

Once a hypoglycemic event has started, the investigator should perform further bedside testing at regular intervals (for example, every 15 to 30 minutes) until normoglycemia (plasma glucose ≥70 mg/dL) is documented. If symptoms are present during the hypoglycemic event, then the end time of the hypoglycemic event should be either the time of resolution of symptoms or when normoglycemia is achieved, whichever is later.

Investigators should use the following classification of hypoglycemia based on plasma glucose measurements:

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 of absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

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

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

Nocturnal hypoglycemia:

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

To avoid duplicate reporting, all consecutive plasma glucose values ≤70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013)

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established by the investigator. The participant should receive additional education, if deemed appropriate. If applicable, please refer to the protocol section regarding management of increased hypoglycemia risks.

8.2.5.4. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom must be provided to the sponsor in the electronic CRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of generalized urticaria or anaphylaxis, additional blood samples should be collected as described in Appendix 8, Section 10.8. Laboratory results are provided to the sponsor via the central laboratory.

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

8.2.5.5. Skin Burning Sensations and Related AEs

Healthy participants in this short-exposure study may experience AEs of skin burning sensation and related AEs. Skin burning sensation and related AEs were reported in a total of 28 participants from 2 of the four Phase 1 studies. If this AE does occur within the present study, a

dedicated CRF will be used by site personnel to collect detailed information about the event on initial presentation of this AE, and on subsequent visits until the AE resolves.

In addition, on first presentation of these events, a detailed neurologic examination by a neurologist may be conducted if deemed clinically appropriate, per investigator's discretion. The goal of these activities is to describe the distribution and character of the symptoms, as well as their time course and relieving/exacerbating factors.

8.2.6. Glucose Monitoring

Blood glucose will be monitored for safety according to the SoA (Section 1.3). The study participant's blood glucose concentrations for safety assessment will be monitored during the inpatient part of the study and on Day 6, using a validated method (for example, glucose analyzer) available at the site.

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

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

- AEs
- SAEs, and
- product complaints

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study 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 up each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10.2.1.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	N/A
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	N/A
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Approximately 6 weeks after last dose. If a pregnancy is reported, the investigator should inform the sponsor and should follow the procedures outlined in Section 8.3.2	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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	

* SAEs 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

Male participants with partners who become pregnant

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

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

Female participants who become pregnant

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

Nausea, vomiting, and diarrhea events, skin burning sensations and related AEs are considered AEs of interest; each occurrence will be recorded as a discrete AE in the CRF. For each event, assessment of severity, duration (actual date together with onset and end times) and investigator's opinion of relatedness to IP and protocol procedure will be captured.

8.4. Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of study intervention as specified in the SoA (Section 1.3).

A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

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

Samples will be used to evaluate the PK of study intervention. Samples collected for analyses of study intervention plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Drug concentration information will not be reported to the site.

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of LY3493269, SNAC, and C10 will be assayed using validated liquid chromatography with tandem mass spectrometry methods.

8.4.1. Bioanalysis

Bioanalytical samples collected to measure study intervention 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 metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

8.5. Pharmacodynamics

Not applicable.

8.6. Genetics

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to the drug target and mechanism of action of LY3493269 or diabetes, obesity, and diabetic complications including NASH and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3493269 and interventions of this drug class and diabetes, obesity, and diabetic complications including NASH. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to LY3493269 or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on LY3493269, similar study interventions of this class, or diabetes, obesity, and diabetic complications including NASH continues but no longer than 15 years or other period as per local requirements.

8.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements. Exploratory biomarker measures may also include potential markers of GIP and GLP-1 receptor target engagement.

Serum and plasma samples for nonpharmacogenetic biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3493269, pathways associated with T2DM, obesity, or diabetes complications including NASH, mechanism of action of LY3493269, and/or research method, or for validating diagnostic tools or assay(s) related to T2DM, obesity, or diabetes complications including NASH.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the Site personnel.

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and/or ethical review boards impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3493269 or after LY3493269 or is commercially available.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected and stored for future analysis to determine antibody production against LY3493269. Antibodies may be further characterized for cross-reactive binding to native GIP and GLP-1. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of LY3493269.

In the case that ADA samples are tested before end of study and if the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken every 3 months until the ADA signal returns to baseline (that is, no longer TE-ADA positive) or for up to 1 year after last dose.

TE-ADAs are defined in Section 9.3.4.

A PK sample will continue to be collected at each time point at the investigator's discretion. Participants followed up for at least 1 year since last dose, whose titer has not returned to within 2-fold of the baseline, will be assessed for safety concerns. If no clinical sequelae are recognized by the clinical team, then no further follow-up will be required.

Refer to Appendix 10.1.9 for details on sample retention.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

This study will evaluate and compare PK of LY3493269 administered as multiple once-daily oral doses in heathy participants. Descriptive statistics, instead of hypothesis testing, will be used for evaluating PK and safety.

9.1.1. Multiplicity Adjustment

No adjustment or control is needed for multiple testing.

9.2. Analyses Populations

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF
Randomized/ Enrolled	All participants assigned to treatment, regardless of whether they take any doses of study treatment, or whether they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.
Safety	All enrolled participants who received at least 1 dose of LY3493269. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All enrolled participants who received at least 1 dose of LY3493269 and have at least 1 evaluating PK sample.

9.2.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study. All participants who discontinue from the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

9.2.2. Study Participant Characteristics

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

9.2.3. Treatment Compliance

At the inpatient visit, the study intervention will be administered and documented at the clinical site.

9.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes. PK analyses will be conducted on data from all participants who receive at least 1 dose of study intervention and have evaluable PK, respectively.

Safety analyses will be conducted for all randomly assigned participants who received at least 1 dose of study intervention, whether or not they completed all protocol requirements.

9.3.1. General Considerations

Data listings will be provided for all data that are databased. Summary statistics and statistical analysis will only be presented for data where detailed in the statistical analysis plan. For continuous data (for example, the demography data, clinical laboratory data, vital signs data, ECG data), summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and the number of observations; for log-normal data (for example, the PK parameters: AUC during 1 dosing interval [AUC{0-τ}] and C_{max}), the geometric mean and geometric coefficient of variation (%) will also be presented. For categorical data (for example, the AE data and hypoglycemic classification data), frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally be performed only for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the time point. Baseline is defined to be Day 1 predose measurements unless otherwise stated.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.3.2. Pharmacokinetic Analyses

9.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3493269, C10, and SNAC will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max}, AUC, and time of maximum observed concentration (t_{max}). PK parameters for C_{max} and AUC will be

computed after the first, second, and third doses. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

9.3.2.2. Pharmacokinetic Statistical Inference

PK parameters will be evaluated to estimate the relative bioavailability. Log-transformed C_{max} and AUC of LY3493269 from Treatments A1 to A3 and B1 and B2 will be evaluated in a linear mixed-effects model with a fixed effect for formulation and study day, and a random effect for subject. The estimated ratios of geometric means of different formulations compared to reference (SNAC) and the corresponding 90% CIs will be reported.

The parameter t_{max} of LY3493269, C10, and SNAC will be analyzed nonparametrically using a Wilcoxon rank sum test. Estimates of the median difference and the corresponding 90% CIs will be calculated.

All PK parameters will be summarized using descriptive statistics.

Additional analysis may be conducted if deemed necessary.

9.3.3. Safety Analyses

All safety analyses will be made on the Safety Population.

All AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with the study drug as perceived by the investigator. Symptoms reported to occur prior to the first study drug dosing will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

All SAEs will be reported.

In addition to AEs, safety parameters that will be assessed include laboratory tests, vital signs, immunogenicity, hypoglycemic events, injection-site reactions, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analyses may be performed if warranted based upon review of the data.

Laboratory measurements will be summarized regarding observed values and change from baseline by treatment group, at each time point, using descriptive statistics. In addition, all clinical chemistry, hematology, and urinalysis data outside the reference ranges will be tabulated by parameter and treatment group.

Vital signs will be summarized regarding observed values and change from baseline values by treatment at each time point using descriptive statistics. For change from baseline values, a mixed-model repeated-measure model with treatment, day (of measurement), and treatment-by-day interaction as fixed effects, participant as random effect, and baseline as covariate will be used to determine the effects of LY3493269. Least-squares means as well as 90% CIs will be reported.

9.3.4. Evaluation of Immunogenicity

Upon full assay validation, TE-ADAs may be assessed. The frequency and percentage of participants with preexisting ADA and with TE-ADA+ to LY3493269 may be tabulated.

TE-ADAs are defined as those with a

- titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA), or
- 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

The frequency of cross-reactive binding to native GIP, GLP-1, or neutralizing antibodies may also be tabulated in TE-ADA+ participants, when available.

The relationship between the presence of antibodies and PK exposures and PD response including safety and efficacy to LY3493269 may be assessed.

9.4. Interim Analysis

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

Interim access to PK and safety data is planned to occur as described in Section 6.5.1.

9.5. Sample Size Determination

Up to approximately 70 participants may be randomly assigned to study intervention to ensure approximately 10 evaluable participants from each of the 5 planned treatment groups complete the study. CCI [redacted]

Participants who are randomly assigned but not administered treatment prior to discontinuation may be replaced to ensure that the target number of participants complete the study.

Participants who discontinue early may be replaced after consultation with the investigator and sponsor. The replacement participant will be assigned to the same treatment as the discontinued participant.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulation 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 and is kept on file.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

10.1.3. 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 that 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.

10.1.4. Dissemination of Clinical Study Data

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

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation.

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.

10.1.5. 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.
- Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data 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).
- Study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

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

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

Data collected via the sponsor-provided data capture systems will be stored at third 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 relevant reports (if any) 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.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. 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, and
- 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.

10.1.8. 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.

10.1.9. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3493269 or after LY3493269 becomes commercially available T2DM.

Sample Type	Custodian	Retention Period After Last Patient Visit*
Long-term storage samples	Sponsor or designee	15 years
Pharmacokinetic	Sponsor or designee	1 year
Genetics	Sponsor or designee	15 years
Immunogenicity	Sponsor or designee	15 years

*Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the following table will be performed by the local laboratory. Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. 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.

Hematology	Clinical Chemistry (fasting)
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium, total
Mean cell hemoglobin concentration	Phosphate
Leukocytes (WBC)	Magnesium
Absolute counts of	Creatinine
Neutrophils	Glucose (fasting)
Lymphocytes	Urea
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
Platelets	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
Urinalysis	Alanine aminotransferase (ALT)
Specific gravity	Lipase
pH	Amylase
Protein	Triglyceride
Glucose	Total cholesterol
Ketones	High-density lipoprotein
Bilirubin	Low-density lipoprotein
Urobilinogen	HbA1c[a]
Nitrite	Creatine kinase
Blood	
Leukocytes	
Microscopy[b]	
	Serology (at Screening only)
	Hepatitis B surface antigen[c]
Follicle-stimulating hormone (FSH)[d]	Hepatitis B core antibody, total[c]
	Hepatitis C virus serology (anti-HCV)[c]
	Human immunodeficiency virus (HIV)[c]

Abbreviations: HbA1c = glycated hemoglobin; RBC = red blood cell; WBC = white blood cell.

[a] Predose at Day 1 only.

[b] Test only if dipstick result is abnormal and are further definable by microscopy. Microscopy to be performed at the local safety laboratory, if clinically indicated, per investigator's discretion.

[c] Tests may be waived if they have been performed within 6 months before screening with reports available for review.

[d] Performed for females at screening, if needed to confirm postmenopausal status.

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.

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Blood Volume (mL)
Screening tests[a] (local laboratory)	20	1	20
Clinical laboratory tests[a] (local laboratory)			
• Study visit: Day 1	13	1	13
• Study visits: Days 5, 8, and 15	10	3	30
• Follow-up visit: Days 29, 43	10	2	20
LY3493269 and SNAC/C10 pharmacokinetics (1 blood sample for both analytes)	3	44	132
Potential additional LY3493269 and SNAC/C10 pharmacokinetic samples	3	2	6
Blood discard for cannula patency	0.3	55	16.5
Point-of-care safety glucose (on-site)	0.3	18	5.4
Pharmacogenetic sample (stored)	10	1	10
Nonpharmacogenetic sample (stored)			
• Plasma	2	6	12
• Serum	2.5	6	15
• P800	2	6	12
Immunogenicity	10	4	40
Total			331.9
Total for clinical purposes (rounded up to the nearest 10 mL)			**340**

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 sign 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 preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

a. Results in death

b. 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. 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.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship/
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE Reporting via SAE Report

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Females of childbearing potential

Adult females are considered women of childbearing potential unless they are WNOCBP.

Females less than 18 years of age are considered women of childbearing potential if they have

- had at least 1 cycle of menses, or
- Tanner Stage 4 breast development.

Any amount of spotting should be considered menarche.

Females NOT of childbearing potential

Females are considered WNOCBP if they

- have a congenital anomaly such as Müllerian agenesis
- are infertile due to surgical sterilization, or
- are postmenopausal.

Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.

Postmenopausal state

The postmenopausal state is defined as a woman

- at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or
- aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], 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
- 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or ·
- aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

a 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.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

Female participants of childbearing potential are excluded from this study.

Female participants who are not of childbearing potential may participate in this study.

10.4.2.2. Male Participants

Male participants with partners of childbearing potential, must agree to either

1. remain abstinent (if this is their preferred and usual lifestyle), or
2. use condoms during intercourse
    a. for the duration of the study, and
    b. for approximately 5 months.

Contraception for men in exclusively same-sex relationships, as their preferred and usual lifestyle are not required.

Male participants should refrain from sperm donation for the duration of the study plus 105 days, which corresponds to approximately 5 months or until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus.

10.4.2.3. Contraception Methods

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

Methods	**Examples**
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed through hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives

	• periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post-coital douche • lactational amenorrhea

Abstinence

Participants who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) must agree to either remain abstinent without sexual relationships with the opposite sex.

10.5. Appendix 5: Genetics

Use/analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to LY3493269 or T2DM and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3493269 and/or interventions of this drug class and T2DM. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3493269 or study interventions of this class or T2DM continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

See Section 8.2.5.1 for guidance on appropriate test selection.

The sponsor-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
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
Coagulation	Copper
Prothrombin time, INR (PT-INR)	Ethyl alcohol (EtOH)
Serology	Haptoglobin
Hepatitis A virus (HAV) testing:	Immunoglobulin IgA (quantitative)
HAV total antibody	Immunoglobulin IgG (quantitative)
HAV IgM antibody	Immunoglobulin IgM (quantitative)
Hepatis B virus (HBV) testing:	Phosphatidylethanol (PEth)
Hepatitis B surface antigen (HBsAg)	**Urine Chemistry**
Hepatitis B surface antibody (anti-HBs)	Drug screen
Hepatitis B core total antibody (anti-HBc)	Ethyl glucuronide (EtG)
Hepatitis B core IgM antibody	**Other Serology**
Hepatitis B core IgG antibody	Anti-nuclear antibody (ANA)
HBV DNA[b]	Anti-smooth muscle antibody (ASMA)[a]
Hepatis C virus (HCV) testing:	Anti-actin antibody[c]
HCV antibody	Epstein-Barr virus (EBV) testing:
HCV RNA[b]	EBV antibody
Hepatitis D virus (HDV) testing:	EBV DNA[b]
HDV antibody	Cytomegalovirus (CMV) testing:
Hepatitis E virus (HEV) testing:	CMV antibody
HEV IgG antibody	CMV DNA[b]
HEV IgM antibody	Herpes simplex virus (HSV) testing:
HEV RNA[b]	HSV (Type 1 and 2) antibody
Microbiology[d]	HSV (Type 1 and 2) DNA[b]
Culture:	Liver kidney microsomal type 1 (LKM-1) antibody
Blood	
Urine	

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

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

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

[c] Not required if ASMA is tested.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.7. Appendix 7: Pancreatic Monitoring

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

To enhance understanding of the natural variability of pancreatic enzymes in the T2DM population and, to assess for any potential effects of LY3493269 on the exocrine pancreas, amylase and lipase values will be monitored in all current and future clinical trials with LY3493269.

Additional monitoring will be requested for amylase or lipase values ≥3x the ULN at any visit after randomization. Lipase and amylase values may also be obtained at any time during the clinical trials for any participant suspected of having symptoms suggestive of pancreatitis (such as severe GI signs and/or symptoms), at the investigator's discretion.

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

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3x ULN, and
- characteristic findings of acute pancreatitis on CT scan or magnetic resonance imaging.

Most participants with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back in approximately one-half of the cases. The pain is often associated with nausea and vomiting.

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

10.8. Appendix 8: Hypersensitivity Event Tests

This table lists the recommended tests that should be obtained in case of a clinically significant hypersensitivity/allergy event. Selected tests may be obtained in the event of anaphylaxis or generalized urticaria.

Anti-LY antibodies (immunogenicity)	Tryptase
LY concentration (PK)	N-methylhistamine
	Drug-specific IgE[a]
	Basophil activation test[a]
	Complements
	Cytokine panel

Abbreviations: Ig = immunoglobulin; LY = LY3493269; PK = pharmacokinetics.

[a] Basophil activation test will be performed if a drug-specific IgE assay is unavailable.

10.9. Appendix 9: Provisions for Changes in Study Conduct during Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local ethical review boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for

- participation in remote visits, as defined in Section "Remote Visits,"
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Telephone- or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, review of AEs and concomitant medications.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit are valid for a maximum of 28 days. The following rules will be applied for active, non-enrolled participants whose participation in the study must be paused due to exceptional circumstances:

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. Allowable visit interval tolerance limits are included in the SoA (Section 1.3). To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
ADA	Antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BP	Blood pressure
C10	sodium caprate
CI	confidence interval
C_{max}	maximum observed drug concentration
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
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.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
CT	computed tomography
CV	cardiovascular
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
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP	glucagon-like peptide
GZHA	Study J1X-MC-GZHA
GZHB	Study J1X-MC-GZHB
GZHC	Study J1X-MC-GZHC
GZHF	Study J1X-MC-GZHF
GZHI	Study J1X-MC-GZHI
HR	Heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
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.
IP	investigational product
IRB	institutional review board
NASH	nonalcoholic steatohepatitis
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PK/PD	pharmacokinetics/pharmacodynamics
QTcF	QT interval corrected using Fridericia's formula
RA	receptor agonist

SAE	serious adverse event
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SNAC	salcaprozate sodium
SoA	Schedule of activities
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE	treatment emergent
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.
ULN	upper limit of normal
WNOCBP	Women not of childbearing potential

11. References

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