Protocol: J1X-MC-GZHB (a)

A Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3493269 in Healthy Participants

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Title Page

Protocol Title: A Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3493269 in Healthy Participants

Protocol Number: J1X-MC-GZHB(a)

Amendment Number: (a)

Compound: LY3493269

Study Phase: 1

Short Title: A Safety Study of LY3493269 Given as Multiple Oral Doses in Healthy Participants

Acronym: GZHB

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Approval Date: Protocol J1X-MC-GZHB Electronically Signed and Approved by Lilly on 11 June 2020.
Protocol J1X-MC-GZHB Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	11 June 2020

Overall Rationale for Amendment (a):

This amendment addresses feedback from the Health Sciences Authority (HSA) Singapore. Other changes were made for clarity and consistency. This table describes the changes made for Amendment (a).

Section # and Name	Description of Change	Brief Rationale
4.3 Justification for Dose, Table 4.1	The correct version of table from the May 2020 Briefing Document has been inserted.	Addressed error with column alignments.
6.6.2 Dose-Escalation Stopping Criteria	Clarified that severe hypoglycemia will be considered a serious adverse event and added drug-related gastrointestinal effects and clinically significant cardiovascular adverse events to the dose-escalation stopping criteria.	In agreement with Health Sciences Authority comments.
Throughout the protocol	Minor editorial and formatting changes	Minor, therefore not described.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Multiple-Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3493269 in Healthy Participants

Short Title: A Safety Study of LY3493269 Given as multiple oral doses in Healthy Participants

Rationale:

LY3493269 is a dual glucose-dependent insulinotropic polypeptide and glucagon-like-peptide 1 receptor agonist being developed as a treatment for type 2 diabetes mellitus. This study of LY3493269, Study J1X-MC-GZHB (GZHB), will investigate the safety, tolerability, and pharmacokinetics of LY3493269 administered as 3 once-daily oral doses in healthy participants.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of LY3493269 following 3 once-daily oral doses in healthy participants	• TEAEs
Secondary	
• To characterize the PK of LY3493269 following 3 once-daily oral doses in healthy participants	• AUC and C_{max}

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

Overall Design

Study GZHB is a Phase 1, single-center, randomized, placebo-controlled, multiple dose, dose-escalation study in 4 planned cohorts targeting 10 healthy participants to complete in each cohort.

Disclosure Statement: This is a multiple-dose escalation study that is investigator- and participant blind.

Number of Participants:

Up to approximately 56 participants may be randomly assigned to study intervention to ensure approximately 10 evaluable participants (8 receiving LY3493269 and 2 receiving placebo) from each of the 4 cohorts complete the study.

Intervention Groups and Duration:

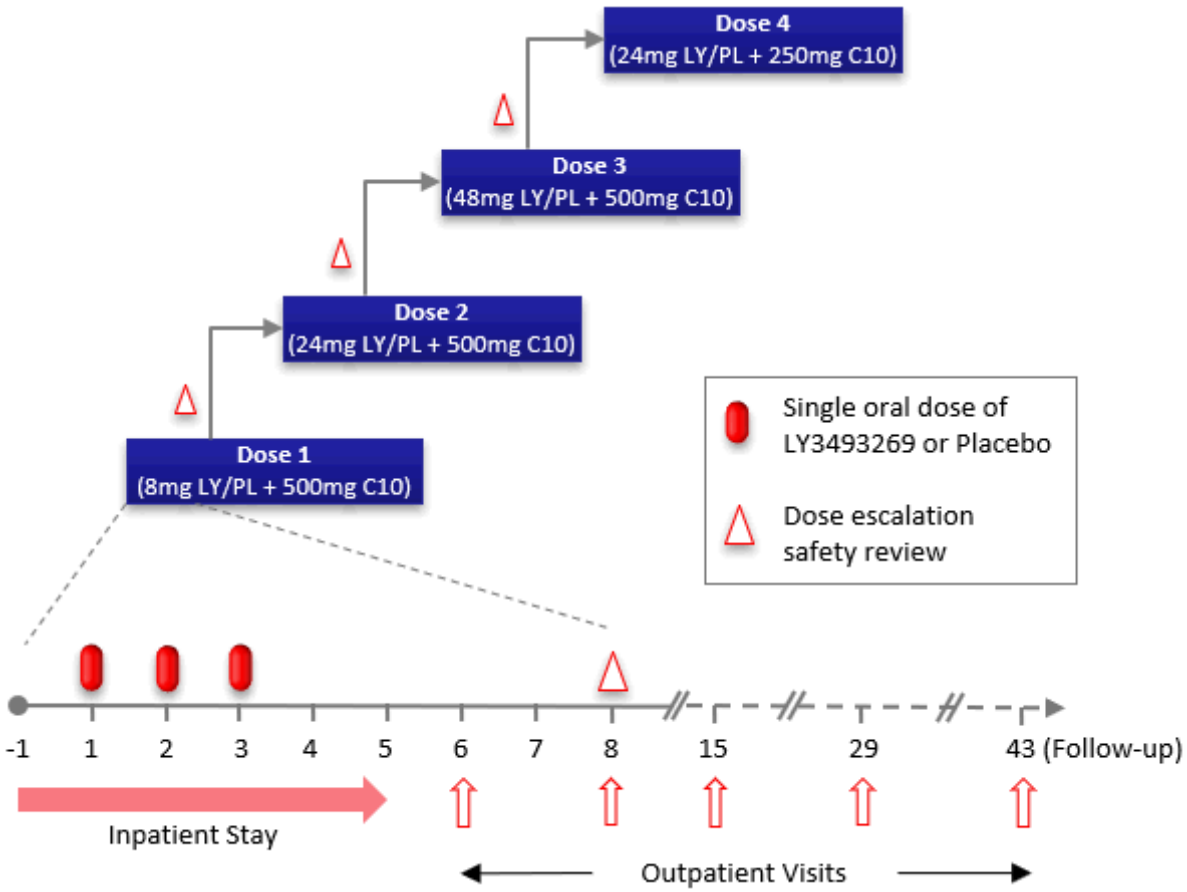
In each cohort, eligible participants will be randomly assigned to receive 3 once-daily doses of either LY3493269 or placebo (targeting 8 participants receiving LY3493269 and 2 receiving placebo).

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
- Treatment period, approximately 15 days
- Follow-up, approximately 28 days

Data Monitoring Committee: No

1.2. Schema



Abbreviations: C10 = permeation enhancer sodium caprate; LY = LY3493269; PL = placebo.

1.3. Schedule of Activities (SoA)

Study Activities	Screening	Treatment Period									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	
Study informed consent	X													
Medical history	X													
Physical examination	X													
Medical assessment			P	P	P		X	X	X	X	X	X	X	Medical review and targeted 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 6.1.1 for details
AEs/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs: supine BP/PR (h)	X		-0.5, -0.25, P, 1, 4, 6, 12	P, 1, 4, 12	-0.5, -0.25, P, 1, 4, 6, 12	X	X	X	X	X	X	X	X	
Body temperature	X		P	P	P									
ECG – single	X										X	X	X	
ECG – triplicate (h)			-0.5, -0.25, P, 1, 4, 6, 12	P, 1, 4, 12	-0.5, -0.25, P, 1, 4, 6, 12	X	X	X	X	X				
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						Days 5-6: Fasted samples collected before breakfast.
LY3493269 PK sampling (h)			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12	P, 1, 2, 3, 4, 12	P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12	X	X	X	X	X	X	X	X	Days 15, 29, 43, and ET: Samples collected anytime during visit.
C10 PK sampling (h)			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12	P, 1, 2, 3, 4, 12	P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12	X	X							

Study Activities	Screening	Treatment Period									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	
PD biomarkers (fasted) • Glucose, Insulin, and C-peptide			P		P		X		X	X	X			
Triglycerides – (fasted)			P		P		X		X	X	X			
Appetite VAS – (fasted)			P	P	P		X		X	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 at any time on Day 1.
Nonpharmacogenetic 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); h = hour; HR = heart rate; min = minutes; P = predose; PD = pharmacodynamics; PK = pharmacokinetics; PR = pulse rate; VAS = visual analog scale.

Notes: 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.

For vital signs and triplicate 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.

Pharmacokinetic and immunogenicity samples are not required at ET for participants who discontinue without receiving study intervention.

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 up to and including 24 hours should be performed within ±10% of the scheduled time, and
- postdose assessments and procedures scheduled after the 24-hour time point should be performed within ±3 hours of the scheduled time.

2. Introduction

2.1. Study Rationale

LY3493269 is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide 1 (GLP-1) receptor agonist being developed as a treatment for type 2 diabetes mellitus (T2DM). In addition to subcutaneous (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 (BG) goals. This study of LY3493269, Study J1X-MC-GZHB (GZHB), will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3493269 administered as multiple once-daily oral doses in healthy participants.

2.2. Background

Type 2 diabetes mellitus is characterized by impaired glycemic control due to insulin resistance and inadequate insulin secretion due to the pancreatic beta-cell failure. Type 2 diabetes mellitus 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 BG levels to augment endogenous glucose production. It stimulates lipolysis and inhibits insulin-induced lipogenesis in human adipocytes.

Glucagon-like peptide-1 is a well-characterized incretin hormone that potentiates insulin secretion and reduces glucagon secretion in a glucose-dependent manner after meal ingestion. Glucagon-like peptide-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 (GLP-1Rs) are expressed throughout the brain, in regions that control

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

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

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

The LY3493269 oral formulation in Study GZHB will include a permeation enhancer (sodium caprate, C10), to enable oral absorption of the LY3493269 peptide. As peptides are otherwise poorly absorbed orally, an enabling excipient such as C10 in an oral enteric-coated capsule

formulation is expected to transiently increase local permeability (Twarog et al. 2019) in the small intestine and result in increased oral bioavailability for therapeutic use.

2.2.1. Summary of Clinical Experience

Study J1X-MC-GZHA (GZHA) was a first-in-human, randomized, placebo-controlled, single-ascending dose (SAD) study investigating the safety, tolerability, and PK of LY3493269 administered as single SC doses in healthy participants. In addition, a cohort of 6 healthy participants was planned to receive a single intravenous dose of LY3493269, to allow estimation of the absolute SC bioavailability of LY3493269.

As of 06 April 2020, 3 cohorts of 6 participants received SC doses of LY3493269 at each of the 0.15-, 0.5-, and 1.5-mg dose levels. There was an increase in the number of adverse events (AEs) (such as nausea, vomiting, and abdominal distension) related to the study drug with increasing doses of LY3493269 as compared to placebo. The top dose of 1.5 mg was considered not well tolerated due to increases in the number of GI events requiring treatment. The prespecified dose-escalation stopping criteria were not met; however, due to concerns about safety and tolerability with the next planned SC dose of 3 mg, the sponsor decided to stop further dosing.

No deaths, serious adverse events (SAEs), or discontinuations due to AEs were noted in this study up to the data cut-off, 06 April 2020.

Of the 30 healthy participants who received either LY3493269 or placebo, 26 (86.7%) reported at least 1 treatment-emergent adverse event (TEAE).

Consistent with the incretin class, GI events such as abdominal distension, nausea, vomiting, and diarrhea were the most commonly reported AEs in Study GZHA. In addition, decreased appetite was also 1 of the most frequently reported AEs. All TEAEs were considered as mild in severity by the investigator, even though some required treatment. In Cohort 2, where subjects received 0.5 mg, 1 subject out of 6 presented nausea, and none presented vomiting. However, 3 subjects out of 6 in Cohort 3 receiving 1.5 mg reported GI AEs of nausea and vomiting, requiring anti-emetics. Several other GI AEs were reported in Cohort 3 (for example, abdominal pain upper, constipation, eructation, epigastric discomfort, dry mouth, and dyspepsia) not previously reported in the other cohorts.

No clinically significant changes in laboratory data, no injection-site reactions, or severe hypoglycemia events were noted.

A dose-dependent increase in heart rate (HR), which is consistent with the incretin class (Lorenz et al. 2017), was noted. While no clinically significant changes were noted in electrocardiogram (ECG) results, 3 participants in Cohort 3 (1.5 mg) presented mild AEs of tachycardia. No significant changes in the blood pressure (BP) measurements were noted. The maximum HR (supine) for all 3 participants occurred at 4 hours postdose; the HR for these 3 participants returned to below 100 bpm between 6 hours and Day 3 postdose.

Six participants received the 0.5-mg intravenous dose as planned. Mild events of decreased appetite and GI events such as abdominal distension and nausea were noted.

Preliminary PK data from the SC route indicated the median time of maximum observed drug concentration (t_{max}) CCI [redacted], close to proportional increase in exposures with increasing dose and a half-life CCI [redacted], which is suitable for a weekly dosing interval.

Preliminary pharmacodynamic (PD) data suggest LY3493269 when administered SC may potentially reduce total body weight, appetite, and glucose concentrations during an oral glucose tolerance test.

Refer to the Investigator's Brochure (IB) for more information about the nonclinical and clinical data of LY3493269.

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 Study GZHA, similar findings were observed, which include

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

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 in any of the toxicology studies/assessments.

Based on the nonclinical studies, 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, and weight loss.

All identified risks from the nonclinical and clinical studies are considered monitorable and manageable at the planned oral dose range of 8 to 48 mg once daily of LY3493269. To further minimize any potential risk, participants will remain at the clinical research unit (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 investigate the safety and tolerability of LY3493269 following 3 consecutive once-daily oral doses in healthy participants	• TEAEs
Secondary	
• To characterize the PK of LY3493269 following 3 consecutive once-daily oral doses in healthy participants	• AUC and C_{max}
Exploratory	
• To investigate the PD effects of LY3493269 following 3 consecutive once-daily oral doses in healthy participants	• Changes from baseline levels of fasting glucose, insulin, C-peptide, triglycerides, and body weight
• To assess PK of C10 following oral administration in healthy participants	• AUC and C_{max}
• To explore the effect of LY3493269 on appetite and food intake following 3 consecutive once-daily oral doses in healthy participants	• Change in VAS score for appetite assessment in a fasted state
• To characterize immunogenicity of LY3493269 following 3 once-daily oral doses in healthy participants	• Incidence of treatment-emergent ADA

Abbreviations: ADA = antidrug antibody; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TEAE = treatment-emergent adverse event; VAS = visual analog scale.

4. Study Design

4.1. Overall Design

Study GZHB is a Phase 1, single-center, randomized, placebo-controlled, multiple dose, dose-escalation study in 4 planned cohorts of up to 14 healthy participants randomly assigned in each cohort.

This study will evaluate the safety, tolerability, and PK of 3 consecutive once-daily oral doses of LY3493269. In addition, the PD effects of LY3493269 on fasting glucose, insulin, triglycerides, and appetite will be explored following the 3 consecutive oral once-daily doses of LY3493269.

In each cohort, up to 14 participants may be randomly assigned to achieve 10 completers with 8 participants receiving LY3493269 and 2 participants assigned to receive placebo. 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.

This is an investigator- and participant-blind study; the sponsor is not blinded.

Study randomization shall occur after confirmation of eligibility.

The planned LY3493269 oral doses for this study range from 8 to 48 mg (Section 1.2), administered in the 4 planned "dose cohorts":

- Cohort 1: 8 mg LY3493269 (with 500 mg C10)
- Cohort 2: 24 mg LY3493269 (with 500 mg C10)
- Cohort 3: 48 mg LY3493269 (with 500 mg C10)
- Cohort 4: 24 mg LY3493269 (with 250 mg C10)

Cohorts 1 to 3 evaluate doses of LY3493269 from 8 to 48 mg, each dose in combination with 500 mg C10. Cohort 4 evaluates a 24-mg dose of LY3493269 with half the amount (250 mg) of C10.

The LY3493269 dose levels may be adjusted (for example, dose increments may be reduced, a dose level may be repeated, or a lower/intermediate dose may be administered) based on ongoing review of available safety, tolerability, PK, and PD data (Section 6.6). Any proposal to adjust doses from those planned and stated in the protocol, together with supporting data, will be reviewed by an independent Safety Review Panel (SRP).

Participants will undergo safety (including but not limited to AEs, medical assessments, clinical laboratory tests, body weight, vital signs, and ECGs), PK, and PD assessments according to the Schedule of Activities (Section 1.3).

Safety data including, but not limited to AEs, clinical laboratory tests, vital signs, ECGs, body weight, hypoglycemic events, and VAS assessments up to Day 8 from at least 8 participants who have received study intervention will be reviewed jointly by the principal investigator and sponsor before a joint decision is made to escalate to the next planned dose level.

4.1.1. Screening Period

The outpatient screening visit may be up to 28 days prior to enrollment. Individuals who are not enrolled within 28 days of screening may be subjected to an additional medical assessment

and/or clinical measurements to confirm their eligibility. Parameters that may be repeated for screening include clinical laboratory tests, ECGs, and vital signs.

4.1.2. Treatment Period

Study participants will be admitted to the CRU on Day -1 and adhere to an overnight fast.

Participants will be randomly assigned to treatment, followed by dosing while inpatient at the CRU. Participants will receive 3 consecutive once-daily doses of either LY3493269 or placebo Days 1 through 3. Fasting requirements including food and water restrictions must be adhered to for each dose administered (Section 6.1.1). Participants should complete the study assessments and procedures planned during this period as specified in Section 1.3. Unless the investigator identifies a safety concern, participants may be discharged from the CRU on Day 5.

Pharmacokinetic and PD sampling and safety assessments will be performed according to the Schedule of Activities (Section 1.3). Pharmacokinetic and PD sampling schedules may be modified based on the available safety and PK/PD data.

4.1.3. Outpatient Visits (Days 6, 8, and 15)

Participants will return to the CRU for outpatient visits on Days 6, 8, and 15, for safety assessments and PK and/or PD sampling at the times specified in the Schedule of Activities (SoA) (Section 1.3). Participants may remain as needed at the CRU for safety monitoring based on the investigator's judgment or to facilitate participant compliance.

4.1.4. Follow-Up Visits (Days 29 and 43)

During the follow-up period, participants should attend the outpatient visits on Days 29 and 43. The study assessments and procedures planned during this period should be performed as specified in Section 1.3.

Participants who received study intervention and who discontinue early will be encouraged to return for an early termination visit with procedures performed as shown in the SoA (Section 1.3) and a follow-up visit for safety monitoring, including but not limited to 28 days after study intervention. Enrolled participants who discontinue without study intervention will not be required to attend the early termination visit.

Participants will be discharged from the study after the investigator has completed review of all final safety assessments from the last follow-up visit.

4.2. Scientific Rationale for Study Design

A population of healthy participants is selected to assess the safety and tolerability of LY3493269 for initiation of oral administration in humans prior to further investigations in patients with T2DM. Using a healthy participant population mitigates possible confounding effects of comorbidities and concomitant medications. Therefore, Study GZHB provides an unbiased assessment of safety, tolerability, and PK of LY3493269 administered as oral doses.

The study is intended to estimate a maximum tolerated exposure or establish that exposures exceeding the expected therapeutic range are tolerated via the oral route of administration. Additionally, the study will inform the target exposure range for subsequent oral dosing of

LY3493269. Safety, tolerability, PK, and preliminary PD data will assist in identifying an appropriate dose range for subsequent clinical studies regardless of administration route.

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 the SC SAD study (GZHA) should be applicable to this study.

To predict the oral PK profiles for each cohort, 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 cohort to remain above the quantification limit of 2 ng/mL to yield meaningful PK results. The PK data from Study GZHA estimated the LY3493269 half-life to be approximately CCI . 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 across all dose levels, including incidence of nausea and/or vomiting, and evaluation of ECGs and vital signs conducted during the study (Section 8.2). A preliminary assessment of the PD effects of LY3493269 will be based on the concentrations of fasting glucose, insulin, and triglycerides up to Day 29 postdose. The effect of LY3493269 on appetite sensations will also be explored. The decision to escalate the dose will be based primarily on safety and tolerability data (Sections 6.6.1 and 6.6.2) and all available PK data will also be reviewed.

4.3. Justification for Dose

The proposed LY3493269 oral dose range CCI mg once daily is selected to attain steady-state exposures anticipated to be within the range equivalent to the Phase 3 dose range CCI of another GIP-GLP molecule currently in Phase 3 development (tirzepatide). The equivalent LY3493269 oral doses are predicted to be between CCI once daily assuming CCI oral bioavailability. Dose equivalents between the 2 molecules were estimated using their preclinical potency ratios for glycemic control and weight loss derived from rodent species. If actual LY3493269 oral bioavailability is only half of the assumed, i.e. CCI then exposures from these doses would also be approximately halved. If oral bioavailability is CCI the anticipated average exposures of the first cohort of 8 mg once daily x 3 days are expected to be within exposures of the CCI dose.

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), Cohort 4 is intended to assess if half the amount (250 mg) of C10 can yield comparable oral bioavailability as 500 mg of C10 at the same 24-mg dose of LY3493269.

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. The margin of safety of oral administered LY3493269 with C10 or C10 alone derived from 1-month repeat-dose toxicity studies is listed in Table 4.1 and Table 4.2.

In conclusion, the safety pharmacology and toxicity assessment of oral administered LY3493269 did not reveal any adverse findings in animals. The nonclinical safety data support the proposed Phase 1 study for an oral formulation of LY3493269.

CCI

CCI

CCI

[redacted]

CCI

[redacted]

4.4. End of Study Definition

A participant is considered to have completed the study if they have 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 must 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 re-screened.

5.1. Inclusion Criteria

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

Participant Characteristics

1. Are male or female not of childbearing potential from 21 to 65 years of age inclusive, at the time of signing the informed consent.

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

2. Body mass index within the range of 19.0 to 40.0 kg/m^2 (inclusive).

Type of Participant and Disease Characteristics

3. Participants who are healthy as determined through medical evaluation including screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.
4. 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.
5. Have glycated hemoglobin level of <6.5%.
6. Have venous access sufficient to allow blood sampling as per the protocol.
7. 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.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. 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)
2. Have a significant history of or current CV (for example, myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism, etc.), respiratory, renal, GI, 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 investigational product (IP); or of interfering with the interpretation of data
3. Have a supine HR less than 50 bpm or greater than 100 bpm. If a repeat measurement shows values within the range, the participant can be included in the trial.
4. 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 (excluding white-coat hypertension); therefore, if a repeated measurement shows values within the range, the patient can be included in the trial.
5. Have undergone any form of bariatric surgery.
6. Have a history of GI bleeding or duodenal ulcers.
7. Have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2.
8. Have a history of acute or chronic pancreatitis, or elevation in serum lipase and/or amylase levels greater than 1.5 times the upper limit of normal (ULN).
9. Have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis.
10. Have evidence of significant active neuropsychiatric disease as determined by the investigator.

Prior/Concomitant Therapy

11. 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®)

12. 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)
13. Intend to use over-the-counter or prescription medication within 7 or 14 days, respectively, prior to planned dosing (apart from vitamin/mineral supplements, occasional paracetamol, and thyroid replacement medication) and throughout the study period. If this situation arises, inclusion of an otherwise suitable participant may be at the discretion of the investigator and sponsor.

Prior/Concurrent Clinical Study Experience

14. 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
15. 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

16. 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 QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for females, short PR interval (<120 msec), or PR interval >220 msec, second and third atrioventricular block, intraventricular conduction delay with QRS >120 msec, right bundle branch block, left bundle branch block or Wolff-Parkinson-White syndrome.
17. Have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5X ULN or total bilirubin level (TBL) >1.5X ULN.
18. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
19. Show evidence of hepatitis C and/or positive hepatitis C antibody.
20. Show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen.

Other Exclusions

21. Are CRU personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling

22. Are Lilly employees.
23. Have previously completed or withdrawn from this study.
24. Have donated blood of more than 450 mL, or have participated in a clinical study that required similar blood volume drawn within the past 3 calendar months.
25. Are women who are lactating.
26. Have known allergies to LY3493269, related compounds, or any components of the formulation (including C10), or a history of significant atopy.
27. Regularly use known drugs of abuse.
28. 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 (Section 5.3.2) (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).
29. Smoke >10 cigarettes per day or the equivalent, or are unable or unwilling to refrain from nicotine during CRU admission.
30. Are unwilling to comply with the dietary restrictions required for this study.
31. 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

Participants will be required to fast overnight for at least 8 hours before taking each dose of LY3493269 (or placebo) on Days 1, 2, and 3 and for each subsequent study day when clinical safety laboratory and PD samples are taken.

Each study intervention dose is taken with 120 mL of water. Any additional water required by the participant to complete the dose must be recorded in the case report form (CRF). After each daily dose, participants must continue to fast for 2 hours before receiving a standard meal. Water ad libitum is allowed only until 1 hour before dosing and following the 2-hour postdose fast.

Throughout the inpatient period, standard meals will be administered in the CRU. While not resident in the CRU, participants will be encouraged to follow their normal diet.

5.3.2. 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 [28]).

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

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention.

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 cohorts, but were not randomized for nonmedical reasons, may be reassessed. Additional medical assessments and clinical measurements include clinical laboratory tests, vital signs, and ECG to confirm their eligibility.

Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

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

Intervention Name	LY3493269	Placebo
Type	Drug	Drug
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	Experimental, supplied as 4 dose strengths: • 4 mg LY + 250 mg C10 • 12 mg LY + 250 mg C10 • 24 mg LY + 250 mg C10 • 36 mg LY + 250 mg C10	Not applicable for placebo
Dose Levels	Each dose described below is administered once daily over 3 consecutive study days. • Cohort 1, 8-mg dose: 2 capsules of 4 mg LY+250 mg C10 • Cohort 2, 24-mg dose: 2 capsules of 12 mg LY+250 mg C10 • Cohort 3, 48-mg dose: 2 capsules of 24 mg LY+250 mg C10 • Cohort 4, 24-mg dose: 1 capsule of 24 mg LY+250 mg C10	Each dose described below is administered once daily over 3 consecutive study days. • Cohort 1: 2 capsules • Cohort 2: 2 capsules • Cohort 3: 2 capsules • Cohort 4: 1 capsule
Route of Administration	Oral, after a minimum fast (no food) of 8 hours prior to each dose, followed by a 2-hour fast (no food/water) after each dose.	Oral, after a minimum fast (no food) of 8 hours prior to each dose, followed by a 2-hour fast (no food/water) after each dose.
Use	Experimental	Placebo

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	Placebo will be provided in bottles. Each bottle will be labeled as required per country requirement

Abbreviations: IMP = investigational medicinal product; LY = LY3493269.

6.1.1. Administration Details

Enteric-coated capsules of either LY3493269 or placebo will be administered orally with approximately 120 mL of room temperature water in the morning of each dosing day in a sitting position. After each daily dose, participants must continue to fast for 2 hours before receiving a standard meal. Water ad libitum is allowed only until 1 hour before dosing and following the 2-hour postdose fast.

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

6.2. Preparation/Handling/Storage/Accountability

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

Only participants enrolled in the study may receive study interventions and only authorized site staff may supply or administer study interventions. 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 site staff.

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

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Method of Treatment Assignment

Randomization tables for allocation of either LY3493269 or placebo to participants will be prepared by the statistician for the study and provided to the unblinded site pharmacists involved in dose preparation. Prior to or on Day 1, eligible participants will be assigned a unique number

(randomization number). The randomization number encodes the participant's assignment to 1 of the 2 arms of the study, according to the randomization schedule.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. Unblinded site pharmacists will be responsible for the dispensing of all study interventions. The allocation and dispensing of the study interventions will be fully documented and verified by a second person. Detailed records of the amounts of the study intervention received, dispensed, and remaining at the end of the study will be maintained by the site pharmacist(s).

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site to verify that randomization/dispensing has been done accurately.

6.3.2. Selection and Timing of Doses

For each study participant, the doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the participant's CRF.

6.3.3. Unblinding

Emergency codes will be available to the investigator to be retained by the investigator (or designee) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the sponsor.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician (CRP) for the participant to continue in 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 study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. 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.

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 (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) 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.

Nausea and/or vomiting during this study may be treated with antiemetics but these medications should not be used prophylactically.

Paracetamol/acetaminophen, at doses of ≤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.

6.6. Dose Modification

Considerations for discontinuation of study intervention in an individual participant are described in Section 7.1.

Dose levels or increments, sampling schedule, and length of stay at the CRU may be adjusted in view of emerging safety, tolerability, or PK/PD data during the study.

If considered appropriate,

- dose increments for LY3493269 may be reduced, a dose level may be repeated, or a lower/intermediate dose may be administered, but dose escalations will not exceed a half-log (3.3-fold) increase in dose.
- the timing of the sampling may be adjusted and additional samples may be collected, as described in Section 8.5, and
- the duration of the CRU stay or the duration of safety follow-up may be increased (for example, if the half-life of LY3493269 is longer than anticipated) but not decreased.

These changes must be appropriately documented and communicated by the sponsor to the investigator. Because these adjustments to timings or dose levels are allowable changes permitted by the protocol, they would not require a protocol amendment. However, any changes to the planned dose levels, together with the supporting data, will be reviewed by an SRP, composed of members independent of the study team and CRU.

6.6.1. Dose Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the maximum tolerated dose is determined or when stopping criteria are met. The highest dose level that is tolerated will be designated as the maximum tolerated dose for 3 consecutive oral doses in healthy participants. Interim access to study data is scheduled to occur during the study to inform dose-escalation decisions, as specified in Section 6.6.3.

Safety data will be the primary criteria for the dose escalation. In addition, if available at the time of dose-escalation decision, PK and/or PD results if available, may be used as supporting data for dose escalation, but such data are not required. All available PK data and PD results, from Cohort 1 will be reviewed prior to initiation of Cohort 3. No dose decision can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist.

Prior to dose escalation, all planned participants in the current cohort should have been dosed prior to escalation to next cohort. The investigator and sponsor must review safety and tolerability data up to study Day 8 from at least 8 participants receiving study intervention at the current dosing level, including but not limited to ECGs, clinical laboratory tests, vital signs, body weight, appetite VAS scores, and AEs. After review of these data, an escalation to the next dose level will be jointly decided by the investigator and sponsor. The magnitude of dose escalation may be reduced following data review, but subsequent escalations cannot be increased by more than approximately 3.3-fold (a half-log increment); dose levels may be repeated if warranted following data review.

Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the study intervention unless there is clear evidence that the event is not related.

6.6.2. Dose-Escalation Stopping Criteria

If any of the following scenarios occur, dosing at the current level and further dose escalation will be discontinued:

1. One treatment-emergent SAE (including severe hypoglycemia) believed to be associated with LY3493269 (see Section 8.2.6.1);
2. One or more participants on active drug experience 2 or more clinically significant events deemed related to LY3493269, defined as moderate to severe AE, abnormal clinical signs, or clinical laboratory findings that may pose a risk to the well-being of the participant and would preclude further dosing of a participant who experiences this effect.. Clinically significant events will be determined by the investigator or suitable designee and may include findings that do not fulfill the criteria for SAEs;
3. Forty percent or more of participants in a dose level experience any of the following deemed related to LY3493269 administration:
    - a symptomatic hypoglycemic episode with BG values ≤2.8 mmol/L (50 mg/dL; corresponding to plasma glucose (PG) levels of ≤3.1 mmol/L [56 mg/dL]), or
    - drug-related GI effects (for example emesis, diarrhea) causing severe distress (prevents daily activities or requires an emergency department visit or hospitalization), or

- clinically significant cardiovascular AEs

4. Two or more participants on active drug develop persistent (>1 week) symptoms suggestive of acute pancreatitis. Refer to algorithm for the monitoring of asymptomatic hyperenzymemia in Section 10.7.

6.6.3. Data Review during the Study

Interim access to safety and tolerability (and any available PK and PD) data is scheduled to occur after every dosing session as described in Section 4. This schedule may be modified as applicable, based on emerging safety and/or tolerability data. The purpose of these reviews is to guide dose selection for the next dosing cohort.

The investigator and the Lilly sponsor team will jointly make the determination regarding dose escalation, based upon their review of the safety and tolerability data, and PK or PD results if available. In addition, these data may be used to guide dose selection and inform the need to adjust timing of procedures/sampling schedules for the current study.

An SRP will be established and composed of experts in early phase medicine independent of the study team and CRU. Any changes to the planned dose levels, together with the supporting data, will be reviewed and approved by the SRP.

6.7. Intervention after the End of the Study

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for appropriate safety monitoring. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Discontinuation of study intervention should be considered by the investigator if any of the following occur in a participant:

- 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.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Hepatic Criteria for Discontinuation

Discontinuation of the study intervention for abnormal liver test results should be considered by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

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

Participants who discontinue from study intervention due to the abnormal liver test results will undergo monitoring as described in Section 10.6.

Discontinuation of the study intervention due to abnormal laboratory results should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the sponsor-designated medical monitor:

- lipase and/or amylase ≥3X ULN (Section 10.7 should be considered by the investigator).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, and
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The replacement strategy for discontinued participants is described in Section 9.2. If deemed appropriate by the investigator, early discontinuation procedures will be performed as shown in the SoA (Section 1.3).

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from using the study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is

medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with IP. Safety follow-up is as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

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 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.

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions related to eligibility criteria are not allowed.

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.

Assessment collection time

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

If multiple procedures take place at the same time point, ECGs and vital signs must be obtained prior to any venipuncture.

Section 10.2 lists the laboratory tests that will be performed for this study.

Section 10.2.1 provides a summary of the anticipated number and volume of invasive samples, for all sampling, during the study.

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

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 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

- cardiovascular
- respiratory
- gastrointestinal, and
- neurological systems.

Height and weight will also be measured and recorded.

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.

Blood pressure and PR 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 (up to 2 additional assessments) 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 and triplicate 12-lead ECGs will be obtained as specified in Section 1.3. Electrocardiograms must be recorded approximately within 30 minutes before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

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

Electrocardiograms will be interpreted by a qualified physician, the investigator, or qualified designee at the site as soon after the time of ECG collection as possible. 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.

The machine-read ECG intervals and HR may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

Single electrocardiograms

Single ECGs will be collected at screening, at early termination, and follow-up on Days 29 and 43 according Section 1.3. Single ECGs may be obtained at additional times when deemed clinically necessary to assess participants' safety. All single ECGs recorded should be stored at the investigational site. Single ECGs will not be transmitted to a central laboratory.

Triplicate electrocardiograms

Triplicate 12-lead ECGs will be obtained as specified in Section 1.3.

Collection of more ECG replicates than expected at a certain time point will be permitted to ensure high-quality records. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

Scheduled and unscheduled digital ECGs will be electronically transmitted to a central ECG laboratory designated by the sponsor. The central ECG laboratory will perform a basic quality control check, for example, demographics and study details, then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. 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 Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly 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, injection-site reactions, 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 (Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

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, 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 patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms[a], or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

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

[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 computed tomography [CT] scan).

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

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

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

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

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

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

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    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)
- 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
- 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.

8.2.5.3. Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea events 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.

8.2.5.4. 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 should be provided to the sponsor in the electronic case report form (eCRF).

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

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

8.2.6. Glucose Monitoring

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

8.2.6.1. Hypoglycemia

Site personnel will collect information on episodes of hypoglycemia at each study visit according to the SoA. Participants will be trained by site personnel about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia. Site personnel will enter this information into the eCRF at each visit.

Investigators should use the following definitions and criteria while diagnosing and categorizing an episode considered to be related to hypoglycemia.

Note: The PG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma equivalent glucose meters and strips (ADA 2019)

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a PG level of ≤70 mg/dL (≤3.9 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a PG level of <54 mg/dL (<3.0 mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG <54 mg/dL (<3.0 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG <54 mg/dL (<3.0 mmol/L).

Severe hypoglycemia (Level 3):

- **Severe hypoglycemia** is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

Other hypoglycemia categories:

- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

If a hypoglycemic event meets the criteria of severe, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

To avoid duplicate reporting, all consecutive PG 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.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following

up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow-up visit or participation in study has ended.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving study intervention, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias while detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.7), 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). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the investigator to the sponsor 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, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., 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.

8.3.5. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until at least 5 terminal half-lives after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Events or Outcomes

Not applicable.

8.3.7. Adverse Events of Special Interest

Adverse events of special interest for this program include

- CV events
- GI events
- hypersensitivity reactions, and
- hypoglycemic events.

Each occurrence will be recorded as a separate AE in the CRF. For each event assessment of severity, duration (actual date, time of onset, and end times), and investigator's opinion of relatedness to study intervention and protocol procedure will be captured.

8.3.8. Product Complaints

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 trial intervention.

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

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Sections 8.3.3 and 10.3 of the protocol.

8.3.8.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug/device is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug/device provided for the study, the investigator will promptly notify the sponsor.

8.3.8.2. Prompt Reporting of Product Complaints to the Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the sponsor by the method provided in the form. If the primary method is unavailable, then an alternative method provided in the form should be utilized.

8.3.8.3. Follow-up of Product Complaints

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, any dose of LY3493269 greater than the daily dose assigned through randomization will be considered an overdose. Treatment for overdose is supportive care.

In the event of an overdose, the investigator should

1. contact the medical monitor immediately.
2. closely monitor the participant for any AE/SAE and laboratory abnormalities until LY3493269 can no longer be detected systemically, and
3. document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant. Refer to the LY3493269 IB for more information about treatment of overdose.

8.5. Pharmacokinetics

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

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 (e.g., 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 that would unblind the study will not be reported to CRUs or blinded personnel until the study has been unblinded.

8.5.1. Bioanalysis

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

Concentrations of LY3493269 and C10 will be assayed using validated liquid chromatography with tandem mass spectrometry methods. Analyses of samples collected from placebo-treated participants are not planned.

Bioanalytical samples collected to measure IP 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.

8.6. Pharmacodynamics

8.6.1. Body Weight

Weight will be measured as indicated in the SoA (Section 1.3). Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will not be moved or recalibrated.

Participants will be weighed in light clothing at approximately the same time in the morning before dosing (on Day 1 only) and after an overnight fast and evacuation of bowel and the bladder, if possible. Weight will be measured twice on each scheduled occasion, with the participant stepping off the scale between measurements. The mean of the 2 weight measurements will be recorded in the source document and the CRF.

8.6.2. Appetite Analysis

To explore the effects of LY3493269 on meal intake and appetite sensation, participants will be asked to rate their appetite sensations using a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption prior to dosing on Day 1, and in the fasted state while

inpatient as well as on scheduled outpatient visits. These measurements shall be performed according to the SoA (Section 1.3).

The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000). The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually “extremely” and “not at all”. Participants are required to rate their subjective sensations on four 100-mm scales combined with questions similar to the following:

1. “How hungry do you feel?”
2. “How satisfied do you feel?”
3. “How full do you feel?”
4. “How much do you think you could eat?”

A staff member will use a caliper to measure the distance from 0 to the mark that the participant placed on the VAS and record the measurement in the source document. Overall appetite score is calculated as the average of the 4 individual scores: satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4 (van Can et al. 2014). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

8.6.3. Pharmacodynamic Markers

Samples for PD markers will be collected at the times specified in Section 1.3.

Fasting serum samples for glucose, insulin, and C-peptide will be evaluated as PD markers.

Fasting lipids (triglycerides only) will be evaluated as exploratory mechanistic markers.

Plasma and serum concentrations of these markers will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

The samples will be stored for up to a maximum of 1 year after the last participant visit for the study at a facility selected by the sponsor.

8.7. Genetics

A blood sample for DNA isolation will be collected from participants.

See Section 10.5 for information regarding genetic research and Section 10.1.9 for details about sample retention and custody.

8.8. 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 include potential markers of GIP and GLP-1R 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 nonalcoholic steatohepatitis (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 CRU 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 ERBs 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.

8.9. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected for 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.

Treatment-emergent-antidrug antibodies (TE-ADAs) are defined in Section 9.4.6. In the case that antidrug antibody (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 and if available, the ADA cross-reactively binds to native GIP and GLP-1, additional samples may be taken every 3 months until the ADA signal returns to baseline (i.e. no longer TE-ADA positive) or for up to 1 year after last dose.

A PK sample will continue to be collected at each time point at the investigator's discretion. Participants followed 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.

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the IP. Any samples remaining after 15 years will be destroyed.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

This study will compare LY3493269 with placebo in healthy adults. The primary study objective is to determine the safety and tolerability of multiple oral doses of LY3493269.

9.2. Sample Size Determination

The sample size is customary for Phase 1 studies evaluating safety and PK and is not powered on the basis of statistical hypothesis testing.

Up to approximately 56 participants may be randomly assigned to study intervention to ensure approximately 10 evaluable participants (8 receiving LY3493269 and 2 receiving placebo) from each of the 4 cohorts complete the study. Participants who are randomized 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.

9.3. Populations for Analyses

The following populations are defined:

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

9.3.1. Study Participant Disposition

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. A detailed description of participant disposition will be provided at the end of the study.

9.3.2. 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.

9.3.3. Treatment Compliance

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

9.4. 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 (SAP) 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.

The SAP will be finalized prior to first patient 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.

Pharmacokinetic and PD analyses will be conducted on data from all participants who receive at least 1 dose of study intervention and have evaluable PK and PD, respectively.

Safety analyses will be conducted for all enrolled participants who received study intervention, whether or not they completed all protocol requirements.

9.4.1. 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 SAP. For continuous data (e.g. the demography data, clinical laboratory data, vital signs data, ECG data, appetite analysis data, and PD data), summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and the number of observations; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [AUC] during 1 dosing interval [AUC{0-τ}] and maximum observed drug concentration [C_{max}]), the geometric mean and geometric coefficient of variation (%) will also be presented. For categorical data (e.g., 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 pre-dose measurements unless otherwise stated.

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

9.4.2. 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% confidence intervals (CIs) will be reported.

Electrocardiogram parameters will be summarized, including the PR, QT, RR, and QTcF intervals, QRS duration, and HR. A concentration-response analysis will also be performed to assess the effect of LY3493269 on QTcF. Additional analyses may be performed to determine the effects of PK and PD parameters on QTcF and other intervals.

9.4.3. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for LY3493269 and C10 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max}, AUC, and t_{max}. Pharmacokinetic 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. If deemed necessary, additional model-based analysis may be performed for LY3493269 or data may be combined with Study GZHA for further analysis.

Pharmacokinetic dose proportionality will be explored. Log-transformed Day 3 C_{max} and AUC of LY3493269 from Cohorts 1 to 3 will be evaluated using a power model (where log-dose acts as an explanatory variable) to estimate ratios of dose-normalized geometric means and corresponding 90% CIs. The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. A subinterval within the highest and lowest doses may also be considered for assessment of dose proportionality using the same approach. Additional details will be provided in the SAP.

The parameter t_{max} of LY3493269 and C10 will be analyzed using a nonparametric method. All PK parameters will be summarized using descriptive statistics.

9.4.4. Pharmacodynamics Analyses

Inferences will be sought regarding the effect of LY3493269 on the PD endpoints. Such effects will be explored over different doses of LY3493269 and at applicable time points as per the SoA (Section 1.3).

Pharmacodynamic parameters may be transformed before statistical analyses, if deemed necessary. Absolute values, as well as change from baseline, in each parameter will be analyzed using mixed-effects models to evaluate treatment effects, as well as treatment comparisons. The model will include treatment, visit, and treatment-by-visit interaction as fixed effects and participant as a random effect. Baseline values, as well as other influencing variables, may be used as covariates. Differences between each LY3493269-treated group and placebo group will be estimated. Participants who received placebo will be pooled across all cohorts. Least squares means and 90% CIs will be reported.

All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment group and visit. Summary statistics will be provided. The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/PD analyses or graphical explorations may be used to assess the relationship between LY3493269 doses and/or concentrations and key

- safety parameters, such as
  - QTcF interval
  - BP
  - HR, and
  - PR interval,
- tolerability parameters, such as
  - nausea, and
  - vomiting, and
- PD parameters, such as
  - fasting glucose, and
  - weight.

Endpoints may include but are not necessarily limited to those listed earlier.

The impact of ADA and its titers on LY3493269 clearance and drug effect, if applicable, will be evaluated.

9.4.6. 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. Treatment-emergent ADAs are defined as those with a signal increase, greater than assay variability, compared to baseline. Treatment-emergent ADAs are defined as those with a

- titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA), or
- 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.

9.5. Interim Analyses

Interim access to safety and tolerability (and any available PK or PD) data is scheduled to occur after every dosing session as described in Section 6.6.1. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

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.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.6. Data Monitoring Committee (DMC)

A Data Monitoring Committee will not be used in this study.

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 International Council for Harmonisation (ICH) good clinical practice (GCP) Guidelines, and
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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.

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 the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement (CTA).

10.1.2. Informed Consent Process

The investigator or his/her 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 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act 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 re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

A participant who undergoes repeat screening tests to confirm eligibility is not required to sign another ICF.

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 his/her 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 his/her 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

Communication of suspended for terminated dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to the investigator (for example, through phone and/or email) as soon as possible. It will be a requirement that the investigator responds upon receipt to confirm that he understands the communication and has taken the appropriate action prior to further dosing any participants with study intervention. A failure by the investigator to respond 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 the investigator 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.

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 eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source data may include laboratory tests, medical records, and clinical notes.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., 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 (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered 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 CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

In addition, 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 system(s) will be stored by third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

10.1.6. 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 the CRF or entered in the eCRF that 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

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

The sponsor 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

- 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 of participants by the investigator, and
- discontinuation of further study intervention development.

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 assures 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. Long-Term 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.

The following table lists the maximum retention period for sample types. The retention period begins after the last participant visit for the study.

The maximum retention times may be shorter, if specified in local regulations and/or if ERBs/IRBs impose shorter time limits.

Any samples remaining after the specified retention period will be destroyed.

The sample retention facility will be selected by the sponsor or its designee.

Sample Type	Custodian	Retention Period after Last Patient Visit[a]
Biomarkers	Sponsor or designee	15 years
PK	Sponsor or designee	1 years
PD	Sponsor or designee	1 year
Genetics	Sponsor or designee	15 years
Immunogenicity	Sponsor or designee	15 years

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

[a] Retention periods may differ locally.

The sponsor has a right to retain a portion of submitted biopsy tissue. Archival blocks will be returned to the study site. Slides and tissue samples collected on study will not be returned.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the local laboratory.

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.

Pregnancy Testing: A serum pregnancy test will be performed at screening and urine pregnancy test at the Day 43 follow-up or early termination visit (if applicable).

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to CRUs or other blinded personnel.

Safety Laboratory Tests

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

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

[a] Performed at screening only

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

[c] If clinically indicated, per investigator's discretion.

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

[e] For females, at screening only.

[f] For females, at Day 43 and if applicable at early termination.

10.2.1. Blood Sampling Summary

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

Protocol J1X-MC-GZHB Blood Sampling Summary

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests[a] (local laboratory)	23	1	23
Clinical laboratory tests[a] (local laboratory)			
• Study visits	10	4	40
• Follow-up visit	10	2	20
LY3493269 and C10 pharmacokinetics (1 blood sample for both analytes)	3	37	111
Potential additional LY3493269 and C10 pharmacokinetic samples	3	2	6
Blood discard for cannula patency	0.3	49	14.7
Point-of-care safety glucose (on-site)	0.3	18	5.4
Pharmacodynamics (central laboratory)			
• Glucose	2	6	12
• Insulin	2	6	12
• C-peptide	2	6	12
Mechanistic biomarker (central laboratory)			
• Triglycerides	3.5	6	21
Pharmacogenetic sample (stored)	10	1	10
Nonpharmacogenetic sample (stored)			
• Plasma	2	6	12
• Serum	2.5	6	15
• P800	2	6	12
Immunogenicity	10	5	50
Total			376.1
Total for clinical purposes (rounded up to the nearest 10 mL)			380

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

10.3. Appendix 3: 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 patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: 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 study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions 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 overdose 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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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 (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised 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. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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 AE/SAE CRF page.
- 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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. 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 consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- The investigator will use clinical judgment to determine the relationship.
- 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 and/or Product Information, for marketed products, in his/her 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 his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used while 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.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. 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.

10.3.5. Sponsor Surveillance Process for Dose Escalation or Cohort Expansion

The sponsor has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with the Food and Drug Administration's expectations for safety assessment committee (SAC) (FDA Draft Guidance: "Safety Assessment for IND Safety Reporting"; FDA Guidance: "Safety Reporting Requirements for INDs and BA/BE Studies"). This includes processes with clearly described roles and responsibilities that are owned by the sponsor's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (that is, review of cumulative SAEs, other important safety information) by designated cross-functional teams in a timely manner at predefined intervals or on an ad hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program are reviewed on a regular basis and that important new safety information such as the need for protocol modification or other relevant safety related material is identified and communicated to regulators and investigators appropriately and in a timely manner. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any serious adverse reaction are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing report of suspected unexpected serious adverse reactions is created and distributed to investigators on a biannual (twice yearly) basis. Any significant potential risk/safety concerns that are being monitored as well as any results being reported in other periodic reports for the compound; SAC decisions; and other significant safety data (for example, nonclinical, clinical findings, removal of serious adverse reactions) are included in the report.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Females NOT of Childbearing Potential

Females in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as, women with
   - 12 months of amenorrhea for women >55 years, with no need for follicle-stimulating hormone
   - 12 months of amenorrhea for women >40 years with follicle-stimulating hormone of ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that induced amenorrhea), and
   - hormone levels consistent with a postmenopausal state per the local laboratory reference range

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, regardless of their fertility status, with partners who are nonpregnant women of childbearing potential, must agree to either

1. remain abstinent (if this is their preferred and usual lifestyle), or
2. use condoms plus 1 additional highly effective contraception method.

Male participants with pregnant partners must agree to use condoms during intercourse.

Male participants must agree to continue abstinence or contraception methods for the duration of the study plus 105 days, which corresponds to approximately 5 months following the last dose of study intervention.

Male participants should refrain from sperm donation for the duration of the study plus 105 days, which corresponds to approximately 5 months and 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

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.

Same-s*ex relationships*

Participants who are in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to stay in a same-sex relationship without sexual relationships with the opposite sex. Participants who are in exclusively same-sex relationships as their preferred and usual lifestyle are not required to use contraception.

Highly *effective and effective contraception methods*

Highly effective methods of contraception (less than 1% failure rate)	
Combined oral contraceptive pill and mini-pill	Intrauterine device (such as Mirena® and ParaGard®)
NuvaRing®	Contraceptive patch – ONLY women less than 198 pounds (90 kg)
Implantable contraceptives	Vasectomy – for men in clinical trials
Injectable contraceptives (such as Depo-Provera®)	Fallopian tube implants (Essure®) if confirmed by hysterosalpingogram
Total abstinence	
Effective methods of contraception (use 2 forms combined except where noted)	
Male condom with spermicide[a]	Diaphragm with spermicide
Female condom with spermicide[a]	Cervical sponge
	Cervical cap with spermicide

[a] Male and female condoms should not be used in combination.

Unacceptable contraception methods

Unacceptable methods of contraception include

- periodic abstinence, such as
  - calendar
  - ovulation
  - symptothermal, or
  - post-ovulation methods
- declaration of abstinence just for the duration of the trial, and
- withdrawal.

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3493269.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. 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 including fetal status (presence or absence of anomalies) and 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, including 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 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. The discontinued participant should follow the standard discontinuation process and continue directly to the follow-up phase.

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 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.

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 anti-smooth muscle antibody (ASMA) is tested.

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

10.7. Appendix 7: Pancreatic Monitoring

Glucagon-like peptide 1 agonists have been associated with a possible risk of acute pancreatitis. In 2006, the United States prescribing information for exenatide was revised to include the event of pancreatitis. In 2007, the 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, even in asymptomatic participants (see the following figure). Lipase and amylase 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.

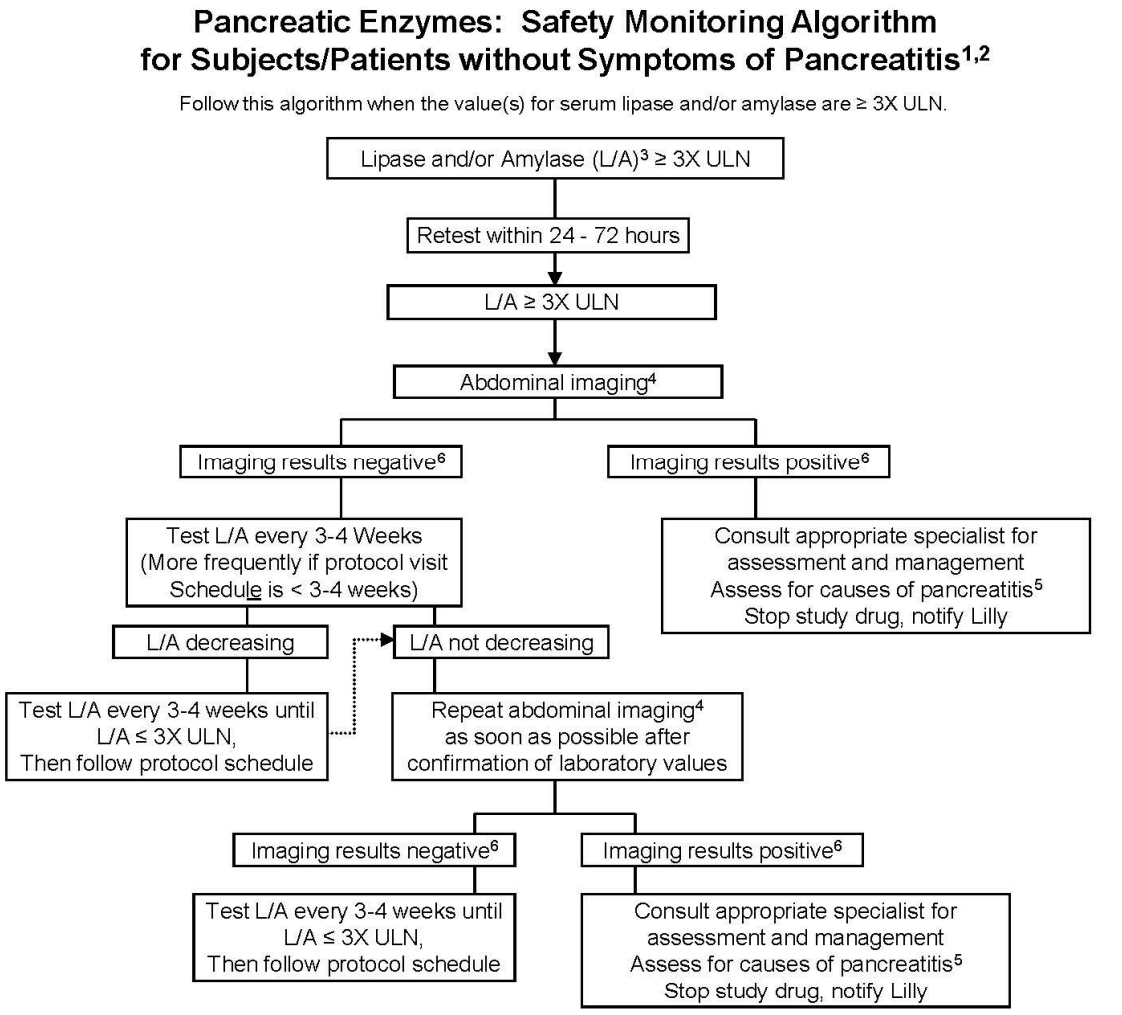
Acute pancreatitis is an AE defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- 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. However, experience with GLP-1 agonists has demonstrated that some participants asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase levels. For participants considered by investigators to be asymptomatic for pancreatitis, but whose value(s) for lipase and/or amylase are ≥3X ULN, an algorithm is in place to follow these participants safely and to quickly reach (or not reach) a diagnosis of pancreatitis.

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. Adverse events that meet the diagnostic criteria of acute pancreatitis will be captured as SAEs. For all other pancreatic AEs (such as idiopathic or asymptomatic pancreatic enzyme abnormalities), the investigator will be responsible for determining the seriousness of the event (AE or SAE) and the relatedness of the event to IP.

Figure 1



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

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

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

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

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

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

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; ULN = upper limit of normal.

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: Abbreviations

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BG	blood glucose
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
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
CTA	clinical trial agreement
CV	cardiovascular
ECG	electrocardiogram
eCRF	electronic case report form

enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1R	GLP-1 receptor
GLP-1RA	GLP-1 receptor agonist
HIV	human immunodeficiency virus
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 his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	International normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	
IP	investigational product
IRB	institutional review board
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level
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

PG	plasma glucose
PR	pulse rate
randomize	the process of assigning participants to an experimental group on a random basis
QTcF	QT interval corrected using Fridericia's formula
SAC	safety assessment committee
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
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.
SoA	Schedule of Activities
SRP	Safety Review Panel
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE-ADA	treatment-emergent-antidrug antibody
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal
VAS	visual analog scale

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