Protocol J1X-MC-GZHC (c)

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple-Ascending Subcutaneous Doses of LY3493269 in Patients with Type 2 Diabetes Mellitus

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Approval Date: 16-Jul-2021

Title Page

Protocol Title: Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple-Ascending Subcutaneous Doses of LY3493269 in Patients with Type 2 Diabetes Mellitus

Protocol Number: J1X-MC-GZHC

Amendment Number: c

Compound: LY3493269

Study Phase: 1

Short Title: Multiple-Ascending Dose Study of LY3493269 Administered Subcutaneously

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number: IND 148278

Approval Date:

Protocol Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 16-Jul-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	*13-October-2020*
Amendment (a)	*11-July-2020*
Original Protocol	*27-May-2020*

Amendment [c]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

This amendment serves to clarify that all samples collected for determination of acetaminophen concentrations (as a pharmacodynamic marker for gastric emptying) must be analyzed, regardless of the treatment assigned to the trial participant.

Section # and Name	Description of Change	Brief Rationale
8.5.1.2. Bioanalysis of Acetaminophen	Removed the sentence "Analysis of samples collected from placebo treated participants are not planned"	The statement was removed as all samples collected for PD markers must be analyzed.
9.4.4. Pharmacodynamic Analysis	Added placebo in the sentence "Baseline-adjusted C_{max} of acetaminophen (ratio to Day -1 value) will be calculated and log transformed to compare the gastric-emptying effect of LY3493269 to that of dulaglutide and placebo"	To clarify that data from placebo-treated participants will also be analyzed.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple-Ascending Subcutaneous Doses of LY3493269 in Patients with Type 2 Diabetes Mellitus

Short Title: Multiple-Ascending Dose Study of LY3493269 Administered Subcutaneously

Rationale:

LY3493269 is a dual glucose-dependent insulinotropic polypeptide and glucagon-like-peptide 1 (GLP-1) receptor agonist being developed as a treatment for type 2 diabetes mellitus (T2DM). This is the first study in participants with T2DM to test multiple subcutaneous (SC) doses of LY3493269 to establish early exposure-responses for key efficacy, safety, and tolerability relationships (for example, blood glucose, glycated hemoglobin). Using a stepwise escalation, it is planned that this study will test dose levels higher than those tested in the single-ascending dose study.

Study J1X-MC-GZHC (GZHC) will investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics (PD) of LY3493269 administered as 4 once-weekly SC doses in patients with T2DM. Trulicity® (dulaglutide) will be used as a positive control for PD of GLP-1 pharmacology.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of LY3493269 following 4 once-weekly SC doses	• TEAEs and SAEs
Secondary	
• To characterize the PK of LY3493269 following 4 once-weekly SC doses	• C_{max} and AUC
• To evaluate the change in FG following 4 once-weekly SC doses of LY3493269 and dulaglutide	• Change from baseline in FG

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; FG = fasting glucose; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

Overall Design

Study GZHC is a Phase 1, multicenter, randomized, investigator- and participant-blind, placebo-controlled, comparator-controlled, 4-week multiple-dose escalation study in patients with T2DM.

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

Number of Participants:

Approximately 64 participants may be randomly assigned to study intervention such that approximately 12 evaluable participants from each of the 4 cohorts complete the study. If participants are discontinued during the study, additional participants may be enrolled to complete the target number of evaluable participants.

Intervention Groups and Duration:

Eligible participants will be randomly assigned to study intervention:

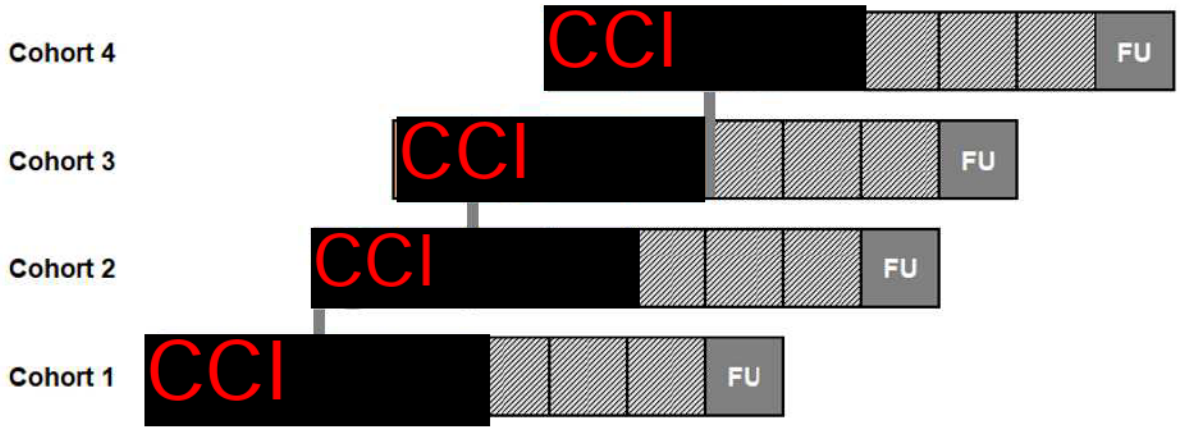
- 8 to LY3493269
- 2 to dulaglutide, and
- 2 to placebo.

Each participant's involvement in the study is expected to last up to 16 weeks, including a

- 6-week screening period
- 1-week baseline period
- 4-week treatment period, and
- a minimum 4-week follow-up period after the last dose.

Data Monitoring Committee: No

1.2. Schema



Abbreviation: FU = follow-up.

Note: The initiation of each cohort will be scheduled such that a planned escalated dose (in bold gray circles) is supported by a review of 2-week safety and tolerability data from the preceding lower dose (indicated by bold vertical gray lines). Participants in Cohorts 3 and 4 will receive the weekly doses in stepwise increments. The dose-escalation scheme and dose may be altered based on emerging safety and tolerability data.

Figure 1. Schema of Study J1X-MC-GZHC.

1.3. Schedule of Activities (SoA)

Study Schedule for Cohorts 1 and 2

Procedure	Screening	Baseline			Treatment (Cohorts 1 and 2)																					FU		Comments
Visit #		1							2		3			4		5				6	7	8			9	10	ED	
Days	**-42 to -4**	**–3**	**–2**	**–1**	**1**	**2**	**3**	**4**	**5**	**7 ±1**	**8 ±1**	**12 ±1**	**14 ±1**	**15 ±1**	**18 ±1**	**21**	**22**	**23**	**24**	**25**	**26**	**28 ±1**	**29**	**30**	**36 ±2**	**57 ±7**		
Informed consent	X																											
Drug/alcohol screen (local laboratory throughout)	X	X														X						X						Per site policy or investigator's discretion during the study.
Admission to site		X*														X						X						*May occur on Day -3 or -2.
Discharge from site								X											X					X				
Outpatient visit	X								X		X			X						X	X				X	X	X	Days 25 and 26 procedures may be conducted while inpatient.
Overnight fast		X	X	X	X	X	X			X			X			X	X	X				X	X					
Administer study drug					**X**						**X**			**X**			**X**											
Medical history	X																											
Physical examination	X																											
Medical assessment					P			X	X		P			P			P	X	X				X	X	X	X	X	Medical review and targeted examination, as appropriate.
Height	X																											
Weight and waist circumference	X		X								P			P			P						X		X	X	X	
Body temperature	X		X	X	P																		X					

Procedure	Screening	Baseline			Treatment (Cohorts 1 and 2)																					FU		Comments
Visit #		1							2		3			4		5				6	7	8			9	10	ED	
Days	**-42 to -4**	**−3**	**−2**	**−1**	**1**	**2**	**3**	**4**	**5**	**7 ±1**	**8 ±1**	**12 ±1**	**14 ±1**	**15 ±1**	**18 ±1**	**21**	**22**	**23**	**24**	**25**	**26**	**28 ±1**	**29**	**30**	**36 ±2**	**57 ±7**		
Vital signs – BP/HR (h)	X		X	X	P, 1, 4, 6, 12	24	48	72	X		P			P			P, 6, 12	24	48				X	X	X	X	X	
ECG – single (h)	X		X																						X	X	X	
ECG – triplicate (h)					-0.5, -0.25, P, 1, 4, 6, 12	24	48	72	X		P			P			P, 6, 12	24	48				X	X				
PK sampling (h)					P, 6, 12	24	48	72	96		P			P			P, 6, 12	24	48	X	X		X		X	X	X	
Clinical laboratory tests - fasting	X				P	X		X			P			P			P						X		X	X	X	
Hemoglobin A1c	X				P																		X		X		X	
AEs/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Phone calls for safety monitoring										X		X	X		X													
SMBG supply distribution, training on self-monitoring and patient diaries			X								X			X			X								X			Complete prior to discharge from Visit 1.
Fasting plasma glucose			X		P						P			P			P		X				X				X	
6-point glucose			X		X		X										X						X					
OGTT • Glucose • Insulin • C-peptide • Glucagon				X		X												X						X				See Table 1 for sampling schedule.
Acetaminophen PK for GE test				X		X												X										See Table 1 for sampling schedule.

Procedure	Screening	Baseline			Treatment (Cohorts 1 and 2)																				FU		Comments
Visit #		1							2		3			4		5				6	7	8			9	10	ED	
Days	**-42 to -4**	**−3**	**−2**	**−1**	**1**	**2**	**3**	**4**	**5**	**7 ±1**	**8 ±1**	**12 ±1**	**14 ±1**	**15 ±1**	**18 ±1**	**21**	**22**	**23**	**24**	**25**	**26**	**28 ±1**	**29**	**30**	**36 ±2**	**57 ±7**		
Lipid panel, fasting • TG • Total cholesterol • LDL-cholesterol • VLDL-cholesterol • HDL-cholesterol					P																		X				X	
Satiety VAS fasting				X	P						P			P			P						X					
PGx sample					P																							
Non-PGx sample fasting (storage)					P						P			P			P						X				X	
Immunogenicity					P									P									X			X	X	

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; GE = gastric emptying; h = hour; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; min = minutes; OGTT = oral glucose tolerance test; P = predose; PD = pharmacodynamics; PGx = pharmacogenetics; PK = pharmacokinetics; SMBG = self-monitored blood glucose; TG = triglyceride; VAS = visual analog scale; VLDL = very low-density lipoprotein; X = at any time during visit (for OGTT and GE test – refer to Table 1).

Table Color Code		Outpatient Visit		Inpatient visit		Off-site activity

Notes:

- Clinical laboratory tests at screening shall be analyzed at a local laboratory. All other clinical laboratory tests, PK, PD, and biomarker samples obtained during the study will be analyzed at a Central Laboratory.
- Where “fasting” is required, participants must have fasted for a minimum of 8 hours prior to the scheduled assessment(s).
- If multiple procedures take place at the same time point, the following order of the procedure should be used: vital signs, ECG, and blood collection at the scheduled time point.
- 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.
- Postdose assessments and procedures scheduled after the 24-hour time point should be performed within ±3 hours of the scheduled time.

Study Schedule for Cohorts 3 and 4

Procedure	Screening	Baseline			Treatment (Cohorts 3 and 4)																						FU		Comments
Visit #		1							2		3				4			5				6	7	8			9	10	ED	
Days	**-42 to -4**	**−3**	**−2**	**−1**	**1**	**2**	**3**	**4**	**5**	**7 ±1**	**8 ±1**	**9±1**	**12 ±1**	**14 ±1**	**15 ±1**	**16±1**	**18 ±1**	**21**	**22**	**23**	**24**	**25**	**26**	**28 ±1**	**29**	**30**	**36 ±2**	**57 ±7**		
Informed consent	X																												
Drug/alcohol screen (local laboratory throughout)	X	X									X				X			X						X					Per site policy or investigator's discretion during the study.
Admission to site		X*									X				X			X						X					*May occur on Day -3 or -2.
Discharge from site								X				X				X					X					X				
Outpatient visit	X								X													X	X				X	X	X	Days 25 and 26 procedures may be conducted while inpatient.
Overnight fast		X	X	X	X	X	X			X				X				X	X	X				X	X					
Administer study drug					**X**						**X**				**X**				**X**											
Medical history	X																													
Physical examination	X																													
Medical assessment					P			X	X		P				P				P	X	X					X	X	X	X	X	Medical review and targeted examination, as appropriate.
Height	X																													
Weight and waist circumference	X		X								P				P				P						X			X	X	X	
Body temperature	X		X	X	P																				X					
ECG – single (h)	X		X																								X	X	X	

Procedure	Screening	Baseline			Treatment (Cohorts 3 and 4)																						FU		Comments
Visit #		1							2		3			4			5			6	7	8			9	10	ED	
Days	-42 to -4	–3	–2	–1	1	2	3	4	5	7 ±1	8 ±1	9±1	12 ±1	14 ±1	15 ±1	16±1	18 ±1	21	22	23	24	25	26	28 ±1	29	30	36 ±2	57 ±7		
ECG – triplicate (h)					-0.5, -0.25, P, 1, 4, 6, 12	24	48	72	X		P, 1, 4, 6, 12	24			P, 1, 4, 6, 12	24			P, 1, 4, 6, 12	24	48				X	X				
Vital signs – BP/HR (h)	X		X	X	P, 1, 4, 6, 12	24	48	72	X		P, 1, 4, 6, 12	24			P, 1, 4, 6, 12	24			P, 1, 4, 6, 12	24	48				X	X	X	X	X	
PK sampling (h)					P, 6, 12	24	48	72	96		P, 4				P, 4				P, 6, 12	24	48	X	X		X		X	X	X	
Clinical laboratory tests - fasting	X				P	X		X			P				P				P						X		X	X	X	
Hemoglobin A1c	X				P																				X		X		X	
AEs/concomitant medications	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Phone calls for safety monitoring										X			X	X			X													
SMBG supply distribution, training on self-monitoring and patient diaries							X				X				X				X								X			Complete prior to discharge from Visit 1.
Fasting plasma glucose			X		P						P				P				P		X				X				X	
6-point glucose			X		X		X												X						X					
OGTT • Glucose • Insulin • C-peptide • Glucagon				X		X														X						X				See Table 1 for sampling schedule.
Acetaminophen PK for GE test				X		X														X										See Table 1 for sampling schedule.

Procedure	Screening	Baseline			Treatment (Cohorts 3 and 4)																					FU		Comments
Visit #		1							2		3			4			5				6	7	8			9	10	ED	
Days	-42 to -4	–3	–2	–1	1	2	3	4	5	7 ±1	8 ±1	9±1	12 ±1	14 ±1	15 ±1	16±1	18 ±1	21	22	23	24	25	26	28 ±1	29	30	36 ±2	57 ±7		
Lipid panel, fasting • TG • Total cholesterol • LDL-cholesterol • VLDL-cholesterol • HDL-cholesterol					P																				X			X	
Satiety VAS fasting				X	P						P				P				P						X				
PGx sample					P																								
Non-PGx sample fasting (storage)					P						P				P				P						X			X	
Immunogenicity					P										P										X			X	

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; GE = gastric emptying; h = hour; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; min = minutes; OGTT = oral glucose tolerance test; P = predose; PD = pharmacodynamics; PGx = pharmacogenetics; PK = pharmacokinetics; SMBG = self-monitored blood glucose; TG = triglyceride; VAS = visual analog scale; VLDL = very low-density lipoprotein; X = at any time during visit (for OGTT and GE test – refer to Table 1).

Table Color Code		Outpatient Visit		Inpatient visit		Off-site activity

Notes:

- Clinical laboratory tests at screening shall be analyzed at a local laboratory. All other clinical laboratory tests, PK, PD, and biomarker samples obtained during the study will be analyzed at a Central Laboratory.
- Where “fasting” is required, participants must have fasted for a minimum of 8 hours prior to the scheduled assessment(s).
- If multiple procedures take place at the same time point, the following order of the procedure should be used: vital signs, ECG, and blood collection at the scheduled time point.
- 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.
- Postdose assessments and procedures scheduled after the 24-hour time point should be performed within ±3 hours of the scheduled time.

Table 1. Assessment Schedule for Oral Glucose Tolerance Test and Gastric Emptying Test

Oral Glucose Tolerance Test (OGTT)			Gastric Emptying (GE) Test		
Timing (h)[a]	**Activity**	**OGTT samples[b]**	**Timing (h)[c]**	**Activity**	**Acetaminophen PK samples**
0[d]	Oral glucose solution intake	X[e]	-0.5		
0.5		X	0	Acetaminophen solution intake	X[f]
1		X	0.5		X
1.25		-	0.75		X
1.5		X	1		X
2	End of OGTT	X	1.5		-
			2		X
			3		X
			4		X
			6		X
			9		X
			12		X
			24	End of GE test	X

Abbreviations: GE = gastric emptying; OGTT = oral glucose tolerance test; PK = pharmacokinetics.

[a] OGTT sample collections are scheduled with reference to the oral glucose solution intake at time "0 h" in this column. Sample collections should occur within ±10% of the scheduled time.

[b] At each OGTT timepoint, samples are collected for glucose, insulin, C-peptide and glucagon.

[c] Acetaminophen PK sample collections are scheduled with reference to the acetaminophen solution intake at time "0 h" in this column. Sample collections should occur within ±10% of the scheduled time.

[d] Time "0 h" for OGTT on Day -1 should be scheduled at least 25 hours before the intended study intervention dosing on Day 1.

[e] Sample collection occurs before intake of glucose solution, after a minimum 8-hour fast.

[f] Acetaminophen pre-dose sample collection. Acetaminophen PK samples and oral dose are scheduled with reference to acetaminophen dosing at time = 0h and approximately 30 minutes after the glucose solution intake for OGTT.

2. Introduction

LY3493269 is a dual-agonist peptide that combines actions of 2 incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide 1 (GLP-1). LY3493269 is being developed as a once-weekly (QW) subcutaneous (SC) treatment for type 2 diabetes mellitus (T2DM). In addition, a once-daily oral formulation of LY3493269 is also in development.

2.1. Study Rationale

Study J1X-MC-GZHC (GZHC) will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of LY3493269 administered as 4 QW SC doses in patients with T2DM compared with placebo. The primary objective is to assess safety and tolerability, and the secondary objectives are to evaluate the PK and change in fasting glucose from baseline.

This is the first study to test multiple weekly SC doses of LY3493269 to establish early exposure-responses for key efficacy, safety, and tolerability relationships (for example, blood glucose, glycated hemoglobin [HbA1c]). Using a stepwise dose-escalation approach, this study will test dose levels higher than those investigated in Study J1X-MC-GZHA (GZHA), the first-in-human single-ascending dose (SAD) study of LY3493269.

Trulicity® (dulaglutide) will be used as a positive control for PD of GLP-1 pharmacology.

2.2. Background

Type 2 diabetes mellitus is characterized by impaired glycemic control due to insulin resistance and inadequate insulin secretion due to the pancreatic beta-cell failure. Type 2 diabetes mellitus is frequently associated with comorbidities such as obesity, hypertension, and dyslipidemia resulting in increased risk of microvascular and macrovascular complications.

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

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

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

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

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

2.2.1. Summary of Clinical Experience

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

As of 06 April 2020, 3 cohorts of 6 participants received SC doses of LY3493269 at each of the CCI [redacted] was considered not well tolerated due to increases in the number of GI events requiring treatment. The prespecified dose-escalation stopping criteria were not met; however, due to concerns about safety and tolerability with the next planned CCI [redacted] the sponsor decided to stop further dosing.

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

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

Consistent with the incretin class, GI events such as abdominal distension, nausea, vomiting, and diarrhea were the most commonly reported AEs in Study GZHA. In addition, decreased appetite was also 1 of the most frequently reported AEs. All TEAEs were considered as mild in severity by the investigator, even though some required treatment. An increase in the number of AEs related to study drug was noted with increasing doses of LY3493269 as compared to placebo. In Cohort 2, where subjects received CCI [redacted] subject out of 6 presented nausea, and none presented vomiting. However, 3 subjects out of 6 in Cohort 3 receiving CCI [redacted] reported GI AEs of nausea and vomiting, requiring anti-emetics. Several other GI AEs were reported in Cohort 3 (for example, abdominal pain upper, constipation, eructation, epigastric discomfort, dry mouth, and dyspepsia.) not previously reported in the other cohorts.

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

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

Six participants received the CCI [redacted] intravenous dose as planned. Mild events of decreased appetite and GI events such as abdominal distension and nausea were noted.

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

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

Further details are available in the Investigator's Brochure (IB) for LY3493269.

2.3. Benefit/Risk Assessment

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

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

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

Refer to the IB for more information about the nonclinical and clinical data of LY3493269.

All identified risks from preclinical and clinical studies are considered monitorable and manageable at the planned dose range of [redacted] of LY3493269. Risks are similar to those noted during development of GIP and GLP-1 agonists. To further minimize any potential risk, participants will remain at the investigative site for at least 4 days after the first dose for safety and tolerability monitoring until discharge. Participants will be closely monitored with scheduled medical assessments, vital signs, and triplicate ECG measurements. The investigator will have the discretion to extend the participant inpatient stay for further safety monitoring.

Refer to the IB for more information about the nonclinical and clinical data of LY3493269. More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3493269 may be found in the IB.

Refer to the Prescribing Information for Trulicity (Trulicity United States Package Insert, 2019) for more information about the known and expected benefits and risks of dulaglutide .

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of LY3493269 following 4 once-weekly SC doses	• TEAEs and SAEs
Secondary	
• To characterize the PK of LY3493269 following 4 once-weekly SC doses	• C_{max} and AUC
• To evaluate the change in FG following 4 once-weekly SC doses of LY3493269 and dulaglutide	• Change from baseline in FG
Exploratory	

• To explore PD effects of LY3493269 and dulaglutide following 4 once-weekly SC doses	• Change from baseline in mean daily PG (6-point PG profile)
	• Change from baseline in HbA1c
	• Change from premeal fasting during OGTT for
	  o PG concentrations
	  o insulin concentrations
	  o C-peptide concentrations
	  o glucagon concentrations
	• Change from baseline in indices of beta-cell function
	  ▪ HOMA2-B
	  ▪ disposition index from OGTT
	  ▪ ΔI30/ΔG30 from OGTT
	  ▪ Insulin $AUC_{0\text{-}120min}$ from OGTT
	• Change from baseline in
	  o fasting insulin sensitivity indices
	  ▪ HOMA2-IR
	  ▪ fasting insulin
	  o postprandial insulin sensitivity indices
	  ▪ Matsuda
	  ▪ OGIS
	  ▪ Stumvoll
	• Change from baseline in fasting lipid parameters
	  ▪ triglycerides
	  ▪ total cholesterol, and
	  ▪ LDL-, HDL-, and VLDL-cholesterol, and
	• Change from baseline in body weight
	• Change from baseline in waist circumference
	• Change from baseline in gastric emptying
	• Change in appetite visual analog scale at fasting

• To characterize the immunogenicity of LY3493269 following 4 once-weekly SC doses	• Incidence of treatment-emergent ADA

Abbreviations: ADA = antidrug antibody; AUC = area under the concentration versus time curve; $AUC_{0\text{-}120min}$ = AUC from 0 to 120 minutes; C_{max} = maximum observed drug concentration; ΔG30 = 30-minute glucose in OGTT- baseline (0 minute) fasting glucose in OGTT; ΔI30 = 30-minute insulin in OGTT- baseline (0 minute) fasting insulin in OGTT; FG = fasting glucose; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HOMA2-IR = homeostatic model assessment for insulin resistance; HOMA2-B = updated homeostatic model assessment for beta-cell function; LDL = low-density lipoprotein; OGIS = oral glucose insulin sensitivity; OGTT = oral glucose tolerance test; PD = pharmacodynamics; PG = plasma glucose; PK = pharmacokinetics; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event; VLDL = very low-density lipoprotein.

4. Study Design

Study GZHC is a Phase 1, randomized, investigator- and participant-blind, placebo-controlled, comparator-controlled, 4-week multiple-dose escalation study in patients with T2DM.

Trulicity (dulaglutide) will be used as a positive control for PD of GLP-1 pharmacology.

4.1. Overall Design

Up to 4 cohorts are planned to receive a weekly dose of study intervention for 4 weeks (Figure 1). The investigator or designee will administer the study intervention at the investigate site.

Participants found to be eligible according to the study entry criteria will be randomly assigned to receive LY3493269, placebo, or dulaglutide. Participants not randomly assigned to LY3493269 will receive a CCI of dulaglutide or a placebo QW for 4 weeks. Depending on their cohort, participants randomly assigned to LY3493269 will receive CCI QW for 4 weeks (Table 2). Cohorts 1 and 2 will receive 4 fixed doses. Cohorts 3 and 4 will receive the weekly doses in stepwise increments, as guided by emerging tolerability, PK, and/or PD data in the preceding dose cohorts.

The need to adjust the starting dose of a cohort (Cohorts 2, 3, and 4) and dose-escalation decisions within Cohorts 3 and 4 will be based on the evaluation of preliminary safety and tolerability data. Any available PK and PD data may be included in the dose-escalation decision, to be made jointly by the investigator and sponsor after review of all available data (Section 6.6).

Each participant's involvement in the study is expected to last up to 16 weeks, including a

- 6-week screening period
- 1-week baseline period
- 4-week treatment period, and
- A minimum 4-week follow-up period after the last dose.

There will be a minimum of 3 inpatient visits and up to 8 outpatient visits, during which participants will receive study intervention and undergo safety, PK, and PD assessments according to Section 1.3. For additional safety monitoring during inpatient visits, participants may remain at the investigative site for additional days after receiving weekly dose at any of the scheduled dosing visits. Discharge from the investigative site will be based on the investigator's

medical judgment. If required, the inpatient period may be extended to facilitate adherence to site policy, local guidelines, and/or regulations.

4.1.1. Screening Period

The outpatient screening visit may be up to 42 days prior to enrollment. Individuals who are not enrolled within 42 days of screening shall undergo an additional medical assessment and/or clinical measurements (including but not limited to clinical laboratory tests, ECG, vital signs, weight, and waist circumference measurements) to confirm their eligibility. Parameters that may be repeated for screening include clinical laboratory tests, ECGs, and vital signs.

4.1.2. Baseline Period

During this baseline period, participants may be admitted to the investigative site on Day -3 and observe an overnight fast of at least 8 hours on that evening. Otherwise, participants may be admitted on Day -2 but should be fasting for at least 8 hours upon arrival to the investigative site. Participants should complete the study assessments and procedures planned during this period as specified in Section 1.3.

Eligible participants will be randomly assigned to study intervention on the morning of Day 1:

- 8 to LY3493269
- 2 to placebo, and
- 2 to dulaglutide.

If eligible per screening window and inclusion/exclusion criteria, participants who complete the baseline assessments but are not assigned to study intervention on the following day may repeat the baseline assessments once, on a later occasion, if it falls within the screening window of 42 days prior to their next planned enrollment.

4.1.3. Treatment Period

While inpatient at the investigative site, participants will receive their first SC dose of study intervention on Day 1. Participants should complete the study assessments and procedures planned during this period as specified in Section 1.3. Unless the investigator identifies a safety concern, participants may be discharged from the investigative site on Day 4.

Participants can be inpatient or outpatient for the study assessments and procedures planned on Day 5. Participants who are discharged on Day 4 must return to the investigative site on Day 5 for an outpatient visit. Participants who are not discharged on Day 4 will complete their inpatient visit on Day 5. If the investigator determines that additional safety monitoring is needed, a sample for clinical laboratory tests may be collected along with the other assessments and procedures planned on Day 5 in Section 1.3.

At the 2 outpatient visits planned on Days 8 and 15, participants will receive their second and third doses of study intervention, respectively. Participants should be fasting for at least 8 hours upon arrival to the investigative site. The study assessments and procedures planned during this period should be performed as specified in Section 1.3, after which the participants shall be discharged from the investigative site. When not at the investigative site, participants should record their fasting BG daily in their patient diary. The investigator or designee must review the diaries at each return visit to the site.

Two additional inpatient visits are planned for this study. Participants will be admitted to the investigative sites on Days 21 and 28. Participants will receive the final dose of study intervention on Day 22. The study assessments and procedures planned during this period should be performed as specified in Section 1.3. Unless the investigator identifies a safety concern, participants will be discharged from the investigative site on Days 24 and 30. Participants may remain resident at the site on Days 25 and 26 per investigator's discretion, to facilitate site logistics and/or compliance to the scheduled assessments on these days.

Three outpatient visits are planned on Days 25, 26, and 36 of the study. The study assessments and procedures planned during this visit should be performed as specified in Section 1.3.

The investigator shall include telephone calls for safety monitoring when participants are not at the investigator site, as specified in Section 1.3.

4.1.4. Follow-up Period

During the follow-up period, participants should attend the outpatient visit on Day 57. The follow-up visit should occur at least 28 days after the last dose of study intervention. The study assessments and procedures planned during this period should be performed as specified in Section 1.3. If a participant is found to be treatment-emergent-antidrug antibody (TE-ADA) positive at the final visit, he or she should undergo additional monitoring as described in Section 9.4.6.

All participants who are discontinued early from the study will be asked to complete a follow-up visit with Day 57 procedures after a washout period of at least 28 days from the last dose of study drug (Section 7.2).

4.2. Scientific Rationale for Study Design

Sequential study design

This study will be the first assessment of the safety and tolerability of multiple doses of LY3493269 administered QW in patients with T2DM. The sequential design ensures that each patient is naive to study intervention at the time of administration and avoids any potential carryover effects or effect of antidrug antibodies (ADAs) on interpretation of clinical data.

Stepwise dose escalation within cohort

The SAD Study GZHA demonstrated that dose levels of CCI were associated with GI AEs. Gastrointestinal events (including nausea and vomiting) were generally dose dependent. Stepwise dose increases may prove useful as a potential mitigation for these GI effects. This approach for escalating doses for a drug with GLP-1R agonist activity is expected to allow participants to reach higher maintenance dose levels with acceptable GI-related AEs.

Comparator and placebo controls

In each cohort, up to 2 participants will be randomly assigned to receive CCI, in a blinded manner for investigator, site staff, and participants, as a positive control to establish a quantitative range for the anticipated GLP-1 pharmacology. Up to 2 participants will be randomly assigned to placebo, which is included as a control, in a blinded manner for investigator, site staff, and participants, to allow an unbiased assessment of the data generated, which will allow a more robust comparison of safety, tolerability, and PD data.

Ongoing data reviews

Safety, tolerability, and any available PK and PD data obtained from the current study in participants with T2DM will assist in identifying an appropriate dose range for

- the next cohort in this study, and
- subsequent clinical studies.

Safety and tolerability assessments will be made over all dose levels, including incidence of nausea and/or vomiting, and evaluation of vital signs and ECGs. See Section 6.6 for decisions on doses.

4.2.1. Participant Input into Design

Throughout this protocol, the term "participant" is used to indicate an individual who participates in a clinical trial, as a recipient of a study intervention. This usage reflects preferences indicated by patient advocates to more accurately reflect the role of people who take part in clinical trials.

4.3. Justification for Dose

Study GZHC plans to evaluate a dose range of CCI of LY3493269 in patients with T2DM. The planned dose levels in this study are selected to provide a full evaluation of the safety and tolerability of LY3493269 following multiple doses administered through SC injection using a QW dose regimen while providing early information on potential glycemic efficacy. CCI This dose range was selected following evaluation of nonclinical data and results (tolerability, safety, PK, and PD) from the SAD study, GZHA. Study GZHA evaluated LY3493269 at CCI in healthy participants.

The starting dose level for this study will be CCI administered QW for 4 weeks in Cohort 1. The exposure multiples of the rat no-observed-adverse-effect level (NOAEL) and monkey NOAEL to this starting dose are 0.69X and 5.11X, respectively. The dose level proposed for CCI of LY3493269 administered QW for 4 weeks.

If safety, tolerability, PK, and PD data are supportive, a dose range up to CCI of LY3493269 may be studied. As stated earlier, a single SC dose of CCI was poorly tolerated in Study GZHA. However, data from prior incretin programs have shown that dose levels at least 2-fold higher than those investigated in a SAD study can be safely attained in a MAD study by utilizing a stepwise dose-escalation approach (Coskun et al. 2018; Frias et al. 2018). In those studies, higher dose levels were better tolerated using a stepwise dose-escalation scheme of administration and were able to increase exposure compared to a SAD study. Safety data from Study GZHA support this approach.

With severe weight loss being the dose-limiting factor in animals, the margin of safety is less than 1 at the NOAEL but the exposure multiple for clinical doses will be kept to above 1 for the highest dose tested in monkeys. All effects observed in the rats and monkeys were consistent with LY3493269 pharmacology. Based on the nonclinical toxicology studies, potential risks for

clinical trial participants receiving LY3493269 include HR increase, body weight loss, GI effects, and appetite loss. All these identified risks are monitorable, manageable, and reversible.

The margin of safety for the proposed MAD is presented in Table 3.


CCI

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all required visits of the study including the last scheduled procedure shown in the Schedule of Activities (SoA). Any participant who does not satisfy this definition but who has completed all the key assessments may be considered a completer at the discretion of the sponsor.

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

5. Study Population

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

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

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

5.1. Inclusion Criteria

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

Informed consent

1. Are capable of giving signed informed consent as described in Section 10.1.2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

Participant characteristics

3. Are male or female not of childbearing potential from 18 to 70 years of age inclusive, at the time of signing the informed consent.

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

4. Have a body mass index of 23 to 50 kg/m^2, inclusive, at screening.
5. Have had a stable body weight (<5% body weight change) for the 3 months prior to screening.
6. Have not modified their diet or adopted any nutritional lifestyle modification in the 3 months prior to screening.

Disease characteristics

7. Have T2DM controlled with diet and exercise alone or are on a stable dose of metformin for at least 3 months before screening. Patients with comorbid conditions commonly associated with diabetes (for example, hypertension, hypercholesterolemia, hypothyroidism) may be eligible for inclusion if conditions are assessed by the investigator to be well controlled and stable for at least 3 months prior to screening.
8. Have an HbA1c of at least 7.0% and no more than 10.5% at screening.

9. Have clinical laboratory test results within the normal range for the population or investigative site, or with abnormalities deemed not clinically significant by the investigator.
10. Have venous access sufficient to allow blood sampling as per the protocol.

5.2. Exclusion Criteria

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

Medical conditions

11. Have type 1 diabetes mellitus or latent autoimmune diabetes in adults.
12. Have uncontrolled diabetes, defined as an episode of ketoacidosis or hyperosmolar state requiring hospitalization in the 6 months prior to screening.
13. Have a history of proliferative diabetic retinopathy, diabetic maculopathy, or severe nonproliferative diabetic retinopathy that requires acute treatment.
14. Have had more than 1 episode of severe hypoglycemia, as defined by the American Diabetes Association criteria, within 6 months before screening or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms.

    Note: Any participant that cannot communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia prior to the first dose of study drug should also be excluded.
15. Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®) or chronically take medications that directly affect GI motility.
16. Have a definitive diagnosis of autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension, or diabetic diarrhea.
17. Have obesity induced by other endocrine disorders, such as Cushing's syndrome or Prader-Willi syndrome.
18. Have an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, as determined by the local laboratory at screening.
19. Have had any of the following within the past 6 months prior to screening:
    - myocardial infarction,
    - unstable angina,
    - coronary artery bypass graft,
    - percutaneous coronary intervention (diagnostic angiograms are permitted),
    - transient ischemic attack,
    - cerebrovascular accident or decompensated congestive heart failure, or
    - New York Health Association Class III or IV heart failure.
20. 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 QT data analysis, such as a QT interval corrected using Fridericia's formula (QTcF) >450 msec for males and >470 msec for women, short PR interval (<120 msec),

or PR interval >220 msec, second and third atrioventricular block, intraventricular conduction delay with QRS >120 msec, right bundle branch block, left bundle branch block, or Wolff-Parkinson-White syndrome.

21. Have a supine HR less than 50 bpm or greater than 100 bpm. If a repeat measurement shows values within the range, the patient can be included in the trial.
22. Have a mean supine systolic blood pressure higher than 160 mmHg and a mean supine diastolic blood pressure higher than 95 mmHg from 2 assessments at screening (excluding white-coat hypertension); therefore, if a repeated measurement shows values within the range, the patient can be included in the trial.
23. Have donated blood in the amount of 450 mL or more in the past 3 months or any blood donation within the last month from screening, or have had a blood transfusion or severe blood loss within the prior 3 months, or have known hemoglobinopathy (alpha thalassemia), hemolytic anemia, sickle cell anemia, or have a hemoglobin value less than 11 g/dL in males or 10 g/dL in females, or any other condition known to interfere with HbA1c methodology.
24. Have liver disease, obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, or have elevations in aminotransferase levels (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) greater than 3X upper limit of normal (ULN) at screening.
25. Have a history of Gilbert's syndrome or have total bilirubin level (TBL) above 1.5X ULN at screening.
26. Have a history of acute or chronic pancreatitis.
27. Have a fasting serum triglyceride level greater than 500 mg/dL at screening.
28. Have a history of atopy or clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).
29. Have a history of or ongoing psychiatric disorders considered clinically significant in the opinion of the investigator.
30. History of drug or alcohol abuse.
31. Have a self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.
32. Have calcitonin levels of 20 pg/mL or more at screening.
33. Have an active or untreated malignancy or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for 5 years prior to screening.
34. Have a history or presence of clinically relevant conditions constituting a risk while taking the study medication; or of interfering with the interpretation of data.

Prior/concomitant therapy

35. Have taken any glucose-lowering medications other than metformin, including insulin, in the past 3 months before screening.

36. Have been treated or plan to be treated with prescription medications that promote weight loss within 3 months prior to screening. Examples include
    - Saxenda® (liraglutide 3.0 mg)
    - Xenical® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Sanorex® (mazindol)
    - Adipex® (phentermine)
    - BELVIQ® (lorcaserin)
    - Qsymia™ (phentermine/topiramate combination)
    - Contrave® (naltrexone/bupropion), or
    - other similar body weight loss medication including over-the-counter (OTC) medications (for example, alli®).
37. Have received chronic (lasting more than 14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intra-articular, intranasal, or inhaled preparations) in the past year or have received any glucocorticoid therapy within 30 days before screening.
38. Are currently taking central nervous system stimulant(s) (for example, Ritalin-SR®) with the exception of caffeinated beverages, at screening.
39. Intend to use OTC or prescription medication 4 weeks before planned dosing, apart from occasional intake of vitamin/mineral supplements and allowable concomitant therapies provided in Section 6.5.

Prior/concurrent clinical study experience

40. Have completed or withdrawn from this study or any other study investigating LY3493269, and have previously received the study intervention.
41. Are currently enrolled in a clinical trial involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study.
42. Are currently enrolled in or past participation, within the 30 days prior to screening, in a clinical study involving a study intervention for which at least 5 half-lives or 30 days (whichever is longer) have not passed.

Diagnostic assessments

43. Have positive findings on drug screening.
44. Show evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies at screening.
45. Show evidence of hepatitis B, positive hepatitis B core antibody, and/or positive hepatitis B surface antigen.
46. Show evidence of hepatitis C and/or positive hepatitis C antibody.

Other exclusions

47. 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 from 24 hours prior to dosing day, until the patient has been discharged from the clinical research site (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).
48. Smoke more than 10 cigarettes, or cigarette equivalent (as determined by investigator), per day or are unable to abide by investigative site restrictions on smoking and nicotine-containing products.
49. Are females who are breastfeeding.
50. Have known allergies to LY3493269, GLP-1 analogs, or related compounds, or acetaminophen.
51. Are investigative site personnel directly affiliated with this study and their immediate families, defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
52. Are employees of the sponsor or the investigative site.
53. Are otherwise unsuitable for inclusion in the study in the opinion of the investigator or sponsor.

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

As specified in Section 1.3, participants are required to fast for at least 8 hours before

- receiving study intervention
- each study day when clinical safety laboratory and PD samples are collected, and
- OGTTs are administered.

Water may be consumed freely.

Standard meals will be administered in the investigative site.

While outpatient, participants are encouraged to follow their usual dietary regimen that is a part of their diabetes management, as agreed with the investigator or his/her designee.

5.3.2. Caffeine, Alcohol, and Tobacco

Caffeine

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

Alcohol

No alcohol is allowed

- at least 24 hours before each weekly dosing,

- at least 24 hours before each investigative site admission or outpatient visit, and
- throughout the duration of each investigative site visit.

A maximum of 21 units per week for males and 14 units per week for females is permitted at all other times.

Tobacco

Participants will be questioned about their nicotine consumption habits at screening.

Smoking, and the use of other tobacco or nicotine-containing products, will

- be limited during the study confinement according to investigative site guidelines, and
- not be permitted for 1 hour before assessments of vital signs and ECG.

5.3.3. Activity

Participants will be advised to maintain their regular levels of physical activity/exercise during the study.

Participants will abstain from strenuous exercise within 24 hours prior to admission to the investigative site.

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

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. However, participants who were eligible for inclusion in previous cohorts, but were not randomly assigned for nonmedical reasons, may be reassessed. Additional medical assessments and clinical measurements must include clinical laboratory tests, vital signs, and ECG to confirm their eligibility. Repeat of laboratory tests will be acceptable if judged pertinent by the investigator.

6. Study Intervention

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

The investigator or designee is responsible for

- explaining the correct use of the study interventions to the site personnel,
- verifying that instructions are followed properly,
- maintaining accurate records of study intervention dispensing and collection, and
- returning all unused medications to the sponsor 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 the clinical materials

6.1.1. Administration Details

All injections will be administered into the SC tissue of the abdominal wall. Injection sites will be alternated weekly among 4 sites (that is, right and left upper quadrants and right and left lower quadrants) on the abdominal wall. Whenever possible, study drug administration should be carried out by the same personnel.

6.2. Preparation/Handling/Storage/Accountability

Preparation

Investigators should consult the information provided in the Pharmacy Instructions for specific preparation and administration information of LY3493269 and placebo. The study intervention

must be prepared by an unblinded pharmacist or other unblinded qualified designee who is not involved in any other study-related procedures.

Handling and storage

Only authorized site staff may supply or administer study intervention. Study interventions 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 site staff.

Accountability

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

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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. Otherwise, the investigator or designee will return all unused study interventions to the sponsor or designee at the end of the study.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Interactive web-response system

All participants will be centrally assigned to randomized study intervention using an interactive-web response system (IWRS) prior to or on Day 1. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at the study visits summarized in the SoA. Returned study interventions should not be re-dispensed to the participants.

Blind break

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified immediately after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

Blinded study with unblinded site pharmacist who is dispensing drug

Participants will be randomly assigned to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

To maintain this blind, an otherwise uninvolved third party (for example, the pharmacist) will be responsible for the reconstitution and dispensing of all study interventions and will endeavor to ensure that there are no differences in time taken to dispense following randomization. In addition, the site personnel administering the study interventions will not be blinded and will not perform other protocol assessments to avoid bias.

The dosing team may blindfold the study participant to maintain the blind at the time of dose administration. The participant will be instructed to avoid discussing the packaging of the study intervention with the investigator.

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

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

6.4. Study Intervention Compliance

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

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

6.5. Concomitant Therapy

Recording of concomitant therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use
- route of administration, and
- dates of administration, including start and end dates.

Participants will be instructed to consult the investigator or other appropriate investigative site personnel before taking any new medications or supplements during the study. The sponsor's medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Allowed concomitant therapy

Participants will maintain their usual medication regimen throughout the study unless specifically excluded in the protocol (Section 5.2). Doses must be stable as stated in the exclusion criteria. Participants who have been on stable doses of OTC or prescription medications for at least 4 weeks for the treatment of concurrent medical conditions are permitted to continue these medications during the study. These medications may include

- antihypertensive agents
- aspirin
- lipid-lowering agents, and
- metformin.

Participants must be on a stable dose of metformin for at least 3 months prior to screening. Doses of metformin must remain stable between screening and randomization. Doses of metformin may be adjusted after randomization per label, if required for safety reasons. Participants on metformin must meet local label requirements.

Additional concomitant medications for treatment of T2DM are not permitted during the study.

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

Acetaminophen, at doses of ≤2 g/day, is permitted for use any time during the study. However, acetaminophen should not be allowed after midnight and until the last acetaminophen PK sample is taken for the gastric-emptying test.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the sponsor's medical monitor, if required.

6.6. Dose Modification

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the maximum dose is determined or when stopping criteria are met. Safety data, in particular AEs, SAEs, and clinically important laboratory abnormalities, are the primary criteria for dose escalation. Interim access to study data is scheduled to occur during the study to inform dose-escalation decisions, as specified in Section 6.6.1.

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum dose will not exceed [redacted] of LY3493269. If considered appropriate in view of emerging safety, tolerability, or PK data,

- actual doses, increments, and/or duration of dosing in each cohort at each dose level may be adjusted.
- the timing of the sampling may be adjusted and additionally the number of samples to be collected may be adjusted, as described in Section 8.5.
- the duration of the inpatient stay or the duration of safety follow-up may be increased but not decreased.

No dose decision can occur without prior discussion and agreement between the investigator and sponsor. Changes must be appropriately documented and communicated by the sponsor to the

investigator. Because these adjustments to timing or dose levels are allowable changes permitted by the protocol, they would not require a protocol amendment.

6.6.1. Dose Escalation

Dose Decisions between Cohorts

Preliminary safety and tolerability data from the current dose level, and any available data from preceding doses, are the primary criteria for decisions jointly made by the investigator and sponsor on

1) a dose escalation between successive cohorts, and
2) starting doses for Cohorts 2 to 4.

The initiation of each cohort shall be scheduled such that a planned escalated dose is supported by a review of 2-week safety and tolerability data from at least 5 participants who received LY3493269 through Day 15 at the preceding lower dose (Figure 1).

If available at the time of the dose-escalation decision, PK and PD results may be used as supporting data. Initiation of dosing for the last 2 planned cohorts will be based on review of the following:

1) All available PK data from Cohort 1, prior to initiation of Cohort 3
2) All available PK data from Cohort 2, prior to initiation of Cohort 4.

Dose Decisions within Cohorts 3 and 4

For Cohorts 3 and 4, progression of planned doses from Weeks 1 through 4 shall be based on the ongoing evaluation of individual patient-level safety and tolerability data. Any available safety and PK data from preceding cohorts will also be considered.

If individual participants on LY3493269 in either Cohort 3 or 4 experience tolerability issues after dose escalation, these participants may receive the previously tolerated dose for the remainder of the treatment period. The planned dose for escalation between cohorts and within cohorts may be further reduced if warranted by safety or tolerability data. Any subsequent dose increments will not be greater than those originally planned.

6.6.2. Dose-Escalation Stopping Criteria

If any of the following scenarios occur, dosing at the current level and further dose escalation within a cohort and to the next cohort may be discontinued after a discussion between the sponsor and the investigator:

1. One treatment-emergent SAE believed to be associated with LY3493269; For more details see Section 7.1.2.
2. One or more participants on active drug experience 2 or more clinically significant events (CSEs) deemed related to LY3493269. Clinically significant events are defined as moderate to severe AE, abnormal clinical signs, or clinical laboratory findings that may pose a risk to the well-being of the participant and would preclude further dosing of a participant who experiences this effect. Clinically significant events will be determined

by the investigator or suitable designee and may include findings that do not fulfill the criteria for SAEs.

3. Three or more participants at the same dose level experience any of the following deemed 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 AE.
4. 40 % or more of participants in a dose level experience a symptomatic hypoglycemic episode with BG values ≤2.8 mmol/L (50 mg/dL; corresponding to plasma glucose (PG) levels of ≤3.1 mmol/L [56 mg/dL]) and these events are deemed to be related to LY3493269 administration (see Section 7.1.2), or
5. Two or more participants on active drug develop persistent (>1 week) symptoms suggestive of acute pancreatitis. Refer to algorithm for the monitoring of asymptomatic hyperenzymemia in Section 10.7.

6.6.3. Data Review during the Study

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

The decision to proceed to the next cohort will be made by the sponsor and the investigator based on safety, tolerability data (including but not limited to AEs, concomitant medications, clinical laboratory tests, vital signs, ECGs) from at least 5 participants who have received LY3493269 through Day 15 at the prior dose level. If available, PK and PD data will be reviewed. In addition, these data may be used to guide dose selection and inform the need to adjust timing of procedures and sampling schedules for the current study.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.7.

7.1. Discontinuation of Study Intervention

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

Participants experiencing CSEs thought to be related to the study intervention will be encouraged to complete a 28-day follow-up period before study discharge.

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

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

7.1.1. Liver Enzymes and Other Laboratory

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

- ALT or AST >8X ULN
- ALT or AST >5X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio (INR) >1.5 or
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

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

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

- lipase and/or amylase ≥3X ULN (Section 8.2.5.1 should be considered by the investigator).

7.1.2. Persistent Hyperglycemia/Hypoglycemia

Discontinuation of the study intervention should be considered for participants with any persistent severe hyperglycemia, defined as a persistent fasting PG level above 240 mg/dL, without an identified cause (for example, intercurrent illness).

Discontinuation of the study intervention should be considered for participants with any severe hypoglycemia (Level 3 according to Section 8.2.6.1), or persistent hypoglycemic events (Level 2), for example 3 or more hypoglycemic events over any 7-day period.

7.1.3. Hypersensitivity Reactions

If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from using the study intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

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

Discontinuation is expected to be uncommon.

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow-up is as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

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

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

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

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

Assessment collection time

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF. Failure or being late (that is, outside stipulated time allowances) to perform procedures or obtain samples within the stipulated time allowances due to legitimate clinical issues (for example, equipment technical problems, venous access difficulty) will not be considered protocol deviations. However, the clinical research unit is required to notify the sponsor in writing using a file note.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

Height and weight will also be measured and recorded.

8.2.2. Vital Signs

Vital signs, blood pressure, PR, and body temperature, should be measured as specified in Section 1.3 and as clinically indicated. Additional vital signs may be measured during each study period if warranted.

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

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

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

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

8.2.3. Electrocardiograms

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

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

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

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

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

Single electrocardiograms

Single ECGs will be collected at screening, baseline, at early termination, and follow-up on Days 36 and 57 according Section 1.3. Single ECGs may be obtained at additional times when deemed clinically necessary to assess participants' safety. All single ECGs recorded should be stored at the investigational site. Single ECGs will not be transmitted to a central laboratory.

Triplicate electrocardiograms

Triplicate 12-lead ECGs will be obtained as specified in Section 1.3. Collection of triplicate ECGs on Days 23, 24, 29, and 30 should be time matched to the predose triplicate ECG collected on Day 22.

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

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

8.2.4. Clinical Safety Laboratory Assessments

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

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

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

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Safety Monitoring

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

The sponsor will review SAEs within time frames mandated by company procedures. The sponsor's clinical pharmacologist or CRP will periodically review

- trends in safety data

- laboratory analytes, and
- AEs.

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Section 10.6), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

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

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

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

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

Comprehensive hepatic evaluation

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

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

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

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

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

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

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

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

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

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

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

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

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

8.2.5.2. 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 investigational product and protocol procedure will be captured.

8.2.5.3. Pancreatic Safety

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with LY3493269, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi et al. 2006):

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

If acute pancreatitis is suspected, the investigator should

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

Discontinuation for acute pancreatitis

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

8.2.5.4. Injection-Site Reactions

Symptoms of a local injection-site reaction may include

- erythema
- induration
- pain
- pruritus, and
- edema.

If an injection-site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the electronic case report form (eCRF).

8.2.5.5. Hypersensitivity Reactions

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

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

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

8.2.6. Glucose Monitoring

8.2.6.1. Hypoglycemia

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

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

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

Glucose Alert Value (Level 1):

- **Documented symptomatic hypoglycemia** is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a PG level of ≤70 mg/dL (≤3.9 mmol/L).

- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured PG ≤70 mg/dL (≤3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

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

Severe hypoglycemia (Level 3):

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

Other hypoglycemia categories:

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

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

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

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

8.2.6.2. Self-Monitoring of Blood Glucose

Prior to the first outpatient visit after the first SC dose, participants will receive training on routine BG monitoring and paper diary completion required during the study.

When outpatient, participants should measure their fasting BG daily during the study. In addition, participants should test their glucose whenever they experience symptoms of hypoglycemia.

Participants will be trained to record their results in their diaries. The investigator or designee must review the diaries at each return visit to the site.

8.3. Adverse Events and Serious Adverse Events

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

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

All SAEs will be collected from the signing of the ICF until the participation in study has ended.

All AEs will be collected from the signing of the ICF until the follow-up visit.

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

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

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.6), will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.1.

8.3.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Pregnancy (maternal or paternal exposure to study intervention) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Section 10.4.3 to collect data on the outcome for both mother and fetus.

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and for the duration of the study plus 105 days, which corresponds to approximately 5 months following the last dose of study intervention.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interests

Adverse events of special interest for this program include

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

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

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

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

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

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 10.3.3 of the protocol.

8.3.7.1. Time Period for Detecting Product Complaints

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

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

8.3.7.2. Prompt Reporting of Product Complaints to Sponsor

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

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

8.3.7.3. Follow-up of Product Complaints

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

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

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

8.4. Treatment of Overdose

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

In the event of an overdose, the investigator or treating physician should

1. contact the medical monitor immediately.
2. closely monitor the participant for any AE/SAE and laboratory abnormalities until LY3493269 can no longer be detected systemically.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of LY3493269 as specified in Section 1.3.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

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

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

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

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

8.5.1. Bioanalysis

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

The retention period for bioanalytical samples collected to measure LY3493269 concentrations is provided in Section 10.1.9. During this time, samples remaining after the bioanalyses may be used for exploratory metabolism studies or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

8.5.1.1. Bioanalysis of Study Intervention

Concentrations of LY3493269 will be assayed using a validated liquid chromatography with tandem mass spectrometry method. Analyses of samples collected from participants who received either placebo or dulaglutide are not planned.

8.5.1.2. Bioanalysis of Acetaminophen

Concentrations of acetaminophen will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

8.6. Pharmacodynamics

8.6.1. Oral Glucose Tolerance Test

Glucose, C-peptide, glucagon, 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 Section 1.3.

1. Participants will maintain adequate carbohydrate intake (125 to 150 g/day) 3 days before the scheduled OGTT and fast for approximately 8 hours overnight before administration of the OGTT.
2. A 75-g glucose dose will be given orally. Participants should consume the glucose load within 5 minutes.
3. Blood samples will be drawn for assessment of glucose, C-peptide, glucagon, and insulin concentrations pre-test and at 0.5, 1, 1.5, and 2 hours after the initiation of the glucose load.
4. If participants develop symptoms of hypoglycemia, bedside BG concentration may be measured. The participant will be treated per investigator's discretion.

8.6.2. Gastric-Emptying Test

Acetaminophen is a well-established marker of gastric emptying (Young 2005). It is rapidly absorbed from the duodenum upon release from the stomach. A delay in gastric emptying is reflected in the alterations to the concentration versus time profile of acetaminophen, specifically, decreasing its maximum observed drug concentration (C_{max}) and likely delaying t_{max} without altering the extent (total drug amount) absorbed.

The acetaminophen dose should be given approximately 30 minutes after the 75-g glucose dose for the OGTT.

A dose of approximately 1 g acetaminophen is considered to be sufficient for bioanalytical detection and will be administered at the times specified in Section 1.3.

Venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of acetaminophen.

8.6.3. Six-Point Plasma Glucose Profiles

The samples for the 6-point glucose profiles will be collected as specified in the Section 1.3 and analyzed at a central laboratory.

Six-point glucose profiles consisting of PG measurements should be obtained at investigative site before each meal (breakfast, lunch, and dinner) and approximately 2 hours after the end of each meal.

8.6.4. Pharmacodynamic Markers

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

Fasting serum samples for glucose, insulin, and C-peptide will be evaluated as PD biomarkers. Fasting lipids (triglycerides, cholesterol, very low-density lipoproteins, low-density lipoproteins, and high-density lipoproteins) will be evaluated as exploratory mechanistic markers.

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

8.6.5. Appetite Analysis with a Visual Analog Scale

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 visual analog scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption prior to dosing and in the fasted state while inpatient as well as on scheduled outpatient visits, according to Section 1.3.

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

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

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

8.6.6. Body Weight

Weight will be measured as indicated in the SoA. 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. 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 at each scheduled timepoint or visit, and after an overnight fast and evacuation of bowel and bladder, if possible.

8.6.7. Waist Circumference

Waist circumference will be measured twice on each scheduled occasion according to Section 1.3. The mean of the 2 measurements will be recorded in the source document and the eCRF.

- Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest.

- The patient should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing.
- The patient should be relaxed, and the measurements should be taken at the end of a normal expiration.

8.7. Genetics

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

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

8.8. Biomarkers

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

Sample use

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

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

Exploratory biomarker measures may include potential markers of GIP and GLP-1R target engagement and mechanism of action.

Confidentiality

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.

Sample retention

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples are described in Section 10.1.9.

8.9. Immunogenicity Assessments

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

TE-ADAs are defined in Section 9.4.6. In the case that ADA samples are tested before end of study and if the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA positive, additional samples may be taken every 3 months until the ADA signal returns to baseline (that is, no longer TE-ADA positive) or for up to 1 year after last dose.

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.

The purpose of retention, the maximum duration of retention, and facility for long-term storage of samples are described in Section 10.1.9.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary study objective is to determine the safety and tolerability LY3493269 following 4 QW doses. Additional hypotheses will include the comparison of study intervention with placebo and/or dulaglutide for the prespecified objectives and endpoints defined in Section 3.

9.2. Sample Size Determination

Approximately 64 participants may be randomly assigned to study intervention such that approximately 12 evaluable participants from each of the 4 cohorts complete the study. In each cohort, participants will be randomly assigned to

- 8 LY3493269
- 2 dulaglutide, and
- 2 placebo.

If participants are discontinued during the study, additional participants may be enrolled as replacements for these participants.

The sample size is considered sufficient for evaluating the primary objective of this study.

Participant replacement

A total of 12 participants are aimed to complete the study in each cohort.

Participants who discontinue from the study, for reasons other than an AE suspected to be related to study drug, may be replaced as agreed between the sponsor and investigator. The replacement participant will be assigned to the same treatment as the participant being replaced.

Participants who discontinue from the trial due to an AE considered by the investigator to be probably or most likely related to study intervention will not be replaced.

9.3. Populations for Analyses

The following populations are defined:

Population	Definition
Entered	All participants who sign the ICF.
Enrolled	All participants randomly assigned to study intervention.
Safety	All participants randomly assigned to study intervention and who received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All participants who received at least 1 dose of LY3493269 and have evaluable PK sample.
Pharmacodynamic Analysis	All participants who received at least 1 dose of study intervention and have evaluable PD sample.

Abbreviations: ICF = informed consent form; PD = pharmacodynamics; PK = pharmacokinetics.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor or its designee. Statistical analyses will be conducted on the populations as described in Section 9.3. Safety analyses will be conducted on the safety population whether or not they completed all protocol requirements.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to the first patient visit and it will include a more technical and detailed description of the statistical analyses provided in this section.

9.4.1. General Considerations

Data listings will be provided for all data that are databased. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted.

Summary statistics and statistical analysis will only be presented for data where detailed in the SAP. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used (Table 4).

Table 4. Data Presentation Methods

Parameters	Summary Statistics
• demography • clinical laboratory • vital signs • ECG • appetite analysis, and • PD data	• arithmetic mean • arithmetic standard deviation • median • minimum • maximum, and • the number of observations
• PK data ○ $AUC_{(0-\tau)}$, and ○ C_{max}	• geometric mean and • CV%
• adverse event data • hypoglycemic classification data, and • injection-site reaction data	• frequency count and • percentages

Abbreviations: $AUC_{(0-\tau)}$ = area under the concentration versus time curve during 1 dosing interval; C_{max} = maximum observed drug concentration; CV% = geometric coefficient of variation; ECG = electrocardiogram; PD = pharmacodynamics; PK = pharmacokinetics.

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

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

9.4.2. Safety Analyses

All safety analyses will be made on the safety population.

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

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

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

Analysis for clinical laboratory tests

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.

Analysis for vital signs

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 for repeated measurement with treatment, visit of measurement, and treatment-by-visit 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.

Analysis for electrocardiograms

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

9.4.3. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for LY3493269 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} and area under the concentration versus time curve (AUC) of LY3493269 after the first and last dose. Other parameters, such as t_{max}, half-life, apparent clearance, apparent volume of distribution, and accumulation ratio, may be reported. If deemed necessary, additional population PK modeling may be performed or data may be combined with other studies for further analysis.

Pharmacokinetic dose proportionality will be explored for the first dose of each cohort. 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. Additional details will be provided in the SAP.

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

9.4.4. Pharmacodynamic Analyses

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

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 model for repeated measurement to evaluate treatment effects, as well as treatment comparisons. The model will include treatment, visit, and treatment-by-visit interaction as fixed effects and participant as a random effect. Baseline values, as well as other influencing variables, may be used as covariates.

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

Differences between each LY3493269-treated group and dulaglutide group will be estimated. Participants who received dulaglutide will be pooled across all cohorts.

Differences between each LY3493269-treated group and placebo group will be estimated. Participants who received placebo will be pooled across all cohorts. Least-squares means and 90% CIs will be reported.

Acetaminophen parameters will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max}, AUC, and t_{max} of acetaminophen. Other PK parameters of acetaminophen may be reported where appropriate. Baseline-adjusted C_{max} of acetaminophen (ratio to Day -1 value) will be calculated and log transformed to compare the gastric-emptying effect of LY3493269 to that of dulaglutide and placebo. A mixed model for repeated measurement with treatment, day, and treatment-by-day interaction as fixed effects, participant as random effect, and baseline (Day -1) as covariate will be used to perform the analysis. Least-squares means as well as 95% CIs will be reported. The parameter t_{max} of acetaminophen will be analyzed using a nonparametric method.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

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

- safety parameters, such as
  - QTcF interval
  - blood pressure
  - HR, and
  - PR interval,
- tolerability parameters, such as
  - nausea and
  - vomiting, and
- PD parameters, such as
  - fasting glucose
  - HbA1c, and
  - weight.

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

9.4.6. Evaluation of Immunogenicity

Upon full assay validation, TE-ADAs may be assessed. The frequency and percentage of participants with preexisting ADA and with TE-ADA+ to LY3493269 may be tabulated. Treatment-emergent ADAs are defined as those with a signal increase, greater than assay variability, compared to baseline. Treatment-emergent ADAs are defined as those with

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

- a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA).

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

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

9.5. Interim Analyses

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

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

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

9.6. Data Monitoring Committee (DMC)

Not applicable.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable International Council for Harmonisation (ICH) good clinical practice (GCP) Guidelines
- applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant and is kept on file.

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

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

Reports

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

Data

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

10.1.5. Data Quality Assurance

Investigator responsibilities

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

Data monitoring and management

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Data Capture System

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

An electronic data capture system will be used in this study. 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 collected via the sponsor-provided data capture systems will be stored by third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

10.1.6. Source Documents

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

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. Study and Site Start and Closure

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

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

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

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

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.8. Publication Policy

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

10.1.9. Long-Term Sample Retention

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

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

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

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

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

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

Abbreviations: PD = pharmacodynamics; PK = pharmacokinetics.

[a] Retention periods may differ locally.

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the Safety Laboratory Tests table will be performed by the local laboratory at screening, and at the central laboratory for all scheduled assessments from Day -3 through the treatment period and follow-up.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests (for example, drug/alcohol screen) may be performed at any time during the study as determined necessary by the investigator or as required by local regulations.
- Pregnancy testing will occur as indicated in the SoA.

Investigators must document their review of each laboratory safety report.

Laboratory and analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Safety Laboratory Tests (Screening - Local Laboratory)

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	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
Platelets	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
Urinalysis	Alanine aminotransferase (ALT)
Specific gravity	Lipase
pH	Amylase
Protein	Triglyceride
Glucose	Total cholesterol
Ketones	HbA1c
Bilirubin	Calcitonin
Urobilinogen	
Nitrite	
Blood	**Serology**
Leukocytes	Hepatitis B surface antigen[a]
Microscopy[b]	Hepatitis B core antibody, total[a]
	Hepatitis C virus serology (anti-HCV)[a]
Follicle-stimulating hormone (FSH)[c]	Human immunodeficiency virus (HIV)[a]
Serum pregnancy test (females only)	

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

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

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

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

Safety Laboratory Tests (Central Laboratory - from Day -3 through Follow-up)

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Absolute Counts of
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets

Urinalysis
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Nitrite
- Blood
- Leukocytes
- Microscopy[a]

Pregnancy test[b]

Clinical Chemistry (fasting)
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphate
- Magnesium
- Creatinine
- Glucose (fasting)
- Urea
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Lipase
- Amylase
- Triglyceride
- Total cholesterol
- HbA1c[c]

Tests will be performed at a central laboratory unless otherwise specified.

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

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

[b] Local laboratory test for females only: urine pregnancy test at the Day 57 follow-up or early discontinuation.

[c] HbA1c samples obtained according to the Schedule of Activities (Section 1.3).

10.2.1. Blood Sampling Summary

These tables summarize the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Blood Sampling Summary Table (Cohorts 1 and 2)

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests (local laboratory)[a]	25	1	25
Clinical laboratory tests[a] (central laboratory)			
• HbA1c	3	3	9
• Study Visits	10	8	80
• Follow-up	10	1	10
LY3493269 pharmacokinetics	3	19	57
Potential additional LY3493269 pharmacokinetic samples	3	3	9
Blood discard for cannula patency	0.5	19	9.5
Fasting plasma glucose	2	7	14
6-point glucose	2	30	60
OGTT (central laboratory)			
• Glucose	2	20	40
• Insulin, C-peptide	3	20	60
• Glucagon	2	20	40
Gastric-emptying test (acetaminophen PK)	2	33	66
Biomarkers (central laboratory) • Lipid panel (triglycerides, total cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol)	3.5	2	7
Pharmacogenetic sample (stored)	10	1	10
Nonpharmacogenetic sample (stored)			
• Plasma	2	5	10
• Serum	2.5	5	12.5
• P800	2	5	10
Immunogenicity	10	4	40
Total			569
Total for clinical purposes (rounded up to the nearest 10 mL)			570

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

Blood Sampling Summary Table (Cohorts 3 and 4)

Purpose	Blood Volume per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Volume (mL)
Screening tests (local laboratory)[a]	25	1	25
Clinical laboratory tests[a] (central laboratory)			
• HbA1c	3	3	9
• Study Visits	10	8	80
• Follow-up	10	1	10
LY3493269 pharmacokinetics	3	21	63
Potential additional LY3493269 pharmacokinetic samples	3	3	9
Blood discard for cannula patency	0.5	21	10.5
Fasting plasma glucose	2	7	14
6-point glucose	2	30	60
OGTT (central laboratory)			
• Glucose	2	20	40
• Insulin, C-peptide	3	20	60
• Glucagon	2	20	40
Gastric-emptying test (acetaminophen PK)	2	33	66
Biomarkers (central laboratory) • Lipid panel (triglycerides, total cholesterol, low-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol)	3.5	2	7
Pharmacogenetic sample (stored)	10	1	10
Nonpharmacogenetic sample (stored)			
• Plasma	2	5	10
• Serum	2.5	5	12.5
• P800	2	5	10
Immunogenicity	10	4	40
Total			576
Total for clinical purposes (rounded up to the nearest 10 mL)			580

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

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

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

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The investigator will consider any AEs, SAEs, and clinically important laboratory abnormalities as related to the study intervention unless there is clear evidence that the event is not related.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used while determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

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

10.3.5. Sponsor Surveillance Process for Dose Escalation or Cohort Expansion

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

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

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

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

10.4.1. Definitions

Females of Childbearing Potential

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

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

Females NOT of Childbearing Potential

Females in the following categories are not considered women of childbearing potential

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

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

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

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

Female participants of childbearing potential are excluded from this study.

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

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

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

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

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

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

10.4.2.3. Contraception Methods

Abstinence

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

Same-sex relationships

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

Highly effective and effective contraception methods

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

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

Unacceptable contraception methods

Unacceptable methods of contraception include

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

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive LY3493269.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and indication for the procedure.

Female participants who become pregnant

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

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. The discontinued participant should follow the standard discontinuation process and continue directly to the follow-up phase.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

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

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

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

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

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

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

See Section 8.2.5.1 for guidance on appropriate test selection.

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

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

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

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

Abbreviations: Ig = immunoglobulin; INR = international normalization ratio; PT = prothrombin time.

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

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

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

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

10.7. Appendix 7: Pancreatic Monitoring

Glucagon-like peptide 1 agonists have been associated with a possible risk of acute pancreatitis. In 2006, the 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 LY3493269 on the exocrine pancreas, amylase, and lipase values will be monitored in all current and future clinical trials with LY3493269.

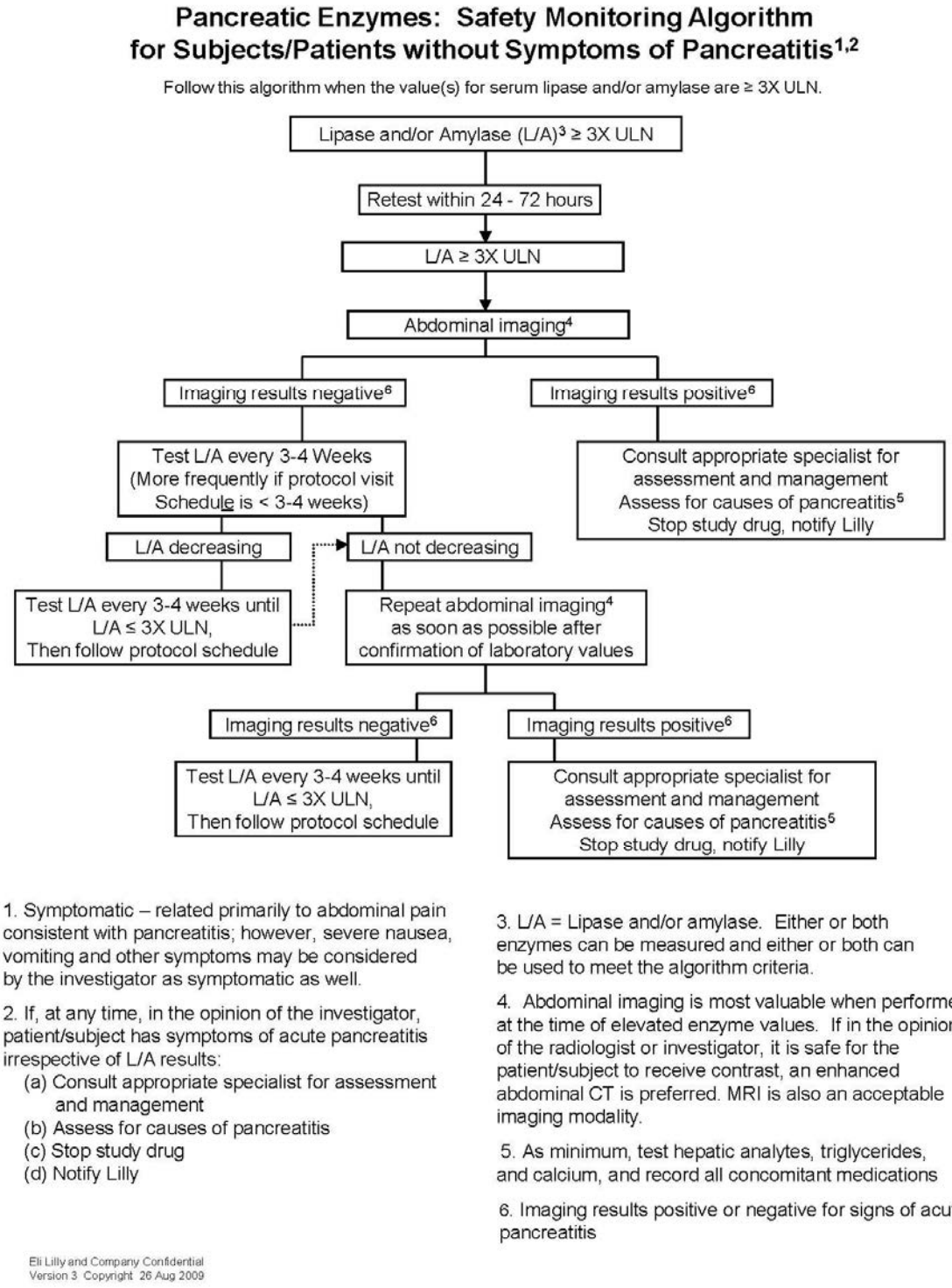
Additional monitoring will be requested for amylase or lipase values ≥3X the ULN at any visit after randomization, even in asymptomatic participants (see the following figure). Lipase and amylase may also be obtained at any time during the clinical trials for any participant suspected of having symptoms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

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

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3X ULN
- characteristic findings of acute pancreatitis on the CT scan or MRI

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.

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 investigational product.



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

10.8. Appendix 8: Hypersensitivity Event Tests

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

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

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

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

10.9. Appendix 9: Abbreviations

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BG	blood glucose
blinding/masking	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 subjects are aware of the treatment received.
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSE	clinically significant events
CT	computed tomography
CV	cardiovascular

ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FSH	follicle-stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon- like peptide-1
GLP-1R	GLP-1 receptor
GLP-1RA	GLP-1 receptor agonist
HbA1c	glycated hemoglobin
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	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.
IRB	institutional review board

IWRS	interactive web-response system
MRI	magnetic resonance imaging
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level
OGTT	oral glucose tolerance test
OTC	over the counter
p-amylase	pancreatic amylase
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PD	pharmacodynamics
PG	plasma glucose
PK	pharmacokinetics
PR	pulse rate
randomize	the process of assigning participants to an experimental group on a random basis
QTcF	QT interval corrected using Fridericia’s formula
QW	once weekly
SAC	safety assessment committee
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
study intervention	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
TBL	total bilirubin

T2DM	type 2 diabetes mellitus
TE-ADA	treatment-emergent-antidrug antibody
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal
VAS	visual analog scale

10.10. Appendix 10: Protocol Amendment History

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

Amendment [a]: 11-July-2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	For Cohorts 3 and 4, the following timepoints were added: • Visits on Days 9 and 16, • Drug/alcohol screen on Days 8 and 15, • Triplicate ECGs and vital signs at 1, 4, 6, and 12 hours post dose on Days 8 and 15, at 24 hours postdose on Days 9 and 16, and at 1 and 4 hours postdose on Day 22, and • Pharmacokinetic samples at 4 hours postdose on Days 8 and 15.	Based on feedback from the FDA
1.3 Schedule of Activities	Table 1 shows Assessment Schedules for Oral Glucose Tolerance and Gastric Emptying Tests with separate sampling schedules for each test.	Original table revised for clarity.
4.3 Justification of Dose	In Table 3, an error in the human maximum dose (mg/kg) was corrected from 0.556 to 0.0556.	Based on feedback from the FDA.
5.1 Inclusion Criteria	Upper age limit for participants reduced to 65 years.	Based on feedback from the FDA.
6.6.2 Dose-Escalation Stopping Criteria	Added the follow stopping criteria: Three or more participants at the same dose level experience drug-related GI effects causing severe distress and/or clinically significant cardiovascular AE deemed related to LY3493269 administration.	Based on feedback from the FDA.
7.1.2 Persistent Hyperglycemia/ Hypoglycemia	Added details on the number and duration of hypoglycemic events to be considered for discontinuation of study intervention.	Based on feedback from the FDA.
8.9 Immunogenicity Assessments	Removed that ADA cross-reactively binds to native GIP ad GLP-1 would necessitate additional ADA samples	Based on feedback from the FDA.
10.4.2.1 Female participants	Removed the contraception restriction for female participants not of childbearing potential.	These restrictions did not provide the participant with any additional safety benefit.

Amendment [b]: 13-October-2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment serves to clarify that dose escalation between cohorts will be based on a review of 2-week safety and tolerability data from participants who received LY3493269 through Day 15 at the preceding lower dose.

Section # and Name	Description of Change	Brief Rationale
1.2. Schema	Diagram was updated to reflect data reviews for dose-escalation decisions.	
4.2. Scientific Rationale for Study Design	Text updated to allow "up to 2" from "2" participants to be assigned to dulaglutide or placebo treatment per cohort. Deleted the redundant text "The decision to escalate doses between and within the cohorts will be based primarily on safety and tolerability data from preceding dose cohorts and within the cohort". This text was reported in Section 6.6.1.	Editorial change to align with intended completion of "approximately" 12 evaluable participants in each cohort.
5.1. Inclusion Criteria	Upper age limit for participants revised to 70 years.	The protocol is amended to increase the age limit to 70 years for the following reasons: (1) No relevant differences with regard to safety between individuals aged <65 years and those >65 years have been observed with incretin agents (Boustani et al. 2016, Warren et al. 2018); (2) One common concern in elderly population is the risk of severe hypoglycemia (Warren et al. 2018); (3) Severe hypoglycemia occurs rarely with incretin therapy as these agents are not insulin secretagogues;

Section # and Name	**Description of Change**	**Brief Rationale**
		(4) There were no events of severe hypoglycemia after single dose of LY3493269 in healthy participants; (5) To enable enrolment during the current COVID-19 pandemic; (6) To allow for a broader population to be safely studied.
6.6.1. Dose Escalation	Text updated to describe dose-escalation decisions between successive cohorts, which would be based on data from preceding doses. Clarified language describing dose adjustments for participants with tolerability issues after dose escalations within Cohorts 3 and 4.	Dose escalations between successive dose levels are based on data from preceding lower doses, and not "cohorts". Dose adjustments will be based on individual patient-level safety and tolerability data.

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