Protocol J1X-MC-GZHA

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

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LY3493269

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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

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1. Protocol Synopsis

Title of Study:

Protocol J1X-MC-GZHA A Single-Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3493269 in Healthy Participants.

Rationale:

LY3493269 is a dual-agonist peptide that combines actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). LY3493269 is being developed for the treatment of type 2 diabetes mellitus (T2DM) as a once-weekly (QW) subcutaneous (SC) administration.

Study J1X-MC-GZHA is designed to assess the safety, tolerability, and pharmacokinetics (PK) of single doses of LY3493269 when administered in healthy participants, as single SC doses, and as a single IV dose.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To evaluate the safety and tolerability of LY3493269 following single SC and IV doses in healthy participants	TEAEs and SAEs
Secondary To characterize the PK of LY3493269 following single SC and IV doses in healthy participants	AUC, C_{max}, and t_{max}

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; IV = intravenous; PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse events; t_{max} = time to maximum observed drug concentration

Summary of Study Design:

Study J1X-MC-GZHA is a single center, randomized, placebo controlled study with 6 cohorts receiving SC doses and 1 cohort receiving IV doses. The investigator and participants will be blinded to treatments administered via the subcutaneous route.

Treatment Arms and Planned Duration for an Individual Healthy Participant:

Up to 6 cohorts of approximately 8 participants each (6 LY3493269 and 2 placebo) receiving a SC dose and 1 cohort of approximately 6 participants receiving an IV dose of LY3493269 are planned. Screening may occur up to 28 days prior to enrollment; each participant may be in the study for up to 71 days including the screening period.

Number of Healthy Participants:

Approximately 70 healthy participants may be enrolled so that approximately 54 participants complete the study.

Statistical Analysis:

Safety analyses will be conducted for all enrolled participants who receive 1 dose of the investigational product (IP), whether they completed all protocol requirements. Pharmacokinetic analyses will be conducted on data from all participants who receive 1 dose of the IP and have evaluable PK data.

Safety and tolerability: All IP and protocol procedure-related adverse events will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety parameters that will be assessed include safety laboratory parameters, vital signs, injection site reactions, and electrocardiogram parameters. All serious adverse events will be reported.

Pharmacokinetics: Pharmacokinetic parameter estimates for LY3493269 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum observed drug concentration (C_{max}) and area under the concentration-time curve (AUC). Other noncompartmental parameters, such as half-life, apparent clearance, time to C_{max} (t_{max}), and apparent volume of distribution may also be reported.

2. Schedule of Activities

Study Schedule Protocol J1X-MC-GZHA – for Subcutaneous Cohorts

Procedure	Screening	Treatment Period: SC Cohort										Follow-up			Comments/ Notes
Days	**-28 to -2**	**−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/ Medical assessment	X		X	P	X			X	X	X	X	X	X	X	Complete physical examination at screening. Symptom-directed physical examination across study at other timepoints.
Height and weight	X			P						X	X	X	X	X	Height at Screening only.
Confirmation of eligibility followed by randomization		X													
Admit to CRU		X													
Discharge from CRU – on completion of inpatient procedures							X								Participants may remain inpatient longer than Day 4, at the investigator's discretion.
Administer study drug				X											Refer to Section 7.1.
AEs/ concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs: supine BP and PR (h)	X			P, 1, 4, 6, 12	24	48	72	96	120	168	X	X	X	X	For Day 15 and subsequent visits, vital signs should be measured within 30 min of the scheduled PK sample.
Body temperature (h)	X			P, 6, 12	24										
ECG – single	X											X	X	X	

Procedure	Screening	Treatment Period: SC Cohort										Follow-up			Comments/ Notes
Days	**-28 to -2**	**−2**	**−1**	**1**	**2**	**3**	**4**	**5**	**6**	**8**	**15 ± 1**	**29 ± 3**	**43 ± 3**	**ET**	
ECG – triplicate (m, h)				-30m, -15m, 0, 1, 4, 6, 12h	24	48	72	96	120	168	X				Day 1 Predose ECGs will be taken in triplicates at -30, -15 and 0 min to establish a baseline. Day 15 ECG should be measured within approximately 30 min of the PK sample.
Clinical safety lab tests (fasted)	X			P	X		X			X	X	X	X	X	Collected following ≥8h overnight fast. See Appendix 2, Clinical Laboratory Tests, for details.
Serology • Hepatitis B surface antigen, Hepatitis B core antibody • Hepatitis C antibody • HIV	X														
Point of care safety glucose samples				Days 1 – 3: Pre-meals (breakfast, lunch and dinner) and before bedtime			X	X	X						Days 4 -6: Fasted samples collected before breakfast.
PK sampling (h)				P, 6, 12	24	48	72	96	120	168	X	X	X	X	Days 15, 29, 43 and ET: Samples collected anytime during visit. The ET sample is not required for participants who discontinued without receiving IP.
OGTT – 75 g glucose challenge (h)			X		24										Conducted following overnight fast.

Procedure	Screening	Treatment Period: SC Cohort										Follow-up			Comments/ Notes
Days	-28 to -2	−2	−1	1	2	3	4	5	6	8	15 ± 1	29 ± 3	43 ± 3	ET	
PD biomarkers (h): • Glucose • Insulin and C-peptide • CCI			Pre-OGTT, 0.5, 1, 1.5, and 2h post-OGTT	P	Pre-OGTT, 0.5, 1, 1.5, and 2h post-OGTT	48	72			X	X	X			Days 1, 3, 4, 8, 15 and 29: Samples drawn after minimum 8-hour fast.
CCI [redacted]				[redacted]		[redacted]				[redacted]					[redacted]
Immunogenicity				P							X	X	X	X	
Appetite VAS (h)				P	24	48		X		X	X	X			Obtained after an overnight fast.
Pharmacogenetic sample				X											Sample may be obtained at any time on Day 1.
Nonpharmacogenetic sampling (storage) (h)				P	24	48				X					Samples drawn after minimum 8-hour fast.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; h = hour; IGFBP2 = insulin-like growth factor binding protein 2; m = minutes; P = predose; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous

Notes: If multiple procedures take place at the same time point, ECGs and vital signs must be obtained prior to any blood sample collection.

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 timepoint should be performed within ±3 hours of the scheduled time.

Study Schedule Protocol J1X-MC-GZHA – Intravenous Cohort

Procedure	Screening	Treatment Period: IV Cohort									Follow-up			Comments/ Notes
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/ Medical assessment	X		P	X			X	X	X	X	X	X	X	Complete physical examination at screening. Symptom-directed physical examination across study at other timepoints.
Height and weight	X		P						X	X	X	X	X	Height at Screening only.
Confirmation of eligibility followed by randomization		X												
Admit to CRU		X												
Discharge from CRU – on completion of inpatient procedures						X								Participants may remain inpatient longer than Day 4, at the investigator's discretion.
Administer study drug			X											Refer to Section 7.1.
AEs/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs: supine blood pressure and pulse rate (m, h)	X		P, 5m, 15m, and 30m, 8h, 12h	24	48	72	96	120	168	X	X	X	X	For Day 15 and subsequent visits, vital signs should be measured within 30 min of the scheduled PK sample.
Body temperature (h)	X		P, 0.5, 8, 12	24										
ECG – single	X										X	X	X	
ECG – triplicate (m, h)			-30m, -15m, P, 0.5, 8, 12h	24	48	72	96	120	168	X				Day 15 ECG should be measured within 30 min of the PK sample. Day 1 Predose ECGs will be taken in triplicates at -30, -15 and 0 min to establish a baseline.
Clinical safety lab tests (fasted)	X		P	X		X			X	X	X	X	X	Collected following ≥8h overnight fast. See Appendix 2, Clinical Laboratory Tests, for details.

Procedure	Screening	Treatment Period: IV Cohort									Follow-up			Comments/ Notes
Days	-28 to -2	−1	1	2	3	4	5	6	8	15 ± 1	29 ± 3	43 ± 3	ET	
Serology • Hepatitis B surface antigen, Hepatitis B core antibody • Hepatitis C antibody • HIV	X													
Point of care safety glucose samples			Days 1- 3: Pre-meals (breakfast, lunch and dinner) and before bedtime			X	X	X						Days 4 -6: Samples collected before breakfast, following ≥8h overnight fast.
PK sampling (m, h)			P, EI, 15m, 30m, 1, 2, 4, 8, 12 h	24	48	72	96	120	168	X	X	X	X	Days 15, 29, and 43 and ET: samples are collected anytime during visit. The ET sample shall be omitted for participants who discontinued without receiving IP.
Immunogenicity			P							X	X	X	X	
Pharmacogenetic sample			X											
Nonpharmacogenetic sampling (storage) (h)			P	24	48				X					Collected following ≥8h overnight fast.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; EI = end of study drug administration; ET = early termination; h = hour; IV = intravenous; m = minutes; P = predose; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous

Notes: If multiple procedures take place at the same time point, ECGs and vital signs must be obtained prior to any blood sample collection.

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 timepoint should be performed within ±3 hours of the scheduled time.

3. Introduction

3.1. 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). This first-in-human study of LY3493269, J1X-MC-GZHA (GZHA), will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3493269 administered as single subcutaneous (SC) doses in healthy participants. In addition, a cohort of healthy participants will receive a single intravenous (IV) dose of LY3493269, to allow estimation of the absolute bioavailability of LY3493269.

3.2. Background

Type 2 diabetes mellitus is characterized by impaired glycemic control due to insulin resistance and inadequate insulin secretion due to beta-cell failure. Frequently, T2DM is associated with comorbidities such as obesity, hypertension, and dyslipidemia resulting in increased cardiovascular (CV) risk. LY3493269 is being developed as a once-weekly (QW) subcutaneous treatment for T2DM; a once-daily oral formulation of LY3493269 is also being developed. LY3493269 is a dual-agonist peptide that combines actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

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

A well-characterized incretin hormone, GLP-1 potentiates insulin 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-1Rs (GLP-1 receptors) are expressed throughout the brain, in regions that control glucose homeostasis, gut motility, food intake, aversive signaling, and CV function (Campbell and Drucker 2013). Currently, there are several approved GLP-1 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-1 receptors may enhance insulin secretion, improve insulin sensitivity, and reduce body weight beyond the effect of selective GLP-1R stimulation (Frias et al. 2018; Coskun et al. 2018). For example, Lilly is currently developing tirzepatide, a dual GIPRA (GIP receptor agonist)/GLP-1RA, now in Phase 3 development, targeted as a subcutaneous once-weekly (QW) therapy, to improve glycemic control in adults with T2DM, as an adjunct to diet and exercise.

Nonclinical safety of 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 repeat-dose toxicity studies were generally consistent with, or secondary to, GIP and/or GLP-1 pharmacology and included body weight loss and/or reduced body weight gain and decreased food consumption. Additional findings from the monkey studies, including changes in CV parameters (such as increases in heart rate and blood pressure), were attributed to on target GLP-1 and/or GIP pharmacology. More information about the toxicologic profile of LY3493269 is available in the Investigator's Brochure (IB).

3.3. Benefit/Risk Assessment

The nonclinical safety information for LY3493269 adequately supports the transition from preclinical status to a clinical, single-dose study.

The sponsor has evaluated the risks associated with LY3493269 and does not consider it to be a high-risk or high uncertainty compound based on the nonclinical data, published criteria (Butler et al. 2017) and other factors described below:

- Findings in the toxicology studies were consistent with, or secondary to, the expected pharmacology for the drug class.
- The animal toxicity models are believed to adequately reflect human toxicity for the GIP receptor (GIPR) and GLP-1R target.
- Target engagement and activity will be clinically measurable with biomarkers employed during the study; anticipated effects on CV parameters, body weight loss, gastrointestinal effects, appetite loss are clinically monitorable and reversible.

This protocol reflects the fact that LY3493269 has not been administered to humans previously, and to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the European Medicines Agency (EMA) Guideline (2017) on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products.

Any identified risks from preclinical studies (for example CV effects, gastrointestinal [GI] effects, decreased/loss of appetite, and weight loss) are similar to those noted during development of GIP and GLP-1 agonists; these are considered to be monitorable and manageable at the planned dose range of 0.15 to 7.5 mg for LY3493269 in healthy participants. To further minimize any potential risk, study participants will remain at least 3 days in the clinical research unit (CRU) where they will be monitored for safety and tolerability until discharge, at the discretion of the investigator. During the 3-day CRU residence and through 7 days postdose, 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 if necessary, for further safety monitoring.

There is no anticipated therapeutic benefit for the healthy participants in this study. However, it is well known that co-administration of a GIPR mono-agonist and a GLP-1R mono-agonist, as well as the administration of a unimolecular dual-acting GIPR and GLP-1R agonist, has shown profound weight-lowering benefits that exceed that of either agent alone (Finan et al. 2016).

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3493269 are to be found in the IB.

4. Objectives and Endpoints

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

Table GZHA.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the safety and tolerability of LY3493269 following single SC and IV doses in healthy participants	TEAEs and SAEs
Secondary To characterize the PK of LY3493269 following single SC and IV doses in healthy participants	AUC, C_{max}, and t_{max}
Exploratory To investigate the PD effects of LY3493269 following single SC doses in healthy participants	Changes from baseline levels of • fasting glucose, insulin and C-peptide • glucose, insulin and C-peptide AUC during an OGTT • body weight, CCI [redacted]
To explore immunogenicity of LY3493269 following single doses in healthy participants	Incidence of TE-ADA
To explore the effect of LY3493269 on appetite and food intake following single SC doses in healthy participants	Change in VAS score for appetite assessment in a fasted state

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; IGFBP2 = insulin-like growth factor binding protein 2; IV = intravenous; OGTT = oral glucose tolerance test; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; SC = subcutaneous; TE-ADA = treatment-emergent antidrug antibodies; TEAE = treatment-emergent adverse events; T_{max} = time to maximum observed drug concentration; VAS = visual analog scale

5. Study Design

5.1. Overall Design

Study GZHA is a Phase 1, single-site, randomized, placebo controlled, single-ascending dose (SAD) study in healthy participants, to evaluate the safety, tolerability, and PK of LY3493269 administered as single SC doses and as a single IV dose. The PD effects of SC doses of LY3493269 on glycemic effects (including fasting glucose, insulin, and glucose and insulin during an OGTT) and appetite will be explored. For the SC cohorts, the investigator and participants will be blinded. The IV Cohort is open-label with no placebo.

The planned LY3493269 SC doses for this study range from 0.15 mg to 7.5 mg (Section 5.5). These 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 7.4). Any proposal to adjust SC or IV 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 2).

Study governance considerations are described in detail in Appendix 3.

Subcutaneous Administration Cohorts 1 through 6

Study GZHA includes up to 6 planned SC cohorts:

- SC Cohort 1: 0.15 mg (6 LY3493269: 2 Placebo)
- SC Cohort 2: 0.5 mg (6 LY3493269: 2 Placebo)
- SC Cohort 3: 1.5 mg (6 LY3493269: 2 Placebo)
- SC Cohort 4: 3.0 mg (6 LY3493269: 2 Placebo)
- SC Cohort 5: 5.0 mg (6 LY3493269: 2 Placebo)
- SC Cohort 6: 7.5 mg (6 LY3493269: 2 Placebo)

Cohorts 2 to 6 will be initiated only if the investigator and the Eli Lilly and Company (Lilly) clinical pharmacologist deem the safety results (AEs, clinical safety laboratory tests, vital signs, 12-lead ECGs, and medical assessments) in the preceding cohort to be acceptable through Day 8 (that is, 7 days postdose) from at least 6 participants dosed. In addition, all planned participants in the current cohort should have been dosed prior to escalation to the next cohort.

Intravenous Administration Cohort

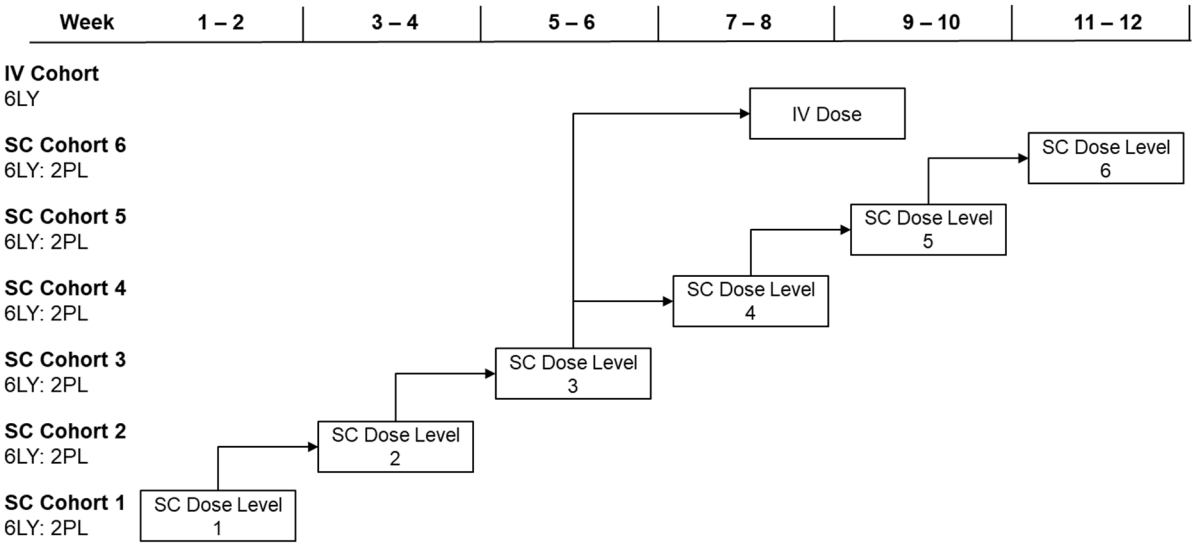
Study GZHA includes a single IV cohort (IV Cohort), where up to 6 healthy participants should complete dosing at the same dose level to provide sufficient PK sampling. The IV Cohort will

be initiated based on review of safety and tolerability data from SC Cohort 3 (SC dose 1.5 mg) and available 7-day PK data and/or PD data from at least 2 preceding SC cohorts.

All participants will receive LY3493269 only (that is no placebo group), as a single IV bolus dose. The planned dose is 0.5 mg. This dose is expected to be safe while providing plasma concentrations that can be adequately measured over the sampling time period enabling adequate characterization of the PK profile. The IV dose may be increased to a maximum of 1.5 mg or decreased to a minimum of 0.25 mg depending on emerging data (see details in Sections 5.5 and 7.5). It is intended that the IV dose will be administered sequentially, with 1 participant having completed the dosing and observed for at least 20 minutes before the next participant is dosed.

In the IV Cohort, 2 participants will initially receive the planned 0.5 mg dose. An additional 4 participants will receive IP following joint investigator and sponsor review of safety and tolerability data through at least 4 days postdose (including Day 5 safety labs and assessments) from the 2 initial participants.

Figure GZHA.1 illustrates the study design.



Abbreviations: IV = intravenous; LY = LY3493269; PL = Placebo; SC = subcutaneous.

Figure GZHA.1. Illustration of study design for Protocol J1X-MC-GZHA.

Participant eligibility for this study will be determined at a screening visit; participants will be required to attend the CRU on at least 8 occasions:

- A screening visit (may occur up to 28 days prior to enrollment)
- An inpatient stay comprising admission on Day -2 for SC administration cohorts or Day -1 for the IV administration cohort, with subsequent dosing on Day 1 followed by inpatient monitoring up to Day 4
- Four outpatient visits on Days 5, 6, 8, and 15
- Two outpatient follow-up visits on Days 29 and 43

If the investigator decides not to administer the planned dose to a participant or not to enroll a participant on a certain day, the participant may be rescheduled to participate in a subsequent dose cohort if he/she consents to doing so. If this situation arises:

- The investigator documents the agreement by the participant to proceed
- Any procedures performed up to that point may be repeated to obtain predose measurements and/or to confirm eligibility of the participant for the study

5.1.1. Inpatient Visit (Day -2/ Day -1 through Day 4)

Eligible participants will be admitted to the CRU on Day -2 or Day -1 (for SC or IV administration cohorts, respectively) and adhere to an overnight fast.

Participants in the SC administration cohorts will undergo baseline assessments on Day -1, including an oral glucose tolerance test (OGTT), blood sampling for PD/biomarker assessments, and an appetite assessment using a visual analog scale (VAS).

On the morning of Day 1, participants will receive a single-dose of their assigned treatment (either LY3493269 or placebo) in the fasted state. The IP will be administered either as a SC or IV dose, per treatment assigned for each participant.

Pharmacokinetic and PD sampling and safety assessments, including AE, medical assessments, clinical laboratory tests, vital signs and ECGs, will be performed according to the Schedule of Activities (Section 2). Pharmacokinetic and PD sampling schedules may be modified based on the available safety and PK/PD data.

If deemed medically fit by the investigator, participants will be discharged from the CRU on Day 4 after completing the scheduled assessments. Participants may remain as needed at the CRU for safety monitoring based on the investigator's judgement.

5.1.2. Outpatient Visits (Days 5, 6, 8, and 15)

Participants will return to the CRU for outpatient visits on Days 5, 6, 8 and 15, for safety assessments, PK, PD and/or immunogenicity (antidrug antibody [ADA]) sampling at the times specified in the Schedule of Activities (Section 2). Participants may remain as needed at the

CRU for safety monitoring based on the investigator's judgement or to facilitate participant compliance.

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

On Days 29 and 43, two follow-up visits will occur where participants will undergo study assessments specified in the Schedule of Activities (Section 2).

Participants who received IP and who discontinue early will be encouraged to return for follow-up visit(s) for safety monitoring, including but not limited to 28 days after IP administration. All enrolled participants who discontinue without receiving IP will observe an early termination visit with procedures performed as shown in the Schedule of Activities (Section 2).

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

5.2. Number of Participants

Up to 70 participants may be enrolled so that approximately 54 participants complete the study. For purposes of this study, a participant completes the study when all scheduled procedures shown in the Schedule of Activities have been finished.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

A population of healthy participants is selected to assess the safety and tolerability at the initial starting doses in humans. Using this participant population mitigates possible confounding effects of comorbidities and concomitant medications. Therefore, Study GZHA provides an unbiased assessment of safety, tolerability, and PK of LY3493269.

The study is intended to estimate a maximum tolerated exposure or establish that exposures exceeding the expected therapeutic range are tolerated. 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 single cohort of participants will be administered LY3493269 via the IV route. This approach provides an estimate of the absolute SC bioavailability of LY3493269 and enables estimation of bioavailability for alternative routes of administration, including oral dosing.

While European Medicines Agency guidelines (EMA 2017) recommend using sentinel dosing in first-in-human studies, it allows for flexibility in dosing approaches based on the available scientific and preclinical assessments of a given molecule. The intended and exaggerated pharmacological responses of LY3493269 have been well characterized in multiple preclinical pharmacology models. Toxicology studies have suggested that non-monitorable or clinically

unmanageable concerns would be unlikely to occur in humans treated with LY3493269. Based on the available data, LY3493269 does not present an uncertainty profile necessitating a sentinel dosing approach.

Nonclinical safety of 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 repeat-dose toxicity studies were generally consistent with, or secondary to, incretin pharmacology and included body weight loss and/or reduced body weight gain and decreased food consumption. Additional findings in monkeys included changes in CV parameters (for example, increases in heart rate and blood pressure) were attributed to on target GLP-1 pharmacology and are clinically monitorable. Due to the effects on body weight, food consumption, and clinical condition, dosing holidays were required in order to avoid the need to remove animals from the studies; these effects were considered adverse in both rats and monkeys. These pharmacological effects declined as systemic exposure decreased in animal models, and they are clinically monitorable.

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 2). A preliminary assessment of the PD effects of LY3493269 will be based on the concentrations of fasting glucose, insulin, and C-peptide 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 5.1 and 7.4) and all available PK data will also be reviewed.

5.5. Justification for Dose

The planned dose range of LY3493269 in GZHA is intended to provide an adequate evaluation of safety and tolerability. Based on current preclinical pharmacology and toxicology data, a dose range of 0.15 mg to 7.5 mg administered as single SC doses is planned. The anticipated dose-limiting safety and tolerability profile (nausea and vomiting) of LY3493269 is expected to be consistent with that demonstrated by the GLP-1 receptor agonists and GIP/GLP-1 dual agonist drug classes and should be reversible as PK exposures decline.

Dose were selected by evaluating preclinical pharmacology animal data (insulin secretion from IV glucose tolerance tests in rats and weight loss from diet-induced obese mice) and through benchmarking against the preclinical and clinical data of tirzepatide (LY3298176), another GIP/GLP-1 dual agonist.

Human efficacious doses for LY3493269 were projected through anchoring the relative potency of LY3493269 from preclinical efficacy models to tirzepatide and accounting for translational differences between animals and human to achieve comparable clinical efficacy for HbA1c and weight reduction in humans (Frias et al 2018). CCI [redacted]

CCI [redacted]

Subcutaneous doses may be increased or decreased according to emerging PK data, but SC dose escalations will not exceed a half-log (3.3-fold) increase in dose between 2 SC cohorts. The AUC exposure in healthy participants at the maximum dose should not exceed the predicted AUC of 1250000 ng.h/mL, corresponding to the exposure for the highest dose tested (HDT) in the monkey toxicology study. Adversity at this dose level in the monkey toxicology study was based on the expected pharmacological effects of decreased food consumption/body weight, and the need for a dosing holiday. As these effects are known to reverse based on experience with other members of the incretin class, it is deemed acceptable to use this dose level to calculate clinical exposure multiples. This is an arbitrary exposure limit based on monkey data whereby toxicology findings were attributed to expected pharmacology. It is anticipated that clinical safety and tolerability data will inform the decision for the maximum dose to be tested.

Cardiovascular effects (increases in heart rate and blood pressure) were observed in both the standalone CV safety pharmacology study and the repeat-dose toxicity study in monkeys. These findings have been observed with other GLP-1 RA and GIP/GLP-1 RA molecules. The clinical starting dose will maintain a 7.6x dose multiple and a 15.8x exposure multiple to the lowest-observed-effect level (LOEL) identified in the CV safety pharmacology study. Participants will be closely monitored for effects on CV parameters.

Pharmacokinetic properties of LY3493269 are expected to be consistent with that of acylated peptides. Human PK parameters were scaled with allometry using cynomolgous monkey PK.

CCI [redacted]

To ensure the most conservative human exposure multiple estimate, the highest SC bioavailability observed in animals CCI [redacted] was adopted for calculating human exposure parameters. The planned SC doses to be evaluated are: 0.15 mg, 0.5 mg, 1.5 mg, 3.0 mg, 5.0 mg and 7.5 mg.

A single IV dose of 0.5 mg is planned for one dosing cohort, to be administered approximately after the third SC cohort (planned SC dose of 1.5 mg). An IV dose of 0.5 mg is anticipated to yield LY3493269 exposures close to or slightly higher than SC 0.5 mg. Dosing of the IV Cohort will only proceed when PK exposures from at least 2 preceding SC cohorts exceeds predicted exposures for the planned IV dose. The IV dose may be increased to a maximum of 1.5 mg or decreased to a minimum of 0.25 mg depending on emerging safety and PK data from preceding SC doses. Criteria for IV dose increase or reduction can be found in Section 7.5.

Dose multiples and predicted exposure multiples relative to the no-observed-adverse-effect levels (NOAELs) in rats and monkeys are listed in Table GZHA.2 below. Exposure multiples based on the NOAEL are > 1 for the starting dose and < 1 for the remaining planned doses, with

severe weight loss being the dose-limiting factor in animals which is an expected pharmacological effect.

Participants will be closely monitored and LY3493269 doses may be adjusted before each dose escalation based on safety, tolerability and available PK data throughout the course of the study.

Table GZHA.2 Margin of Safety for Subcutaneous Administration of LY3493269 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose multiple [a]		AUC (ng.hr/mL)	Maximum Con-centration (ng/mL)	Exposure multiple [b]	
			Starting dose	Maximum dose			Starting Dose	Maximum dose
Human starting dose (0.15mg)[c]	0.00214	0.0793			7670	31.2		
Human Maximum dose (7.5mg)[c]	0.11	3.96			386000[d]	1580		
Rat NOAEL[e]	0.05	0.3	3.8	0.076	8020		1.83	0.036
Rat HDT[e]	1	6	75.7	1.52	154000		35.1	0.70
Monkey NOAEL[f]	0.05	0.6	7.6	0.15	59800		7.8	0.15
Monkey HDT[f]	1	12	151.3	3.03	1250000		163	3.24
Monkey CV LOEL[g]	0.05	0.6	7.6	0.15	-	494	15.8	0.3

Abbreviations: AUC = area under the plasma concentration-time curve; CV = cardiovascular; LOEL = lowest-observed-effect level; NOAEL = no-observed-adverse-effect level; HDT = highest dose tested; PK = pharmacokinetics.

a Dose multiple (based on body surface area) is calculated as dose in animals (mg/m^2)/dose in humans (mg/m^2).

b Exposure multiple is the calculated as time-adjusted AUC in animals/predicted AUC in humans;
(1) ([AUC(0-96) in rats Day 29]/96hr)/ ([AUC(0-inf) in humans]/168 hr) OR
(2) ([AUC(0-168) in monkeys Day 29]/168hr)/([AUC(0-inf) in humans]/168 hr)

c Typical body weight of 70 kg was assumed for a healthy participant.

d Plasma PK parameter (AUC) was computed based on PK model-predicted LY3493269 clearance.

e Rat NOAEL and HDT was determined in a 1-month repeat-dose toxicity study (130-735). It is mean Male +Female from Study 130-735 Day 29 toxicokinetic data. All findings in the study were considered secondary to stress and/or pharmacology (decreased body weights and/or decreased food consumption). The only adverse finding in the 1 mg/kg group (HDT) was the need for a single dosing holiday on Day 5 due to pharmacology.

f Monkey NOAEL and HDT was determined in a 1-month repeat-dose toxicity study (130-739). It is mean Male +Female from Study 130-739, Day 29 toxicokinetic data. All findings in the study were considered secondary to stress and/or pharmacology (decreased body weights and/or decreased food consumption). The only adverse finding in the 1-mg/kg group (HDT) was the need for dosing holidays in 1 male and 2 females (of a total of 6 monkeys in the group) due to pharmacology (i.e. body weight loss and decreased body condition score).

g Monkey CV LOEL was determined in a single-dose safety pharmacology study (130-738). Cardiovascular findings at 0.05 mg/kg were limited to increases in heart rate, blood pressure and QRS duration. The effects declined as the systemic exposure decreased, but still notable by the end of the monitor phase (88 - 96 hrs postdose). The mean exposure at 18 hours postdose (approximate C_{max}) from Study 130-738.

6. 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 electrocardiogram (ECG).

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

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

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

6.1. Inclusion Criteria

Participants are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment as applicable, or as otherwise indicated:

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

[1a] male participants:

agree to use an effective method of contraception for the duration of the study (see Section 6.3.4) and for 5 months following the last dose of the IP.

[1b] female participants:

Women not of childbearing potential may participate and include those who are

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), or congenital anomaly such as mullerian agenesis; or
- those who are postmenopausal, defined as either:
  - a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND with a follicle-stimulating hormone of >40 mIU/mL; women in this category must test negative in pregnancy test prior to study entry.
  - a woman 55 years of age or older not on hormone therapy who has had at least 12 months of spontaneous amenorrhea; or
  - a woman of at least 55 years of age with a diagnosis of menopause before starting hormone replacement therapy.

[2] are between the ages of 21 and 65 years, inclusive at screening

[3] have a body mass index of ≥19 and ≤40.0 kg/m^2 at screening

[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 blood pressure of <150/90 mmHg and pulse rate of between 50 to 100 bpm, supine (at screening), or with minor deviations judged to be acceptable by the investigator

[6] have hemoglobin A1c level of <5.7% at screening

[7] have venous access sufficient to allow blood sampling as per the protocol

[8] 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

[9] are able and willing to give signed informed consent and have given written informed consent to participate in this study in accordance with local regulations and the ethical review board (ERB) governing the site

6.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment as applicable, or as otherwise indicated:

[10] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling

[11] are Lilly employees

[12] 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

[13] 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

[14] have previously completed or withdrawn from this study

[15] 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 post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis)

[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 corrected QT interval using Fridericia's formula (QTcF) >450 msec, PR >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 [Note: the QTcF and PR criteria are applicable at screening only]

[17] have a significant history of or current CV (e.g. 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 when taking the IP; or of interfering with the interpretation of data

[18] have undergone any form of bariatric surgery

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

[20] have a history of acute or chronic pancreatitis, or elevation in serum lipase and/or amylase greater than 1.5 times the upper limit of normal (ULN)

[21] have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis

[22] have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2X the ULN or total bilirubin (TBL) >1.5X ULN

[23] have been treated with prescription drugs that promote weight loss (e.g. Meridia® [sibutramine], Sanorex® [mazindol], Adipex-P® [phentermine], BELVIQ® [lorcaserin], Mysimba® [naltrexone/bupropion], Saxenda® [liraglutide] or similar other body weight loss medications including over-the-counter medications (e.g. Alli®) within 3 months prior to screening

[24] 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)

[25] have fasting triglyceride levels ≥5 mmol/L (≥442.5 mg/dL) at screening

[26] have evidence of significant active neuropsychiatric disease as determined by the investigator

[27] regularly use known drugs of abuse

[28] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies

[29] show evidence of hepatitis C and/or positive hepatitis C antibody

[30] show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen

[31] intended 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

[32] 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

[33] 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 6.3.2) (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)

[34] smoke >10 cigarettes per day or the equivalent, or are unable or unwilling to refrain from nicotine during CRU admission

[35] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Participants will be required to fast overnight for at least 8 hours before taking a SC or IV dose of LY3493269 (or placebo) on Day 1 and for each subsequent study day when clinical safety laboratory and PD samples are taken and OGTTs are administered. Water may be consumed freely. Subjects will receive a standard meal shortly after dosing. 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.

6.3.2. Caffeine, Alcohol, and Tobacco

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 Exclusion Criterion [35]). 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. Participants will be allowed to maintain their regular caffeine consumption throughout the study period.

6.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity/exercise during the study. When certain study procedures are in progress at the site, participants may be required to remain recumbent or sitting.

6.3.4. Contraception

Men, 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 (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge).

They must agree to do this for the duration of the study plus 105 days, which corresponds to approximately 5 months.

Additional notes:

- Men and their partners may choose to use a double-barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).
- Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- Men with pregnant partners should use condoms during intercourse for the duration of the study plus 105 days, which corresponds to approximately 5 months following the last dose of IP – for example, until the end of estimated relevant potential exposure in women of childbearing potential.
- Men 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.
- Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened, although screening tests such as clinical laboratory tests and vital signs/ECGs may be repeated at the discretion of the investigator.

7. Treatment

7.1. Treatment Administered

The doses to be administered are presented in Section 5.1.1.

The IP will be administered either via a SC injection or as a slow IV bolus (over at least 1 minute). A maximum of 2 injections may be necessary to achieve higher planned dose levels.

- For SC cohorts, LY3493269 and placebo will be administered at a maximum volume of 2 mL per injection.
- Participants in the IV Cohort will be dosed one at a time, at least 20 minutes apart.

For IV doses, investigative sites must have resuscitation equipment, emergency drugs, and appropriately trained staff available during IV dosing and for at least 6 hours after participants have completed their IV dose.

Table GZHA.3 shows the treatment regimens.

Table GZHA.3. Treatments Administered

Treatment Name	LY3493269	Placebo
Dosage Formulation	Lyophilized powder[a]	0.9% sodium chloride injection
Unit dose strength	5mg/vial LY3493269	N.A.
Route of Administration	SC injection or IV dose	SC injection
Dosing instructions	Single injection or IV dose (at the assigned dose level)	Single injection (volume matched with active drug)

Abbreviations: IV = intravenous, SC = subcutaneous.

a Reconstituted with sterile water for injection.

The investigator or designee is responsible for:

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

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

7.1.1. Injection Sites

All injections will be administered into the SC tissue of the abdominal wall, in the right or left upper or lower quadrant. Where more than 1 injection is required to deliver a full dose, it is recommended that the injections are administered in opposite quadrants, such as upper right and lower left or upper left and lower right. Whenever possible, IP administration should be carried out by the same personnel and at approximately the same time of day in all cohorts. The actual time of dosing and the site(s) of injection(s) will be recorded in the participant's case report form (CRF).

7.1.2. Packaging and Labeling

The drug product LY3493269 is supplied for clinical trial use as 5 mg lyophilized powder in a glass vial. Further dilution may be needed for IV administration. Detailed instructions for the preparation of LY3493269 will be included in the Pharmacy Instructions provided by the sponsor.

Placebo will be provided as sterile saline (0.9% NaCl) in a 50 mL vial. Placebo doses should be held in the pharmacy for an equivalent amount of time as is required to prepare doses of LY3493269.

Both materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Randomization tables for allocation of LY3493269 or placebo to participants will be prepared by the statistician for the study and provided to the site pharmacists involved in dose preparation. The allocation and dispensing of the IPs will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained by the site pharmacist.

7.2.1. Selection and Timing of Doses

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.

7.3. Blinding

This is an investigator- and participant-blind study for SC Cohorts 1 through 6. To preserve the blinding of the study for LY3493269 and placebo, all study site personnel, except pharmacy staff who prepare and dispense study medication, will be blinded to treatment allocation.

Blinding will be maintained throughout the conduct of the study as described in the Blinding/Unblinding Plan.

Emergency codes will be available to the investigator. A code, which reveals the treatment for a specific study participant, may be opened during the study only if the participant's well-being requires knowledge of the participant's treatment assignment.

If the study treatment assignment for participants in the SC cohorts is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician (CRP) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification for Subcutaneous Cohorts Only

In cohorts receiving SC doses, 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 SC doses 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 9.6.
- 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 a SRP, composed of members independent of the study team and investigative site.

7.4.1. Dose Decision/Escalation

By nature of being a dose escalation study, data will be evaluated on an ongoing basis until the maximum tolerated dose (MTD) is determined or when stopping criteria are met. The highest dose level that is tolerated will be designated as the MTD for single SC 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 10.3.6.

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 may be used as supporting data for dose

escalation, but such data are not required. 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 at least 7 days postdose from at least 6 participants receiving IP 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 IP unless there is clear evidence that the event is not related.

7.4.2. Termination of Dosing/Dose Escalation

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

1) One or more participants on active drug experience an SAE considered to be related to LY3493269
2) One or more participants on active drug experience 2 clinically significant events defined as moderate to severe symptoms, clinical signs, and clinical laboratory findings that could cause harm to health. CSEs will be determined by the investigator or suitable designee and may include findings that do not fulfill the criteria for SAEs
3) Three or more participants at the same dose level experience any of the following deemed to be related to LY3493269 administration:
    - drug-related GI effects (for example emesis, diarrhea) causing severe distress (prevents daily activities or requires an emergency department visit or hospitalization); and/or
    - clinically significant cardiovascular AEs
    - a symptomatic hypoglycemic episode with BG values <2.7 mmol/L (48.6 mg/dL; corresponding to plasma glucose levels of <3.0 mmol/L [54 mg/dL])
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 Appendix 6.

7.4.2.1. Premedication for IV Administration

Premedication for the IV administration is not planned. However, if a reaction occurs after dosing the first 2 participants (Section 5.1), appropriate medication may be used in subsequent

participants in the cohort. If postdose reactions are observed in the first 2 participants, but review of the data suggests that dosing of subsequent participants may continue, administration of acetaminophen, 500 to 1000 mg, and/or an antihistamine may be administered orally 30 to 60 minutes prior to the start of the IV injection for subsequent participants.

The decision to implement premedication for IV injections in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation.

Any premedications given will be documented as a concomitant therapy (see Section 7.8).

7.4.2.2. Management of IV Administration Reactions

There is a risk of reaction with any biological agent administered intravenously; therefore, all participants should be monitored closely. Symptoms and signs that may occur as part of an IV injection reaction include, but are not limited to: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant IV injection reaction occurs, the following guidance should be followed:

- Supportive care should be employed in accordance with the symptoms/signs
- If a participant's injection reaction is sufficiently severe, subsequent injections in the cohort may be administered with premedication at the discretion of the investigator following agreement with the Lilly CRP or clinical pharmacologist

7.5. Dose Modification for Intravenous Cohort

If tolerability precludes dosing of the IV 0.5 mg cohort, the IV dose will be reduced to a minimum of 0.25 mg. Based on preclinical data, SC bioavailability for LY3493269 is expected to be close to 100%. If PK exposures from the SC 0.5 mg dose yields largely concentrations below quantification, the IV 0.5 mg dose is likely to be at risk for unmeasurable concentrations. Under such circumstances, the IV dose may be increased to a maximum of 1.5 mg and be initiated only after 7-day safety data is available from the SC 3.0 mg dose and 7-day PK data from at least 2 preceding SC cohorts. Any proposal to adjust IV doses from those planned and stated in the protocol, together with supporting data, will be reviewed by an independent SRP.

7.6. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by sponsor, during transit for all IP received and any discrepancies are reported and resolved before use of the study treatment.

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

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

7.7. Treatment Compliance

The IP will be administered at the CRU, and documentation of treatment administration (date and time of drug administration) will occur at the CRU.

7.8. Concomitant Therapy

Participants on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

In general, concomitant medication should be avoided; however, acetaminophen (1g, maximum 4g/24 hours) may be administered at the discretion of the investigator for treatment of headaches etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the participant may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP. Any medication used during the course of the study must be documented.

7.9. Treatment after the End of the Study

Not Applicable.

8. Discontinuation Criteria

Participants discontinuing from the study prematurely for any reason must complete adverse event and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Participants will only receive 1 dose of IP and hence cannot be discontinued from the study treatment.

8.1.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist and the investigator to determine if the participant may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist to allow the inadvertently enrolled participant to continue in the study.

8.2. Discontinuation from the Study

Participants will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the participant should be discontinued from the study
    - 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
- Participant Decision
    - the participant, or legal representative, requests to be withdrawn from the study.

The replacement strategy for discontinued participants is described in Section 10.1. If deemed appropriate by the investigator, early discontinuation procedures will be performed as shown in the Schedule of Activities (Section 2).

8.3. Participants Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the CRU. Personnel at the CRU 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 CRU.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

The specifications in this protocol for the timings of safety and sample collections are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical (safety and/or PK) information. The scheduled time points may be subject to minor alterations; however, the actual time must be recorded correctly in the CRF.

Unless otherwise stated in the Schedule of Activities (Section 2):

- For predose study assessments and procedures, these should be performed within 3 hours prior to planned dosing
- For postdose assessments and procedures up to and including 24 hours, these should be performed within ±10% of the scheduled time
- For postdose assessments and procedures scheduled after the 24-hour timepoint, these should be performed within ±3 hours of the scheduled time

Failure or delays (i.e. outside stipulated time allowances) in performing procedures or obtaining samples must be notified to the sponsor in writing via a file note to facilitate data reconciliation.

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

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

Appendix 5 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.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study,

or that caused the participant to discontinue the IP before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

The investigator will record all relevant AE and SAE information in the CRF. After the ICF is signed, study site personnel will record, via CRF, the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatment or pathologies.

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

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

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

Participants should 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.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3493269 is considered any dose higher than the dose assigned through randomization. Treatment for overdose is supportive care. Refer to the IB for LY3493269.

9.4. Safety

9.4.1. Laboratory Tests

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

With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the study.

9.4.2. Physical Examination/Medical Assessments

Physical examinations and routine medical assessments will be conducted as specified in the Schedule of Activities and as clinically indicated (Section 2).

9.4.3. Body Weight

Weight will be measured as indicated in the Schedule of Activities (Section 2). 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.

9.4.4. Vital Signs

For each participant, vital signs measurements should be conducted according to the Schedule of Activities (Section 2), and as clinically indicated.

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

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 Schedule of Activities (Section 2), and as clinically indicated.

9.4.5. Electrocardiograms

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

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

9.4.5.1. Single/Triplicate ECGs

For each participant:

- A single 12-lead digital electrocardiogram (ECG) will be collected screening, and at follow-up (Days 29 and 43). All single ECGs recorded should be stored at the investigational site. Single ECGs will not be transmitted.
- At all other scheduled times (Section 2), consecutive replicate ECGs will be obtained in triplicate at approximately 1-minute intervals.

Electrocardiograms (single) may be obtained at additional times when deemed clinically necessary (e.g. to assess participants' safety). Collection of more ECG replicates than expected at a certain timepoint will be permitted to ensure high-quality records.

Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still 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.

If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an adverse event.

Digital ECGs (scheduled and unscheduled) will be electronically transmitted to a central ECG laboratory designated by Lilly. 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.

The machine-read ECG intervals and heart rate 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).

9.4.5.2. 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.

In the event safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the unblinding/blinding plan.

9.4.5.3. 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.

9.4.5.4. Pancreatic Safety (Elevated Lipase or Amylase)

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing at time points specified in the Schedule of Activities (Section 2). Additional measurements may be performed at the investigator's discretion.

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3X ULN at any visit post-treatment sequence allocation even if the participant is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Appendix 6). If pancreatitis is suspected, the case will be further defined during an adjudication process.

To ensure participant safety and compliance with regulatory guidance, the investigator is to consult with the Lilly-designated Clinical Pharmacologist or CRP regarding collection of specific recommended clinical information and follow-up laboratory tests.

9.4.5.5. Hepatic Safety

If a study participant experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated total bilirubin ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly clinical pharmacologist or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.4.5.6. Injection Site Reactions

Injection site assessments for local tolerability will be conducted, when reported as

- an AE from a participant, or
- a clinical observation from an investigator.

If an AE of injection site reaction is reported, the investigator will complete a supplemental injection site reaction form in the eCRF. The injection site reaction form documents the presence of erythema, induration, pain (mild, moderate, or severe), pruritis, and edema. If more than 1 characteristic of ISR (for example erythema and pain) are recorded for a specific injection, a single AE will be reported. The severity of the AE will be that of the highest severity from the

various components, at all assessed timepoints. All injection site reactions reported as AEs should be closely monitored until resolution.

A clinically significant AE of injection site reaction may prompt notification of the sponsor, clinical photography, and referral for dermatologic evaluation.

9.4.5.7. Hypersensitivity Reactions

Clinical manifestations of allergic/ hypersensitivity reactions may include but are not limited to:

- skin rash
- pruritus (itching)
- dyspnea
- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- hypotension
- anaphylactic reaction

Participants with clinical manifestations of systemic allergic/hypersensitivity reactions should be treated per local standard of care. Additional data describing each symptom should be provided to the sponsor in the eCRF.

In case of anaphylaxis or generalized urticaria, additional blood samples should be collected as close as possible to the onset of the event (Appendix 7). Follow-up samples should be obtained at the next regularly scheduled visit or 4 weeks after the event, whichever is later. The lab results are provided to the sponsor via the central laboratory.

9.4.6. Glucose Monitoring

Site personnel will collect information on episodes of hypoglycemia at each study visit according to the Schedule of Activities. 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 when diagnosing and categorizing an episode considered to be related to hypoglycemia (the plasma glucose [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.

9.5. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), 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 (TE)-ADAs are defined in Section 10.3.5. 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 for up to one year from dosing or until the ADA signal returns to baseline (for example, no longer TE-ADA positive).

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.

9.6. Pharmacokinetics

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 5 mL each will be collected to determine the plasma concentrations of LY3493269. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling as well as the date and 24-hour clock time of LY3493269 dosing will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.6.1. Bioanalysis

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

Concentrations of LY3493269 will be assayed using a validated LC-MS/MS method. 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.

9.7. Pharmacodynamics

Pharmacodynamic 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.

9.7.1. Oral Glucose Tolerance Test

Glucose, C-peptide and insulin will be measured in an OGTT to assess effects of LY3493269 on glycemic control, disposition index, insulin secretion and insulin sensitivity. The schedule for OGTTs is indicated in the Schedule of Activities (Section 2).

Participants will maintain adequate carbohydrate intake 3 days before the scheduled OGTT and fast for approximately 8 hours overnight before administration of the OGTT. A 75-gram glucose dose will be given orally. Participants should consume the glucose load within 5 minutes. If participants develop symptoms of hypoglycemia, bedside BG concentration may be measured. The participant will be treated per investigator discretion.

Blood samples will be drawn for assessment of glucose, insulin and C-peptide concentrations pre-test and at 0.5, 1, 1.5 and 2 hours after the initiation of the glucose load.

9.7.2. Pharmacodynamic Markers

Fasting serum samples for glucose, insulin, and C-peptide will be evaluated as PD biomarkers. CCI [redacted]

Plasma/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.

9.8. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable exposure or response to LY3493269 and to investigate genetic variants thought to play a role in T2DM, obesity, or diabetes complications including nonalcoholic steatohepatitis (NASH). Assessment of variable response may include evaluation of AEs or differences in efficacy.

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 investigative site personnel.

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

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.9. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, 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-1 receptor target engagement.

Serum and plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

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

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

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and/or 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.

9.10. 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 Schedule of Activities (Section 2).

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.

9.11. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. 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.

Participants who are randomized but not administered treatment prior to discontinuation may be replaced to ensure that approximately 8 participants may complete each SC Cohort, and 6 to complete the IV cohort.

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

10.2. Populations for Analyses

10.2.1. 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.

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on data from all participants who receive a dose of the IP and have evaluable PK.

Pharmacodynamic analyses will be conducted on the full analysis dataset.

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

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses. Statistical analyses will be fully detailed in the statistical analysis plan.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IP and protocol procedure 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 IP as perceived by the investigator. Symptoms reported to occur prior to the first dose of IP will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include laboratory tests, vital signs, body weight, 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, time (of measurement), and treatment-by-time 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 heart rate. Outliers for these parameters may be summarized by dose groups. 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 exposures on QTcF and other intervals.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3493269 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum drug concentration (C_{max}), time to maximum concentration (t_{max}) and area under the concentration versus time curve (AUC) of LY3493269. Other noncompartmental parameters, such as half-life, clearance, and volume of distribution may be reported. Subcutaneous bioavailability will also be reported. All PK

parameters will be summarized using descriptive statistics. If necessary, additional population PK modeling may be performed.

The relationship between LY3493269 doses and/or concentrations and key safety (such as QT interval, blood pressure, heart rate, PR), tolerability (such as nausea, vomiting) and efficacy (fasting glucose) measures may be assessed via PK/PD analyses or graphical explorations. Endpoints may include but are not necessarily limited to those listed above.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetics dose proportionality will be assessed. Log-transformed C_{max} and AUC of LY3493269 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.

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

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

Inferences will be sought regarding the effect of LY3493269 on the PD endpoints of fasting glucose, and insulin. Exploratory PD may include, but are not limited to, OGTT-derived glycemic control parameters. Such effects will be explored over different doses of LY3493269 and at applicable time points as per the Schedule of Activities (Section 2).

10.3.3.2. Pharmacodynamic Statistical Inference

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, day, and treatment-by-day interaction as fixed effects, and participant as a random effect. Baseline values, as well as other influencing variables, may be used as covariates.

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

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

The relationships between LY3493269 doses or concentrations and key safety, tolerability and efficacy endpoints and their time-course profiles may be evaluated via modeling, or graphically if there is sufficient data.

10.3.5. Evaluation of Immunogenicity

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.

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.

10.3.6. 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 5.1. 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. Prior to confirming the dose and initiating the IV Cohort, preliminary PK data from at least 1 preceding SC cohort must be reviewed.

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.

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

10.3.7. Interim Analyses

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.

11. References

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
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.
ADA	Anti-drug antibody
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BG	Blood glucose
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received
BP	Blood pressure
CBC	Complete blood count
CK	Creatine kinase
CNS	Central nervous system
CIOMS	Council for International Organizations of Medical Sciences
Cmax	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 the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist
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
CSE	Clinically significant events
CV	Cardiovascular
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.
ERB	ethical review board
FSH	Follicle-stimulating hormone
GCP	good clinical practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GIPRA	Glucose-dependent insulinotropic polypeptide receptor agonist
GLP-1	Glucagon-like peptide-1
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
HR	Heart rate
IB	Investigator’s Brochure
ICF	informed consent form

ICH	International Council for Harmonization
Ig	immunoglobulin
IGFBP2	Insulin-like growth factor binding protein 2 (IGFBP2)
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.
Investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ISR	injection site reaction
IV	intravenous
LDL	low-density lipoprotein
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study.
LOEL	Lowest-observed-effect level
MTD	maximum tolerated dose
NASH	nonalcoholic steatohepatitis
NOAEL	No-observed-adverse-effect levels
OGTT	Oral glucose tolerance test
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
randomize	the process of assigning participants/s to an experimental group on a random basis
PK/PD	pharmacokinetic/pharmacodynamic
PG	Plasma glucose

PR	pulse rate
QW	once-weekly
RBC	red blood cell
SAD	single-ascending dose
SAE	serious adverse event
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SRP	safety review panel
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
T2DM	Type 2 diabetes mellitus
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
Tmax	Time to maximum observed drug concentration
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

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[b]
Ketones	Total cholesterol[b]
Bilirubin	HbA1c[b]
Urobilinogen	
Nitrite	Serology
Blood	Hepatitis B surface antigen[b,c]
Leukocytes	Hepatitis C virus serology (Anti-HCV)[b,c]
Microscopy[a]	Human immunodeficiency virus (HIV)[b,c]
	Follicle-stimulating hormone (FSH)[b,d]
	Pregnancy test[e]

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FSH = follicle-stimulating hormone; HCV = Hepatitis C virus; HIV = Human immunodeficiency virus; RBC = red blood cells; WBC = white blood cell.

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

[b] Performed at screening only.

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

[d] To be performed for women at screening, if needed to confirm postmenopausal status.

[e] For females only: A serum pregnancy test will be performed at screening and urine pregnancy test at the Day 43 follow-up.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Inclusion or omission of calculated values will not be considered as a protocol deviation.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the participant understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each participant or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP.
- answering any questions the participant may have throughout the study and sharing in a timely manner any new information that may be relevant to the participant's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for participants. Individual investigators may have additional local requirements or processes. Study specific recruitment material should be approved by Lilly.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, the principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor,

applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability

Appendix 5. Blood Sampling Summary

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

Protocol J1X-MC-GZHA

Subcutaneous Dosing Cohorts

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	5	50
Follow-up/Early discontinuation visit	8	3	24
LY3493269 pharmacokinetics	5	12	60
Potential additional LY3493269 pharmacokinetic samples	5	3	15
Blood discard for cannula patency	0.3	13	3.9
Point-of-care safety glucose (on-site)	0.3	15	4.5
Pharmacodynamics (central laboratory)			
• Glucose	2	16	32
• Insulin, C-peptide	3	16	48
• CCI	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Pharmacogenetic sample (stored)	10	1	10
Non-pharmacogenetic sample (stored)			
• Plasma	2	4	8
• Serum	2.5	4	10
• P800	2	4	8
Immunogenicity	10	4	40
Total			390.9
Total for clinical purposes (rounded up to the nearest 10mL)			400

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

Intravenous Dosing Cohort

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	5	50
Follow-up/Early discontinuation visit	8	3	24
LY3493269 pharmacokinetics	5	18	90
Potential additional LY3493269 pharmacokinetic samples	5	3	15
Blood discard for cannula patency	0.3	13	3.9
Point-of-care safety glucose (on-site)	0.3	15	4.5
Pharmacogenetic sample (stored)	10	1	10
Non-pharmacogenetic sample (stored)			
Plasma	2	4	8
Serum	2.5	4	10
P800	2	4	8
Immunogenicity	10	4	40
Total			263.4
Total for clinical purposes			270

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

Appendix 6. Pancreatic Monitoring

Glucagon-like peptide 1 agonists have been associated with a possible risk of acute pancreatitis. In 2006, the United States (US) 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 LY3437943 on the exocrine pancreas, amylase and lipase values will be monitored in all current and future clinical trials with LY3437943.

Additional monitoring will be requested for amylase or lipase values ≥3X the ULN at any visit after randomization, even in asymptomatic participants (see figure below). 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.

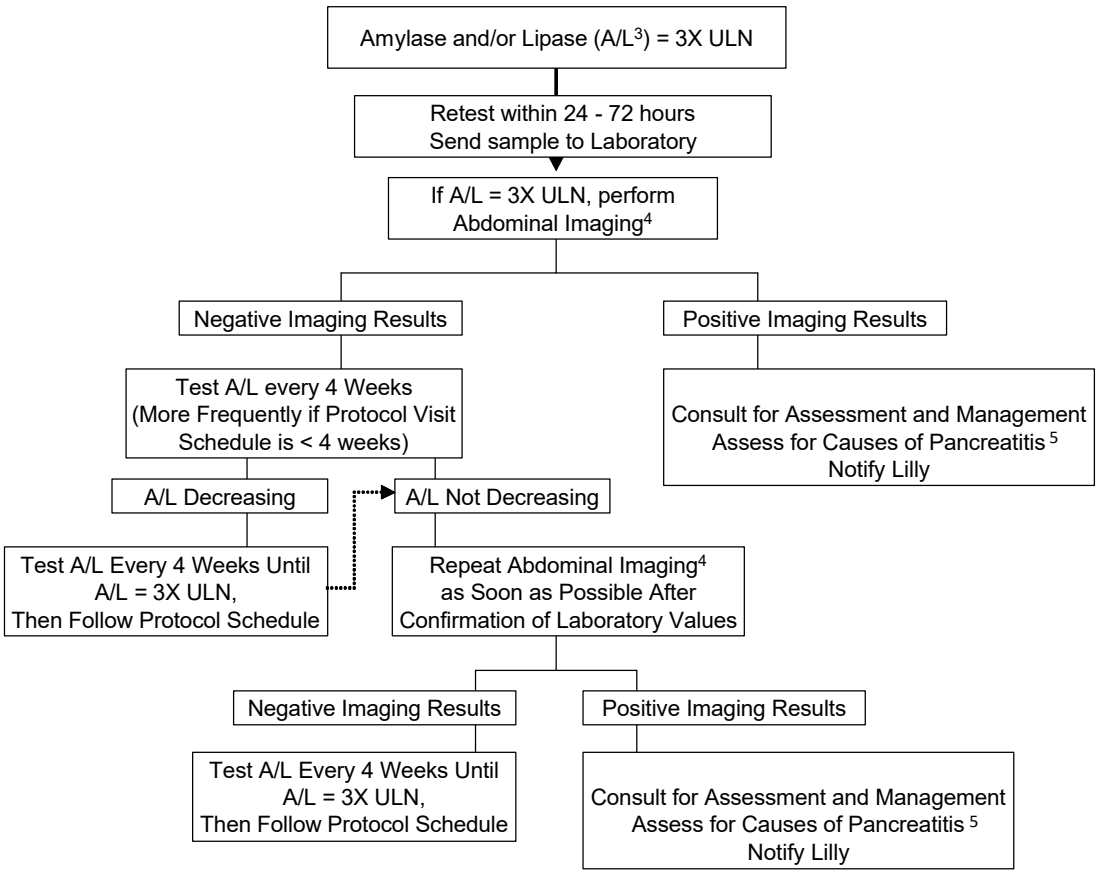
Acute pancreatitis is an AE defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3X ULN
- characteristic findings of acute pancreatitis on computed tomography 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. 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.

Pancreatic Enzymes: Safety Monitoring Algorithm In Patients without Symptoms of Pancreatitis[1,2]

Follow this algorithm when the value(s) for serum amylase and/or lipase are = 3x upper limit of normal (ULN)



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

2. If in the opinion of the investigator, the patient has symptoms of acute pancreatitis:
   (a) Stop injectable study drug
   (b) Consult for assessment and management
   (c) Assess for causes of pancreatitis
   (d) Notify Lilly

3. A/L = amylase and/or lipase. Either or both enzymes 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. At a minimum, order a CBC and a pancreatic panel (which includes LFTs, calcium and triglycerides). Record all concomitant medications.

Abbreviations: CBC = complete blood count; CT = computed tomography; LFT = liver function test; MRI = magnetic resonance imaging; ULN = upper limit of normal.

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.

Appendix 7. Hypersensitivity Event Tests

This table list 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.

Hypersensitivity Tests[a]	
Anti-LY antibodies (immunogenicity)	Tryptase
LY concentration (PK)	N-methylhistamine
	Drug Specific IgE[b]
	Basophil Activation Test[b]
	Complements
	Cytokine Panel

Abbreviations: PK = pharmacokinetic; LY = LY3493269

a Assayed by Lilly-designated laboratory

b Basophil Activation test will be performed if a drug specific IgE assay is unavailable.

Appendix 8. Guidance on Clinically Significant Events

The table below summarizes the type and severity of symptoms, clinical signs, and clinical laboratory findings that may qualify as a CSE. These are intended as a guideline to the investigator(s), not as a set of absolute criteria. The underlying principle is to define a level of moderate to severe abnormality in safety findings that could cause harm to health and which should trigger consideration of whether or not it would be appropriate to continue dosing of a participant who experiences this effect. Safety parameters not included in this table may be interpreted in a similar manner according to investigators' judgment.

Parameter	CSE level
Symptoms	
Dizziness/hypotension	Orthostatic CNS symptoms (dizziness, confusion) that are not vasovagal responses to provocative stimuli (for example, phlebotomy, nausea, bowel, or bladder function), and are associated with orthostatic SBP decrease >20 mm Hg or DBP decrease >10 mm Hg or heart rate >105 bpm, for >3 hours
Sensorium	Disorientation to time, place, or identity. Any abnormal ideation
Mood	Feelings of grief or loss that interfere with study procedures or activities of daily living. Any suicidal ideation
Headache/pain	Any focal or generalized head pain that disrupts normal activities and is not responsive to medical therapies
Pruritus	Generalized itching over >24 hours unresponsive to oral antihistamine
Signs	
Systolic blood pressure	>30 mm Hg increase from baseline values and an absolute level >190 mm Hg
Diastolic blood pressure	>20 mm Hg increase from baseline values and an absolute level >115 mm Hg
Heart rate	Resting (sitting or recumbent) HR >120 bpm
Cardiac rhythm	Any symptomatic rhythm other than sinus rhythm, mild sinus bradycardia, or mild sinus tachycardia
QTc	>500 msec and >60 msec increase from baseline value
QRS morphology	Significant prolongation of QRS interval or new onset of bundle branch block
Tremor	Readily visible tremor during normal movement deemed unrelated to hypoglycemia
Reflexes	New onset of clonic reflexes
Clinical Laboratory	(if confirmed by repeat measurements within 48 hours)
Hemoglobin	Absolute value <10 g/dL and >2 g/dL reduction from baseline
Neutropenia	Absolute neutrophils <1,500/μL and >1,000 μL decrease from baseline
Lymphopenia	Absolute lymphocyte count <800/μL and >500/μL decrease from baseline
Platelet count	<75,000/μL and >50,000/μL decrease from baseline
Creatinine	>180 μmol/L and >30 μmol/L increase from baseline value
Urea	>8 mmol/L and >3 mmol/L increase from baseline value
Alanine aminotransferase	≥5-fold above laboratory reference upper limit value [also see section 9.4.5.2 Hepatic Safety]
Potassium	<2.5 or >5.5 mmol/L and >0.5 mmol/L change from baseline value
Sodium	<130 or >150 mmol/L and >10 mmol/L change from baseline value

Abbreviations: CNS = central nervous system; CSE = clinically significant event; DBP = diastolic blood pressure; HR = heart rate; QTc = corrected QT interval; SBP = systolic blood pressure.

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