Protocol: J2A-MC-GZGA(f)

A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Healthy Subjects.

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LY3502970

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1. Protocol Synopsis

Title of Study:
A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Healthy Subjects

Rationale:
LY3502970 is a glucagon-like peptide-1 (GLP-1) receptor agonist being developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Unlike the peptide GLP-1 receptor agonists approved by regulators to-date, LY3502970 is a small molecule being developed for daily oral administration.

This first-in-human study will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple oral doses of LY3502970 in healthy subjects. Safety and tolerability evaluations will be conducted over a wide range of doses, and dose escalation will not proceed until safety, tolerability, and available PK and PD data from previous doses have been reviewed. The data generated in this study will be used to help design subsequent clinical studies.

Objectives/Endpoints:

Primary Objective	**Endpoints**
To investigate the safety and tolerability of single and multiple oral doses of LY3502970 in healthy subjects	Incidence of TEAEs and SAEs
Secondary Objective	**Endpoints**
To characterize the PK of LY3502970 after single and multiple oral doses in healthy subjects (Parts A and B)	Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}

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

Summary of Study Design:
Study GZGA is a Phase 1, single site, 5-part study in healthy subjects. The study design includes:

- Part A: randomized, placebo-controlled, investigator- and subject-blind, single-ascending dose (SAD)
- Part B: randomized, placebo-controlled, investigator- and subject-blind, 4-week, multiple-ascending dose (MAD) with or without dose titration
- Part C (exploratory): single-dose, randomized, 2-treatment arm, 2-period, open-label, crossover to evaluate food effects
- Part D (exploratory): randomized, placebo-controlled, investigator- and subject-blind, single dose to evaluate the LY3502970 controlled-release prototype

- Part E (exploratory): randomized, investigator- and subject-blind, multiple dose to evaluate 2 different formulations of LY3502970 with dose titration.

Planned Treatment Arms and Planned Duration for an Individual subject:
Part A (SAD) will consist of up to 6 escalating single-dose levels of LY3502970 or placebo. Approximately 48 subjects will be randomized into 6 groups (Cohorts A through F). For each cohort, it is planned that approximately 8 subjects will be randomly assigned to either LY3502970 (6 subjects) or placebo (2 subjects).

Part B (MAD) will consist of up to 5 escalating multiple-dose levels of LY3502970 or placebo. Approximately 60 subjects will be randomized into 5 groups (Cohorts G through K). For each cohort it is planned that approximately 12 subjects will be randomly assigned to LY3502970 (9 subjects) or placebo (3 subjects). In Cohort J, subjects will be administered atorvastatin and midazolam on Days -2 and 27. In Cohort K, subjects will be administered simvastatin on Days -2 and 27. The dose levels in Part B will be determined on the basis of safety, tolerability, and available PK and PD data from Part A. A fixed dose may be administered to subjects in Cohort G. In Cohorts H through K, LY3502970 dose regimens may be evaluated via dose titration.

Part C (exploratory food effect) may consist of up to 12 subjects enrolled into 1 group (Cohort L). Subjects will receive a single oral dose of LY3502970 in each of 2 treatment periods. Subject will be randomized to 1 of 2 treatment sequences comprised of 2 treatment arms:

- Fasted treatment: Dose administered with approximately 240 mL water following an overnight fast of at least 10 hours;
- Food-effect treatment: Dose administered with approximately 240 mL water following a meal consumed after an overnight fast of at least 10 hours.

Part D (exploratory) may consist of approximately 8 subjects enrolled into 1 group (Cohort M) and randomly assigned to LY3502970 controlled-release prototype (6 subjects) or placebo (2 subjects).

Part E (exploratory) may consist of approximately 20 subjects randomly assigned to two different formulations of LY3502970.

Number of Subjects:
Approximately 180 healthy subjects may be enrolled so that up to 146 subjects complete the study (48 in Part A, 60 in Part B, 12 in Part C, 8 in Part D, and 18 in Part E).

Statistical Analysis:
Safety: All investigational product- and protocol procedure-related adverse events will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety parameters that will be assessed include safety laboratory parameters, vital signs, and electrocardiogram parameters.

Pharmacokinetics: PK parameter estimates for LY3502970, midazolam, atorvastatin, simvastatin, and relevant midazolam, atorvastatin, and simvastatin metabolites will be calculated by standard noncompartmental analysis methods and summarized using descriptive statistics. The primary parameters for analysis will include area under the concentration versus time curve (AUC), maximum observed concentration (C_{max}), and time of C_{max} (t_{max}). Other parameters, such as half-life, apparent clearance, renal clearance, and apparent volume of distribution, may be reported. A model-based preliminary assessment of LY3502970 dose proportionality, food effect, and PK of a controlled-release prototype may be conducted. Midazolam, atorvastatin, and simvastatin PK will be used for preliminary assessment of potential drug-drug interactions (DDIs) of LY3502970.

Pharmacodynamics: Inferences will be sought regarding the ability of LY3502970 over a range of doses to reduce fasting or dynamic glucose together with the effects on insulin. The AUC for glucose and insulin during an oral glucose tolerance test will be calculated using the trapezoidal rule.

Acetaminophen will be used to assess the effect of LY3502970 on gastric emptying. Acetaminophen PK parameter estimates will be calculated by standard noncompartmental analysis methods and summarized using descriptive statistics. The concentration-time profiles of acetaminophen will be presented. Key parameters including C_{max}, AUC, and t_{max} of acetaminophen will be estimated. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Body weight and change from baseline body weight will be summarized by visits.

The PD parameters from each part of the study will be analyzed separately. The PD parameters from placebo-treated subjects within each part of the study will be pooled for the final analysis. Absolute values as well as change from baseline in each parameter will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The main comparisons will be between each LY3502970-treated group and placebo group.

Pharmacokinetic/Pharmacodynamic Analyses: PK/PD modeling may be evaluated to characterize the exposure-response relationships between LY3502970 concentrations and various PD endpoints, provided data are sufficient.

2. Schedule of Activities

Protocol J2A-MC-GZGA study schedules are presented for Part A (SAD; Section 2.1), Part B (MAD; Section 2.2), exploratory Part C (food effect; Section 2.3), exploratory Part D (controlled-release formulation; Section 2.4), and exploratory Part E (formulation optimization; Section 2.5).

2.1. Study Schedule for Part A – Single-Ascending Dose

Procedure	Screening	Baseline	Treatment					Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
Informed consent	X									
CRU admission		X								
CRU discharge						X				Discharge day may be changed after review of preliminary safety and/or PK data. On Day 4, subjects may be discharged after the morning procedures are completed. Subjects may be retained in-house longer than Day 4 at the investigator's discretion.
Outpatient visit	X						X	X		
Medical history	X									
Height/weight	X		Predose					X	X	Height at screening only. Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[b]	X		Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96	X	X	Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position. Time points may be added, if warranted and agreed upon between Lilly and the investigator.
Body temperature (hour)[b]	X	X	Predose, 8	24	48	72				
Safety laboratory tests (hour)[b]	X	X			48			X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.
Liver panel (hour)[b]	X	X				72		X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Lipid panel (hour)[b]	X		Predose		48					Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Serum pregnancy test	X							X		Females only.
Follicle-stimulating hormone	X									For females with spontaneous amenorrhea for 6 to 12 months.

Procedure	Screening	Baseline	Treatment					Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
Serum calcitonin	X									
Hemoglobin A1c	X									
Serology tests	X									See Appendix 2 for details.
Urine drug screen and ethanol test	X	X								See Appendix 2 for details.
Physical examination	X	X								If needed, a symptom-directed physical examination may be conducted.
AE/medication review	X	X	X	X	X	X	X	X	X	
Single 12-lead ECG	X							X	X	ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Triplicate 12-lead ECG (hour)[b]			Predose, 0.5, 1, 4, 8, 12, 16	24	48	72	96			The Day 1 predose ECGs will be taken in triplicates at -30, -15, and 0 minutes predose to establish a baseline. ECGs must be recorded before collecting any vital signs or blood samples and close to the time of the blood draw. ECGs coinciding with meal times should be collected prior to eating. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Telemetry		X	X	X						See Section 9.4.5. The ECG waveform and cardiac rhythm will be monitored from the time of check-in through 48 hours postdose, with occasional 1 to 2 hour hygiene breaks as required. Monitoring time may be extended, if warranted and agreed upon between Lilly and the investigator.
Pharmacogenetic sample[b]			Predose							
Administer study drug			X							

Procedure	Screening	Baseline	Treatment					Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
Point of care safety glucose samples			X	X	X	X	X			Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 3). Prebreakfast samples only will be collected on Days 4 and 5. See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.
Insulin samples (hour)[b]			Predose, 8	24	48	72	96			Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose samples (hour)[b]			Predose, 8	24	48	72	96			Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
LY3502970 PK samples (hour)[b]			Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96			Sampling times may be adjusted after review of preliminary data.
24-hour urine collection for PK of LY3502970 and creatinine (hour)[b]			0 to 12, 12 to 24							Subjects should attempt to empty their bladder within 30 minutes of dosing. Sample collection finishes within ±30 minutes of the 24-hour time point. Sampling times may be adjusted after review of preliminary data.
Serum creatinine samples (hour)[b]			0, 4, 12	24						Sampling times may be adjusted after review of preliminary data.
Coproporphyrin samples (hour)[b]			Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96			Sampling times may be adjusted after review of preliminary data.
OGTT (hour)[b]		X	2							Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.
OGTT – insulin samples (hour relative to glucose dose)		0, 0.5, 1, 1.5, 2	0, 0.5, 1, 1.5, 2							Sampling times may be adjusted after review of preliminary data.

Procedure	Screening	Baseline	Treatment					Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
OGTT – glucose samples (hour relative to glucose dose)		0, 0.5, 1, 1.5, 2	0, 0.5, 1, 1.5, 2							Sampling times may be adjusted after review of preliminary data.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; OGTT = oral glucose tolerance test; PK = pharmacokinetics.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Subjects who discontinue early will be encouraged to return for a follow-up visit at least 14 days after study drug administration.

[b] Sampling times are relative to the time of study drug administration (0 hour).

2.2. Study Schedule for Part B – Multiple-Ascending Dose

Study Schedule for Part B – Cohorts G through I: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline		Treatment					Comments
				Week 1			Week 2		
Day	-28 to -3	-2	-1	1	2	3 to 7	8	9 to 14	
Informed consent	X								
CRU admission		X							
Outpatient visit	X								
Medical history	X								
Height/weight[a]	X			Predose			Predose		Height at screening only. Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[a]	X		X	Predose, 1, 4, 8, 12, 16	24		Predose		Vital measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. Time points may be added, if warranted and agreed upon between Lilly and the investigator. Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Body temperature (hour)[a]	X	X		Predose, 8			Predose		
Physical examination	X								
Medical assessment				Predose			Predose		A symptom-directed physical examination.
Serum pregnancy test	X	X							Females only.
Follicle-stimulating hormone	X								For females with spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X								
Hemoglobin A1c	X								
Serology tests	X								See Appendix 2 for details.
Urine drug screen and ethanol test	X	X							See Appendix 2 for details.
Safety laboratory tests	X	X				Day 7		Day 14	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Blood samples will be collected predose on dosing days. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.

Study Schedule for Part B – Cohorts G through I: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline		Treatment					Comments
				Week 1			Week 2		
Day	-28 to -3	-2	-1	1	2	3 to 7	8	9 to 14	
AE/medication review	X	X	X	X	X	X	X	X	
Liver panel[a]	X			Predose			Predose		Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Lipid panel[a]	X			Predose					Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Single 12-lead ECG	X								ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Triplicate 12-lead ECG (hour)[a]				Predose, 8	24	Predose Days 3 and 4	Predose		The Day 1 predose ECG will be taken in triplicate to establish a baseline. ECGs must be recorded before collecting any vital signs or blood samples and close to the time of the blood draw. ECGs coinciding with meal times should be collected prior to eating. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Sampling times may be adjusted after review of preliminary data.
Telemetry		X		X	X	Day 3	X	Days 9 and 10	See Section 9.4.5. Based on telemetry results from Part A, telemetry may be considered in Part B (specifically around first dose and titration points). The ECG waveform and cardiac rhythm will be monitored using an ECG telemetry monitor during the inpatient stay, with occasional 1 to 2 hour hygiene breaks as required.
Nonpharmacogenetic sample for exploratory biomarker analysis[a]				Predose					Subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Pharmacogenetic sample[a]				Predose					
Administer study drug				X	X	X	X	X	

Study Schedule for Part B – Cohorts G through I: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline		Treatment					Comments
				Week 1			Week 2		
Day	-28 to -3	-2	-1	1	2	3 to 7	8	9 to 14	
Point of care safety glucose samples				X	X	X	X	X	Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 28). See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.
VAS for appetite[a]				Predose			Predose		
Insulin sample (hour)[a]				Predose, 8	24		Predose		Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[a]				Predose, 8	24		Predose		Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
LY3502970 PK samples (hour)[a]				Predose, 0.5, 1, 2, 4, 8, 12, 16	24		Predose		Sampling times may be adjusted after review of preliminary data.
Coproporphyrin samples (hour)[a]				Predose, 0.5, 1, 2, 4, 8, 12, 16	24		Predose		Sampling times may be adjusted after review of preliminary data.
OGTT (hour)[a]			X	2					Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.
OGTT – insulin sample (hour relative to glucose dose)			0, 0.5, 1, 1.5, 2	0, 0.5, 1, 1.5, 2					Sampling times may be adjusted after review of preliminary data.
OGTT – glucose sample (hour relative to glucose dose)			0, 0.5, 1, 1.5, 2	0, 0.5, 1, 1.5, 2					Sampling times may be adjusted after review of preliminary data.

Study Schedule for Part B – Cohorts G through I: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline		Treatment					Comments
				Week 1			Week 2		
Day	-28 to -3	-2	-1	1	2	3 to 7	8	9 to 14	
Acetaminophen dose (hour)[a]			X	2					Acetaminophen dose to assess gastric emptying will be administered on Day -1 and approximately 2 hours postdose (soon after glucose dose for OGTT) on Day 1. Times may be adjusted after review of preliminary data. See Section 7.6 for concomitant therapy restrictions regarding acetaminophen.
Acetaminophen PK samples (hour relative to acetaminophen dose)			Predose, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12	Predose, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12	24				

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; OGTT = oral glucose tolerance test; PK = pharmacokinetics; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Sampling times are relative to the time of study drug administration (0 hour).

Study Schedule for Part B – Cohorts G through I: Multiple-Ascending Dose for Weeks 3, 4, 5, and 6

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
CRU discharge							X					Discharge day may be changed after review of preliminary safety and/or PK data.
Outpatient visit										X	X	
Serum pregnancy test										X		Females only.
Weight[a]	Predose			Predose			X			X	X	Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[a]	Predose, 1, 4, 8, 12, 16	24		Predose		Predose, 1, 4, 8, 12, 16	24			X	X	Vital measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. Time points may be added, if warranted and agreed upon between Lilly and the investigator. Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Body temperature[a]	Predose			Predose								
Medical assessment	Predose			Predose		Predose	X			X	X	A symptom-directed physical examination.
Single 12-lead ECG											X	ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Triplicate 12-lead ECG (hour)[a]	Predose, 8	24		Predose, 8	Predose on Days 23 and 24	Predose, 0.5, 1, 2, 4, 8, 12, 16	X	X	X	X		ECGs must be recorded before collecting any blood samples and close to the time of the blood draw. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Sampling times may be adjusted after review of preliminary data.

Study Schedule for Part B – Cohorts G through I: Multiple-Ascending Dose for Weeks 3, 4, 5, and 6

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Telemetry	X	X	Day 17	X	Days 23 and 24	X	X					See Section 9.4.5. Based on telemetry results from Part A, telemetry may be considered in Part B (specifically around first dose and titration points). The ECG waveform and cardiac rhythm will be monitored using an ECG telemetry monitor during the inpatient stay, with occasional 1 to 2 hour hygiene breaks as required.
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	
Administer study drug	X	X	X	X	X	X						
Point of care safety glucose samples	X	X	X	X	X	X	X					Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 28). Prebreakfast samples only will be collected on Day 29. See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.
Safety laboratory tests			Day 21							X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Blood samples will be collected predose on dosing days. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.
Liver panel[a]	Predose			Predose		Predose					X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Lipid panel[a]	Predose						X				X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Insulin sample (hour)[a]	Predose, 8	24		Predose		Predose, 8	24				X	Except for the 8-hour samples on Days 15 and 28, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[a]	Predose, 8	24		Predose		Predose, 8	24				X	Except for the 8-hour samples on Days 15 and 28, subjects will be required to fast for at least 8 hours before each blood sample is drawn.

Study Schedule for Part B – Cohorts G through I: Multiple-Ascending Dose for Weeks 3, 4, 5, and 6

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
VAS for appetite[a]	Predose			Predose						X		
LY3502970 PK samples (hour)[a]	Predose, 0.5, 1, 2, 4, 8, 12, 16	24		Predose		Predose, 0.5, 1, 2, 4, 8, 12, 16	24, 36	96 ±24	168 ±24	336 ±48	X	Sampling times may be adjusted after review of preliminary data.
Coproporphyrin samples (hour)[a]	Predose, 0.5, 1, 2, 4, 8, 12, 16	24		Predose		Predose, 0.5, 1, 2, 4, 8, 12, 16	24, 36				X	Sampling times may be adjusted after review of preliminary data.
OGTT (hour)[a]						2						Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.
OGTT – insulin sample (hour relative to glucose dose)						0, 0.5, 1, 1.5, 2						Sampling times may be adjusted after review of preliminary data.
OGTT – glucose sample (hour relative to glucose dose)						0, 0.5, 1, 1.5, 2						Sampling times may be adjusted after review of preliminary data.
Acetaminophen dose						X						Acetaminophen dose to assess gastric emptying will be administered approximately 2 hours postdose (soon after glucose dose for OGTT) on Day 28. Times may be adjusted after review of preliminary data. See Section 7.6 for concomitant therapy restrictions regarding acetaminophen.

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Acetaminophen PK samples (hour relative to acetaminophen dose)						Predose, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12	24					
Nonpharmacogenetic sample for exploratory biomarker analysis[a]	Predose			Predose			X					Subjects will be required to fast for at least 8 hours before each blood sample is drawn.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; OGTT = oral glucose tolerance test; PK = pharmacokinetics; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Sampling times are relative to the time of study drug administration (0 hour).

[b] Subjects who discontinue early will be encouraged to return for a follow-up visit at least 14 days after study drug administration.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline			Treatment					Comments
					Week 1			Week 2		
Day	-28 to -4	-3	-2	-1	1	2	3 to 7	8	9 to 14	
Informed consent	X									
CRU admission		X								
Outpatient visit	X									
Medical history	X									
Height/weight[a]	X				Predose			Predose		Height at screening only. Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[a]	X			X	Predose, 1, 4, 8, 12, 16	24		Predose		Vital measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. Time points may be added, if warranted and agreed upon between Lilly and the investigator. Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Body temperature (hour)[a]	X	X			Predose, 8			Predose		
Physical examination	X									
Medical assessment					Predose			Predose		A symptom-directed physical examination.
Serum pregnancy test	X	X								Females only.
Follicle-stimulating hormone	X									For females with spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X									
Hemoglobin A1c	X									
Serology tests	X									See Appendix 2 for details.
Urine drug screen and ethanol test	X	X								See Appendix 2 for details.
Safety laboratory tests	X	X					Day 7		Day 14	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Blood samples will be collected predose on dosing days. In case of BID dosing, time point is related to the morning dose. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline			Treatment					Comments
					Week 1			Week 2		
Day	**-28 to -4**	**-3**	**-2**	**-1**	**1**	**2**	**3 to 7**	**8**	**9 to 14**	
AE/medication review	X	X		X	X	X	X	X	X	
Liver panel[a]	X				Predose			Predose		Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Lipid panel[a]	X				Predose					Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Single 12-lead ECG	X									ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Triplicate 12-lead ECG (hour)[a]					Predose, 8	24	Predose Days 3 and 4	Predose		The Day 1 predose ECG will be taken in triplicate to establish a baseline. ECGs must be recorded before collecting any vital signs or blood samples and close to the time of the blood draw. ECGs coinciding with meal times should be collected prior to eating. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Sampling times may be adjusted after review of preliminary data.
Telemetry		X			X	X	Day 3	X	Days 9 and 10	See Section 9.4.5. Based on telemetry results from Part A, telemetry may be considered in Part B (specifically around first dose and titration points). The ECG waveform and cardiac rhythm will be monitored using an ECG telemetry monitor during the inpatient stay, with occasional 1 to 2 hour hygiene breaks as required.
Nonpharmacogenetic sample for exploratory biomarker analysis[a]					Predose					Subjects will be required to fast for at least 8 hours before each blood sample is drawn.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline			Treatment					Comments
					Week 1			Week 2		
Day	-28 to -4	-3	-2	-1	1	2	3 to 7	8	9 to 14	
Pharmacogenetic sample[a]					Predose					
Administer study drug					X	X	X	X	X	Once daily or BID.
Point of care safety glucose samples					X	X	X	X	X	Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 28). See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.
VAS for appetite[a]					Predose			Predose		
Insulin sample (hour)[a]					Predose, 8	24		Predose		Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[a]					Predose, 8	24		Predose		Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Administer midazolam (Cohort J)			X							Cohort J only. Refer to Section 6.3.1 for water volumes for dose administration.
Administer atorvastatin (Cohort J)			X							Cohort J only. Administer atorvastatin 4 hours after midazolam.
Administer simvastatin (Cohort K)			X							Cohort K only.
Midazolam PK samples (hour relative to midazolam dose) (Cohort J)			Predose, 0.5, 1, 1.5, 2, 5, 8, 12	24						Cohort J only.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline			Treatment					Comments
					Week 1			Week 2		
Day	-28 to -4	-3	-2	-1	1	2	3 to 7	8	9 to 14	
Atorvastatin PK samples (hour relative to midazolam dose) (Cohort J)			Predose, 4.5, 5, 6, 7, 8, 12	24						Cohort J only.
Simvastatin PK samples (hour relative to simvastatin dose) (Cohort K)			Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	24						Cohort K only.
LY3502970 PK samples (hour)[a]					Predose, 0.5, 1, 2, 4, 8, 12*, 16	24		Predose		Sampling times may be adjusted after review of preliminary data. *In case of BID dosing, this sample is obtained prior to the evening dose.
Coproporphyrin samples (hour)[a]										No coproporphyrin samples collected during Weeks 1 and 2.
OGTT (hour)[a]				X	2					Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.
OGTT – insulin sample (hour relative to glucose dose)				0, 0.5, 1, 1.5, 2	0, 0.5, 1, 1.5, 2					Sampling times may be adjusted after review of preliminary data.
OGTT – glucose sample (hour relative to glucose dose)				0, 0.5, 1, 1.5, 2	0, 0.5, 1, 1.5, 2					Sampling times may be adjusted after review of preliminary data.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 1 and 2

Procedure	Screening	Baseline			Treatment					Comments
					Week 1			Week 2		
Day	-28 to -4	-3	-2	-1	1	2	3 to 7	8	9 to 14	
Acetaminophen dose (hour)[a]				X	2					Acetaminophen dose to assess gastric emptying will be administered on Day -1 and approximately 2 hours postdose (soon after glucose dose for OGTT) on Day 1. Times may be adjusted after review of preliminary data. See Section 7.6 for concomitant therapy restrictions regarding acetaminophen.
Acetaminophen PK samples (hour relative to acetaminophen dose)				Predose, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12	Predose, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12	24				

Abbreviations: AE = adverse event; BID = twice daily; CRU = clinical research unit; ECG = electrocardiogram; OGTT = oral glucose tolerance test; PK = pharmacokinetics; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Sampling times are relative to the time of study drug administration (0 hour). In case of BID dosing, time point is related to the morning dose.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 3, 4, 5, and 6

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
CRU discharge							X					Discharge day may be changed after review of preliminary safety and/or PK data.
Outpatient visit								X	X	X	X	
Serum pregnancy test										X		Females only.
Weight[a]	Predose			Predose			X			X	X	Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[a]	Predose, 1, 4, 8, 12, 16	24		Predose		Predose, 1, 4, 8, 12, 16	24			X	X	Vital measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. Time points may be added, if warranted and agreed upon between Lilly and the investigator. Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Body temperature[a]	Predose			Predose								
Medical assessment	Predose			Predose		Predose	X			X	X	A symptom-directed physical examination.
Single 12-lead ECG											X	ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Triplicate 12-lead ECG (hour)[a]	Predose, 8	24		Predose, 8	Predose on Days 23 and 24	Predose, 0.5, 1, 2, 4, 8, 12, 16	X	X	X	X		ECGs must be recorded before collecting any blood samples and close to the time of the blood draw. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Sampling times may be adjusted after review of preliminary data.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 3, 4, 5, and 6

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	**15**	**16**	**17 to 21**	**22**	**23 to 27**	**28**	**29**	**32 ±1**	**35 ±1**	**42 ±2**	**ED[b]**	
Telemetry	X	X	Day 17	X	Days 23 and 24	X	X					See Section 9.4.5. Based on telemetry results from Part A, telemetry may be considered in Part B (specifically around first dose and titration points). The ECG waveform and cardiac rhythm will be monitored using an ECG telemetry monitor during the inpatient stay, with occasional 1 to 2 hour hygiene breaks as required.
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	
Administer study drug	X	X	X	X	X	X						Once daily or BID.
Point of care safety glucose samples	X	X	X	X	X	X	X					Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 28). Prebreakfast samples only will be collected on Day 29. See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.
Safety laboratory tests			Day 21							X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Blood samples will be collected predose on dosing days. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.
Liver panel[a]	Predose			Predose		Predose					X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Lipid panel[a]	Predose						X				X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Insulin sample (hour)[a]	Predose, 8	24		Predose		Predose, 8	24				X	Except for the 8-hour samples on Days 15 and 28, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[a]	Predose, 8	24		Predose		Predose, 8	24				X	Except for the 8-hour samples on Days 15 and 28, subjects will be required to fast for at least 8 hours before each blood sample is drawn.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 3, 4, 5, and 6

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	**15**	**16**	**17 to 21**	**22**	**23 to 27**	**28**	**29**	**32 ±1**	**35 ±1**	**42 ±2**	**ED[b]**	
VAS for appetite[a]	Predose			Predose						X		
LY3502970 PK samples (hour)[a]	Predose, 0.5, 1, 2, 4, 8, 12*, 16	24		Predose		Predose, 0.5, 1, 2, 4, 8, 12*, 16	24, 36	96 ±24	168 ±24	336 ±48	X	Sampling times may be adjusted after review of preliminary data. *In case of BID dosing, this sample is obtained prior to the evening dose.
Administer midazolam (Cohort J)					X (Day 27)							Administer midazolam within 15 minutes after LY3502970 dose on Day 27 (Cohort J). Refer to Section 6.3.1 for water volumes for dose administration. In case of BID dosing, to be administered with the morning dose.
Administer atorvastatin (Cohort J)					X (Day 27)							Administer atorvastatin 4 hours after midazolam on Day 27 (Cohort J).
Administer simvastatin (Cohort K)					X (Day 27)							Simvastatin will be coadministered with either LY3502970 or placebo on Day 27 (Cohort K).
Midazolam PK samples (hour relative to midazolam dose) (Cohort J)*					Predose, 0.5, 1, 1.5, 2, 5, 8, 12	24						Cohort J only. *This is with reference to Day 27 administration of midazolam.
Atorvastatin PK samples (hour relative to midazolam dose) (Cohort J)*					Predose, 4.5, 5, 6, 7, 8, 12	24						Cohort J only. *This is with reference to Day 27 administration of midazolam.

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Simvastatin PK samples (hour relative to simvastatin dose) (Cohort K)*					Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16	24						Cohort K only. *This is with reference to Day 27 administration of simvastatin.
Coproporphyrin samples (hour)[a]						Predose, 0.5, 1, 2, 4, 8, 12, 16					X	Sampling times may be adjusted after review of preliminary data.
OGTT (hour)[a]						2						Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.
OGTT – insulin sample (hour relative to glucose dose)						0, 0.5, 1, 1.5, 2						Sampling times may be adjusted after review of preliminary data.
OGTT – glucose sample (hour relative to glucose dose)						0, 0.5, 1, 1.5, 2						Sampling times may be adjusted after review of preliminary data.
Acetaminophen dose						X						Acetaminophen dose to assess gastric emptying will be administered approximately 2 hours postdose (soon after glucose dose for OGTT) on Day 28. Times may be adjusted after review of preliminary data. See Section 7.6 for concomitant therapy restrictions regarding acetaminophen.

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Acetaminophen PK samples (hour relative to acetaminophen dose)						Predose, 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12	24					
Nonpharmacogenetic sample for exploratory biomarker analysis[a]	Predose			Predose			X					Subjects will be required to fast for at least 8 hours before each blood sample is drawn.

Abbreviations: AE = adverse event; BID = twice daily; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; OGTT = oral glucose tolerance test; PK = pharmacokinetics; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Sampling times are relative to the time of study drug administration (0 hour). In case of BID dosing, time point is related to the morning dose.

[b] Subjects who discontinue early will be encouraged to return for a follow-up visit at least 14 days after study drug administration.

2.3. Study Schedule for Exploratory Part C – Food Effect

Procedure	Screening	Treatment Periods 1 and 2						Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
Informed consent	X									
CRU admission		X								
CRU discharge						X				Discharge day may be changed after review of preliminary safety and/or PK data. On Day 4, subjects may be discharged after the morning procedures are completed. Subjects may be retained in-house longer than Day 4 at the investigator's discretion.
Outpatient visit	X						X	X		
Medical history	X									
Height/weight[b]	X		Predose					X	X	Height at screening only. Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[b]	X		Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96	X	X	Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position. Time points may be added, if warranted and agreed upon between Lilly and the investigator.
Body temperature (hour)[b]	X	X	Predose, 8	24	48	72				
Safety laboratory tests (hour)[b]	X	X			48			X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.
Liver panel	X	X				72		X		Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Serum pregnancy test	X							X		Females only.
Follicle-stimulating hormone	X									For females with spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X									
Hemoglobin A1c	X									
Serology tests	X									See Appendix 2 for details

Procedure	Screening	Treatment Periods 1 and 2						Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
Urine drug screen and ethanol test	X	X								See Appendix 2 for details
Physical examination	X	X								If needed, a symptom-directed physical examination may be conducted.
AE/medication review	X	X	X	X	X	X	X	X	X	
Single 12-lead ECG	X							X	X	ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Pharmacogenetic sample[b]			Predose							
Administer study drug			X							There will be a washout period of at least 5 days between doses.
Point of care safety glucose samples			X	X	X	X	X			Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 3). Prebreakfast samples only will be collected on Days 4 and 5. See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.
Insulin sample (hour)[b]			Predose, 8	24	48	72	96			Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[b]			Predose, 8	24	48	72	96			Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
LY3502970 PK sample (hour)[b]			Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96			Sampling times may be adjusted after review of preliminary data.
Coproporphyrin sample (hour)[b]			Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96			Sampling times may be adjusted after review of preliminary data.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; PK = pharmacokinetics.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Subjects who discontinue early will be encouraged to return for a follow-up visit at least 14 days after the final study drug administration.

[b] Sampling times are relative to the time of study drug administration (0 hour).

2.4. Study Schedule for Exploratory Part D – LY3502970 Controlled-release Formulation

Procedure	Screening	Baseline	Treatment					Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
Informed consent	X									
CRU admission		X								
CRU discharge						X				Discharge day may be changed after review of preliminary safety and/or PK data. On Day 4, subjects may be discharged after the morning procedures are completed. Subjects may be retained in-house longer than Day 4 at the investigator's discretion.
Outpatient visit	X						X	X		
Medical history	X									
Height/weight[b]	X		Predose					X	X	Height at screening only. Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[b]	X		Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96	X	X	Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position. Time points may be added, if warranted and agreed upon between Lilly and the investigator.
Body temperature (hour)[b]	X	X	Predose, 8	24	48	72				
Safety laboratory tests (hour)[b]	X	X			48			X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.
Liver panel (hour)[b]	X	X				72		X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Serum pregnancy test	X							X		For females only.
Follicle-stimulating hormone	X									For females with spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X									
Hemoglobin A1c	X									
Serology tests	X									See Appendix 2 for details.

Procedure	Screening	Baseline	Treatment					Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
Urine drug screen and ethanol test	X									See Appendix 2 for details.
Physical examination	X	X								If needed, a symptom-directed physical examination may be conducted.
AE/medication review	X	X	X	X	X	X	X	X	X	
Single 12-lead ECG	X							X	X	ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Pharmacogenetic sample[b]			Predose							
Administer study drug			X							
Point of care safety glucose samples			X	X	X	X	X			Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 3). Prebreakfast samples only will be collected on Days 4 and 5. See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.
Insulin sample (hour)[b]			Predose, 8	24	48	72	96			Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[b]			Predose, 8	24	48	72	96			Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
LY3502970 PK sample (hour)[b]			Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96			Sampling times may be adjusted after review of preliminary data.
Coproporphyrin sample (hour)[b]			Predose, 0.5, 1, 2, 4, 8, 12, 16	24	48	72	96			Sampling times may be adjusted after review of preliminary data.

Procedure	Screening	Baseline	Treatment					Follow-up		Comments
Days	-28 to -2	-1	1	2	3	4	5	15 ±1	ED[a]	
OGTT (hour)[b]		X	2							Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.
OGTT – insulin sample (hour relative to glucose dose)		Predose, 0.5, 1, 1.5, 2	Predose, 0.5, 1, 1.5, 2							Sampling times may be adjusted after review of preliminary data.
OGTT – glucose sample (hour relative to glucose dose)		Predose, 0.5, 1, 1.5, 2	Predose, 0.5, 1, 1.5, 2							Sampling times may be adjusted after review of preliminary data.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; OGTT = oral glucose tolerance test; PK = pharmacokinetics.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

a Subjects who discontinue early will be encouraged to return for a follow-up visit at least 14 days after the final study drug administration.

b Sampling times are relative to the time of study drug administration (0 hour).

2.5. Study Schedule for Exploratory Part E – Formulation Optimization

Study Schedule for Part E: Titration Periods 1 and 2

Procedure	Screening	Baseline		Treatment					Comments
				Titration Period 1			Titration Period 2		
Day	-28 to -3	-2	-1	1	2	3 to 6	7	8 to 12	
Informed consent	X								
CRU admission		X							
Outpatient visit	X								
Medical history	X								
Height/weight[a]	X			Predose			Predose		Height at screening only. Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[a]	X		X	Predose, 1, 4, 6, 8, 12, 16	24		Predose		Vital measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. Time points may be added, if warranted and agreed upon between Lilly and the investigator. Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Body temperature (hour)[a]	X	X		Predose, 8			Predose		
Physical examination	X								
Medical assessment				Predose			Predose		A symptom-directed physical examination.
Serum pregnancy test	X	X							Females only.

Procedure	Screening	Baseline		Treatment					Comments
				Titration Period 1			Titration Period 2		
Day	-28 to -3	-2	-1	1	2	3 to 6	7	8 to 12	
Administer Heidelberg pH Capsule	X								Subjects will be administered with Heidelberg pH capsule at screening to check whether the subject can swallow the capsule. Subjects who are unable to swallow the Heidelberg pH capsule will be considered as screening failures.
Follicle-stimulating hormone	X								For females with spontaneous amenorrhea for 6 to 12 months.
Serum calcitonin	X								
Hemoglobin A1c	X								
Serology tests	X								See Appendix 2 for details.
Urine drug screen and ethanol test	X	X							See Appendix 2 for details.
Safety laboratory tests	X	X				Day 6		Day 12	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Blood samples will be collected predose on dosing days. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.
AE/medication review	X	X	X	X	X	X	X	X	
Liver panel[a]	X			Predose			Predose		Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Lipid panel[a]	X			Predose					Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.

Procedure	Screening	Baseline		Treatment					Comments
				Titration Period 1			Titration Period 2		
Day	-28 to -3	-2	-1	1	2	3 to 6	7	8 to 12	
Single 12-lead ECG	X								ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Triplicate 12-lead ECG (hour)[a]				Predose, 8	24	Predose Days 3 and 4	Predose		The Day 1 predose ECG will be taken in triplicate to establish a baseline. ECGs must be recorded before collecting any vital signs or blood samples and close to the time of the blood draw. ECGs coinciding with meal times should be collected prior to eating. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Sampling times may be adjusted after review of preliminary data.
Nonpharmacogenetic sample for exploratory biomarker analysis[a]				Predose					Subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Pharmacogenetic sample[a]				Predose					
Administer study drug				X	X	X	X	X	
Point of care safety glucose samples				X	X	X	X	X	Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 28). See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.

Procedure	Screening	Baseline		Treatment					Comments
				Titration Period 1			Titration Period 2		
Day	-28 to -3	-2	-1	1	2	3 to 6	7	8 to 12	
VAS for appetite[a]				Predose			Predose		
Insulin sample (hour)[a]				Predose, 8	24[b]		Predose		Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[a]				Predose, 8	24[b]		Predose		Except for the 8-hour sample on Day 1, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
LY3502970 PK samples (hour)[a]				Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	24[b]		Predose		Sampling times may be adjusted after review of preliminary data.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; OGTT = oral glucose tolerance test; PK = pharmacokinetics; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Sampling times are relative to the time of study drug administration (0 hour).

[b] This is predose sample on Day 2.

Study Schedule for Part E: Titration periods 3, 4, and test period

Procedure	Treatment											Follow-up		Comments
	Titration Period 3			Titration Period 4		Test Period								
Day	**13**	**14**	**15 to 18**	**19**	**20 to 23**	**24**	**27**	**28**	**29 ±1**	**32±1**	**35±1**	**40 ±2**	**ED[b]**	
CRU discharge									X					Discharge day may be changed after review of preliminary safety and/or PK data.
Outpatient visit										X	X	X	X	
Serum pregnancy test												X	X	Females only.
Weight[a]	Predose			Predose		X			X			X	X	Weight will be measured in a consistent way (see Section 9.4.4).
Vital signs (supine) (hour)[a]	Predose			Predose	Predose, 1, 4, 6, 8, 12, 16, 24[c] (Day 23)			Predose, 1, 4, 6, 8, 12, 16	24			X	X	Vital measurements whose nominal times are not listed in the schedule should be taken before PK samples scheduled on the same day. Time points may be added, if warranted and agreed upon between Lilly and the investigator. Blood pressure and pulse rate measurements will be taken after approximately 5 minutes in the supine position.
Body temperature[a]	Predose			Predose										
Medical assessment	Predose			Predose		Predose	X					X	X	A symptom-directed physical examination.
Single 12-lead ECG													X	ECGs must be recorded before collecting any vital signs or blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Procedure	Treatment											Follow-up		Comments
	Titration Period 3			Titration Period 4		Test Period								
Day	13	14	15 to 18	19	20 to 23	24	27	28	29 ±1	32±1	35±1	40 ±2	ED[b]	
Triplicate 12-lead ECG (hour)[a]	Predose, 8	24		Predose, 8	Predose on Day 23	Predose, 0.5, 1, 2, 4, 8, 12, 16	X	X	X	X	X	X		ECGs must be recorded before collecting any blood samples and close to the time of the blood draw. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Sampling times may be adjusted after review of preliminary data.
AE/medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administer study drug	X	X	X	X	X	X	X	X						Study drug will be administered from Days 1 to 28. See Section 5.1.4.
Administer Heidelberg pH capsule					X (Day 23)			X						Heidelberg pH capsule will be administered at least 30 minutes prior to LY3502970 dosing.
Point of care safety glucose samples	X	X	X	X	X	X	X	X	X					Sampling at premeal (breakfast, lunch, and dinner) and before bedtime during CRU stay (Days 1 to 28). Prebreakfast samples only will be collected on Day 29. See Section 9.4.7 for glucose monitoring details. Refer to Section 6.3.1 for meal restrictions.

Procedure	Treatment											Follow-up		Comments
	Titration Period 3			Titration Period 4		Test Period								
Day	13	14	15 to 18	19	20 to 23	24	27	28	29 ±1	32±1	35±1	40 ±2	ED[b]	
Safety laboratory tests					Day 21							X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. Blood samples will be collected predose on dosing days. Includes hematology, clinical chemistry, and urinalysis. See Appendix 2 for details.
Liver panel[a]	Predose			Predose		Predose						X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Lipid panel[a]	Predose						X					X	X	Subjects will be required to fast for at least 8 hours before each blood sample is drawn. See Appendix 2 for details.
Insulin sample (hour)[a]	Predose, 8	24[c]		Predose		Predose, 8, 24[c]						X	X	Except for the 8-hour samples on Days 13 and 24, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[a]	Predose, 8	24[c]		Predose		Predose, 8, 24[c]						X	X	Except for the 8-hour samples on Days 13 and 24, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
VAS for appetite[a]	Predose			Predose		X						X		
LY3502970 PK samples (hour)[a]	Predose			Predose, 0.5, 1, 2, 4, 6, 8, 12, 16, 24[c]	Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 (Day 23)	24[c]		Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	24, 36	96 ± 24	168 ± 24			Sampling times may be adjusted after review of preliminary data.

Procedure	Treatment											Follow-up		Comments
	Titration Period 3			Titration Period 4		Test Period								
Day	13	14	15 to 18	19	20 to 23	24	27	28	29 ±1	32±1	35±1	40 ±2	ED[b]	
Nonpharmacogenetic sample for exploratory biomarker analysis[a]	Predose			Predose				Predose						Subjects will be required to fast for at least 8 hours before each blood sample is drawn.

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; OGTT = oral glucose tolerance test; PK = pharmacokinetics; VAS = visual analog scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Sampling times are relative to the time of study drug administration (0 hour).

b Subjects who discontinue early will be encouraged to return for a follow-up visit at least 14 days after study drug administration.

C This is predose sample.

3. Introduction

3.1. Study Rationale

Multiple glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) therapies are approved, the most commonly prescribed being administered once daily or once weekly by subcutaneous injection. Even with several different GLP-1RAs approved for use in type 2 diabetes mellitus (T2DM), the injection remains a barrier for many patients to initiate and to adhere to therapy long-term. Oral semaglutide (Novo Nordisk), if approved, is expected to provide patients with a viable alternative to subcutaneous injection delivery. However, its administration requires the patient to adhere to multiple steps to ensure proper delivery of the medication through the gastric lining including: fasting for ≥6 hours, no more than approximately 120 mL of water at administration, and no food or fluid for at least 30 minutes after taking the medication (reviewed in Hedrington and Davis 2019). Therefore, providing additional oral GLP-1RA therapies remains an unmet need.

LY3502970 is a chemically synthesized, oral GLP-1RA being developed as a daily oral therapy as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

This first-in-human study will investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple oral doses of LY3502970 in healthy subjects. Safety and tolerability evaluations will be conducted over a wide range of oral doses, and dose escalation will not proceed until safety, tolerability, and available PK and PD data from previous doses have been reviewed. The study is intended to estimate a maximum tolerated dose (MTD) or establish that doses exceeding the expected therapeutic dose are tolerated. The PK, PD, safety, and tolerability data from this study in healthy subjects will assist in identifying an appropriate dose range for subsequent clinical studies.

Duration of action differs among peptide GLP-1RAs, impacting significantly the drug posology: from injection frequency to intake related or not related to meals and hour of the day (Raccah, 2016). Oral semaglutide is an oral GLP-1RA peptide associated with an absorption enhancer compound that allows molecule gastrointestinal absorption, which takes place at the stomach due to enhancer's pH increase (Buckely et al. 2018). Clinical study findings demonstrated acceptable dosing conditions were achieved when oral semaglutide was administered in the fasting state with up to 120 mL water and a postdose fast of 30 minutes (Hedrington et al. 2019). This effect is unknown for LY3502970; therefore, this study may include a preliminary assessment of whether a meal alters the PK of LY3502970.

This study may also include a preliminary evaluation of an LY3502970 controlled-release prototype. In the event the human half-life of LY3502970 is determined to be too short to allow for once-daily dosing, a controlled-release dosage form would be highly preferable to switching to twice-daily or more frequent dosing to achieve the desired PK profile. Introduction of a simple prototype controlled-release formulation would provide preliminary information to help assess whether this approach is feasible as a means to increase the absorption window for this compound. This data would be used to accelerate downstream development of a commercial controlled-release formulation should it be deemed necessary.

3.2. Background

LY3502970 is an oral GLP-1RA that exhibits the antihyperglycemic actions of GLP-1, acting as an insulin secretagogue and increasing glucose-dependent insulin secretion after a glucose challenge.

3.2.1. Nonclinical Studies

The disposition of LY3502970, including PK, toxicokinetics, and metabolism, has been studied in rats and monkeys.

- Single-dose PK studies in rats and monkeys show that LY3502970 has low to moderate oral bioavailability, ranging from 21% to 43%. Following intravenous administration, LY3502970 clearance is low (<12%) relative to hepatic blood flow in both species. Following oral administration, the rate of absorption is similar in both species with time of maximum observed concentration (t_{max}) ranging from 2.25 to 3.50 hours. The terminal elimination half-life ranged from 10.4 to 12.4 hours in rats and from 3.4 to 4.6 hours in monkeys following oral administration.
- Toxicokinetics of LY3502970 determined in the 28-day toxicology studies in rats and monkeys showed less than dose-proportional exposure increases in rats but nearly dose-proportional exposure increases in monkeys. Plasma LY3502970 exposures after single and multiple doses were similar. No sex differences in exposure were observed.
- Preliminary protein-binding studies indicate that LY3502970 is highly bound in plasma from mice, rats, monkeys, and dogs, ranging from 99.55% to 99.85%.
- In screening in vitro metabolism studies using liver microsomes and cryopreserved hepatocytes, several LY3502970 oxidative metabolites were detected.

The nonclinical safety profile of LY3502970 was examined in a set of nonpivotal and pivotal in vitro and in vivo studies, including genetic toxicology assays, safety pharmacology studies, and repeat-dose general toxicity studies, in rats and monkeys. The pivotal good laboratory practice studies consisted of a 28-day treatment period followed by a 28-day nondosing recovery period in rats and monkeys, safety pharmacology studies in monkeys, and in vivo and in vitro genetic toxicology assays.

Species selection for nonclinical safety assessment was based on species-specific receptor activity and metabolism profile. LY3502970 has been shown to be inactive at GLP-1 receptors in mice, rats, pigs, rabbits, and dogs, but active in nonhuman primates and humans. Rats were selected as the most suitable rodent species; however, rats represent an off-target model of toxicology and toxicokinetics. Monkeys were selected as the nonrodent species because they are the pharmacologically relevant species and they have been used as the nonrodent species in the nonclinical safety assessment of the majority of peptide GLP-1RAs.

Key nonclinical safety characteristics of LY3502970 consist of the following effects identified in toxicity studies.

- Effects identified in monkeys include:
    - decreased body weight and food consumption (accompanied by clinical signs of emesis),
    - decreases in erythroid hematology parameters including bone marrow hypocellularity,
    - increased serum bilirubin concentrations, and
    - electrocardiogram (ECG) abnormalities (PR wave interval prolongation).
- Effects identified in rats include:
    - increases in serum bilirubin and bile acid concentrations (hepatobiliary system), and
    - decreases in erythroid hematology parameters.

A no-observed-adverse-effect level (NOAEL) was achieved in both species and are summarized in Section 5.5.

The nonclinical safety profile of LY3502970 included negative genetic toxicity assessments and target-organ effects in general toxicity and safety pharmacology studies that were generally associated with pharmacologic activity (body weight losses and vomiting), known inhibition of liver transporters, or class effects (heart rate and ECG effects). A definitive in vitro CYP inhibition study indicates that LY3502970 may inhibit cytochrome P450 (CYP)3A4. No other tested CYP enzymes (i.e., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6) are significantly inhibited. In vitro studies also indicate LY3502970 may be an inhibitor of organic anion transporter protein (OATP)1B1. A potential embryo-fetal developmental effect was also identified in a pilot study in pregnant rabbits.

3.3. Benefit/Risk Assessment

LY3502970 was examined in nonclinical safety assessment studies including genotoxicity, safety pharmacology, and repeat-dose toxicity studies in rats and monkeys. In concordance with the well-known exaggerated on-target pharmacology of the GLP-1RA class of products, monkeys dosed with LY3502970 experienced vomiting, pronounced decreases in food consumption, and body weight loss in the 28-day toxicology study. Additional GLP-1RA class findings in monkeys consisted of cardiovascular effects such as tachycardia and PR interval prolongation. Due to the dose limitations in monkeys caused by exaggerated pharmacology, monkeys do not adequately inform the off-target effects or offer a high dose multiple-related safety profile of LY3502970.

Rats do not possess on-target activity associated with the GLP-1 receptor agonism of LY3502970; therefore, dose levels in toxicology studies in rats were higher than in monkeys due

to the absence of dose-limiting pharmacology. This differential species-specific activity of LY3502970 allows for an exploration and understanding of the off-target toxicity in rats. As such, LY3502970 was dosed up to 74-fold higher in rats than in monkeys based on dose/body surface area. The toxicity profile at these dose levels shows a lack of toxicologically relevant off-target effects, with findings limited to the metabolism and excretion of the LY3502970 via the liver (reversible altered liver function without liver pathology). Dose and exposure multiples to effect levels in rats were higher than in monkeys (see Section 5.5) providing an understanding of the nonclinical safety profile beyond the limitations of tolerable dose levels in monkeys.

The nonclinical safety profile of LY3502970 in monkeys includes body weight losses and vomiting, as well as known class effects on transient, reversible, and monitorable cardiovascular parameters and effects of low toxicologic impact on the hematopoietic and hepatobiliary system, which are also reversible and monitorable. These findings have been previously documented with other approved GLP-1RAs in their nonclinical and clinical safety profiles, deeming them class effects of GLP-1RAs (van Can et al. 2014; Trulicity package insert 2019). Gastrointestinal effects (nausea, diarrhea, vomiting, abdominal pain, and decreased appetite) are the most common adverse effects in human subjects with GLP-1RA, and are monitorable and reversible (Trulicity package insert 2019). Overall, the nonclinical safety profile supports the transition from preclinical status to single-ascending dose (SAD)/ multiple-ascending dose (MAD) clinical study.

Based on the risk assessment and available data, LY3502970 does not present either a high-risk or high-uncertainty profile (Butler et al. 2017; DeGeorge et al. 2018) that might necessitate a sentinel dosing approach. See also Section 5.4.1 for a more detailed justification with regard to the lack of inclusion of sentinel dosing in this study.

This protocol reflects the fact that LY3502970 has not been administered to humans previously and, to mitigate this risk, the study has been designed to be conducted in accordance with principles outlined in the applicable guidance, such as Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMA 2017). The identified risks of LY3502970 (i.e., cardiovascular effects, gastrointestinal effects, decreased/loss of appetite, weight loss, and hepatobiliary function) were related to well-known pharmacologic activity, or known GLP-1RA class effects, or known metabolism pathways and are considered to be reversible, monitorable, and manageable at the planned dose range for LY3502970 in healthy subjects. To further minimize any potential risk, study participants will remain in the clinical research unit (CRU) at least 3 days postdose in Part A (SAD), Part C (food effect), and Part D (controlled-release formulation) and for the entire 28-day treatment period until at least 24 hours after the final dose in Part B (MAD). Although planned discharge days are included in the study schedule, subjects may be required to remain at the CRU as needed for safety follow-up based on clinical judgment of the investigator.

There is no anticipated therapeutic benefit of LY3502970 for the subjects.

More information about the known and expected benefits and risks, and possible serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3502970 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table GZGA.1. Objectives and Endpoints

Primary Objective	**Endpoints**
To investigate the safety and tolerability of single and multiple oral doses of LY3502970 in healthy subjects	Incidence of TEAEs and SAEs
Secondary Objective	**Endpoints**
To characterize the PK of LY3502970 after single and multiple oral doses in healthy subjects (Parts A and B)	Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}
Exploratory Objectives	**Endpoints**
To evaluate the effect of a meal on the PK of a single oral dose of LY3502970 (Part C)	Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}
To evaluate the PK of a single dose of LY3502970 controlled-release prototype (Part D)	Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}
To investigate LY3502970 effects on markers of OATP function following single and multiple oral doses of LY3502970 in healthy subjects (Parts A, B, C, and D)	Plasma concentrations of coproporphyrin 1 and coproporphyrin 3
To investigate potential DDIs of LY3502970 following multiple oral doses of LY3502970 in healthy subjects (Part B)	Plasma concentrations of midazolam, atorvastatin, and simvastatin
To investigate the PD effects of LY3502970 following single oral doses administered to healthy subjects (Part A)	Glycemic control (including fasting and AUC of glucose and insulin during OGTT), weight, and lipids
To investigate the PD effects of LY3502970 following multiple oral doses administered to healthy subjects (Part B)	Glycemic control (including fasting and AUC of glucose and insulin during OGTT), gastric emptying using acetaminophen, weight, VAS for appetite, and lipids
To investigate the PD effects of LY3502970 following single oral doses administered to healthy subjects following a meal (Part C)	Glycemic control (including glucose) and weight
To investigate the PD effects of LY3502970 controlled-release prototype following single oral doses administered to healthy subjects (Part D)	Glycemic control (including fasting and AUC of glucose and insulin during OGTT) and weight

To investigate the PK of 2 different formulations of LY3502970 following multiple oral doses of LY3502970 in healthy subjects (Part E)	Primary PK parameters for analysis will include C_{max}, AUC, and t_{max}

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed concentration; DDIs = drug-drug interactions; OATP = organic anion transporting peptide; OGTT = oral glucose tolerance test; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time of maximum observed concentration; VAS = visual analog scale.

5. Study Design

5.1. Overall Design

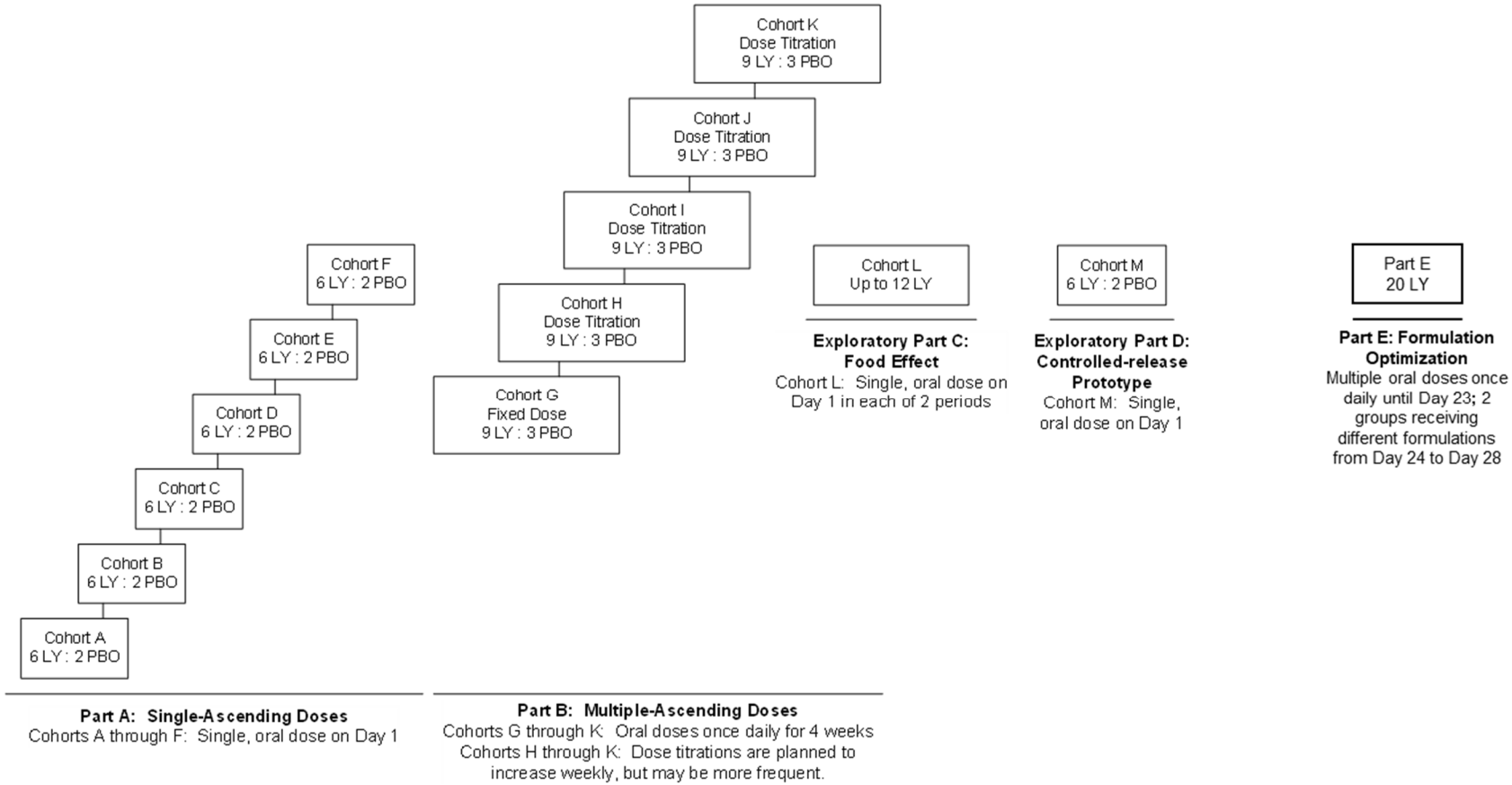
Study GZGA is a Phase 1, single site, 5-part study in healthy subjects. The study design includes:

- Part A: randomized, placebo-controlled, investigator- and subject-blind, SAD
- Part B: randomized, placebo-controlled, investigator- and subject-blind, 4-week, MAD with or without dose titration
- Exploratory Part C: single-dose, randomized, 2-treatment arm, 2-period, open-label, crossover to evaluate food effects
- Exploratory Part D: randomized, placebo-controlled, investigator- and subject-blind, single dose to evaluate the LY3502970 controlled-release prototype
- Exploratory Part E: randomized, investigator- and subject-blind, multiple dose to evaluate two different formulations of LY3502970 with dose titration.

Figure GZGA.1 shows the general schematic of the planned study design.

In all parts of the study, safety and tolerability assessments will include the monitoring of AEs, vital signs, body temperature, blood glucose levels, safety laboratory tests, liver panel tests, medical assessments, body weight, concomitant medication, triplicate ECGs, and telemetry.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: LY = LY3502970; PBO = placebo.

This is a general schematic of the study design. Dose levels may be repeated. Each new dose level will be initiated after evaluation of preliminary safety, tolerability, and available pharmacokinetic and pharmacodynamic data through Day 5 for Part A or Day 15 for Part B for at least 5 subjects receiving LY3502970 in the preceding dose level.

Part B may be initiated after review of safety, tolerability, and available pharmacokinetic and pharmacodynamic data collected up to Day 5 for Cohort C. Part B may be initiated earlier if approximately 10 to 20 mg/dL glucose-lowering effect is observed at a tolerated dose after reviewing interim data.

Maximum tolerated dose needs to be determined in Part A before exploratory Parts C, D, and E may be initiated.

Figure GZGA.1. Illustration of planned study design for Protocol J2A-MC-GZGA.

5.1.1. Single- and Multiple-Ascending Dose Studies (Parts A and B)

Refer to Sections 5.1.1.1 and 5.1.1.2 for details specific to Part A (SAD) and Part B (MAD), respectively.

Subject eligibility for Parts A and B will be determined at a screening visit. If the investigator decides not to administer the Day 1 dose to a subject or not to enroll a subject on a particular day, the subject may be rescheduled to participate in the same part of the study and any procedures performed up to that point may be repeated.

Safety and tolerability data will be reviewed by the sponsor and investigator before each dose-escalation decision in Parts A and B. Although not mandated, available PK and PD data may also be reviewed. Refer to Section 5.5 for planned doses.

5.1.1.1. Single-Ascending Dose Study in Healthy Subjects (Part A)

Part A will consist of up to 6 escalating single-dose levels of LY3502970 or placebo. Approximately 48 subjects will be randomized into 6 groups (Cohorts A through F). For each cohort it is planned that approximately 8 subjects will be randomly assigned to either LY3502970 (6 subjects) or placebo (2 subjects).

Dose escalations will be based on the evaluation of safety, tolerability, and available PK and PD data through Day 5 from at least 5 subjects receiving LY3502970 in the preceding SAD dose level.

Eligible subjects will be admitted to the CRU on Day -1. On the morning of Day 1, a single oral dose of LY3502970 or placebo will be administered, according to randomization, after an overnight fast (at least 8 hours). The PK, PD, and coproporphyrin biomarker sampling and safety assessments will be performed according to the Schedule of Activities (Section 2.1). The PK or PD sampling schedules may be modified based on the available safety and PK data.

The investigator or qualified designee will review all available inpatient safety data before discharging subjects from the CRU after the morning procedures are completed on Day 4, provided they are deemed medically fit by the investigator. Subjects may be required to remain at the CRU as needed for safety follow-up based on clinical judgment of the investigator, or to improve study procedure compliance, e.g., scheduling and transport reasons.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

5.1.1.2. Multiple-Ascending Dose Study in Healthy Subjects (Part B)

The MAD portion of the study may be initiated, at the earliest, after review of safety, tolerability, and available PK and PD data collected up to Day 5 for Cohort C in Part A (refer to Section 10.3.7). Part B may be initiated earlier if data from Part A indicates an approximately 10 to 20 mg/dL glucose-lowering effect at a tolerated dose.

Part B will consist of up to 5 escalating multiple-dose levels of LY3502970 or placebo. Approximately 60 subjects will be randomized into 5 groups (Cohorts G through K). For each cohort, it is planned that approximately 12 subjects will be randomly assigned to LY3502970

(9 subjects) or placebo (3 subjects). In Cohort J, subjects will be administered atorvastatin and midazolam on Days -2 and 27. In Cohort K, subjects will be administered simvastatin on Days -2 and 27. Cohorts J and K may be initiated after Cohort G (does not have to follow completion of Cohorts G through I).

The dose levels in Part B will be determined on the basis of safety, tolerability, and available PK and PD data from Part A. A fixed dose may be administered to subjects in Cohort G. In Cohorts H through K, LY3502970 dose regimens may be evaluated via dose titration. Dose escalations will be based on the evaluation of safety, tolerability, and available PK and PD data from at least 5 subjects receiving LY3502970 through Day 15 in the preceding MAD dose level.

Eligible subjects will be admitted to the CRU on Day -2 for Cohorts G through I and on Day -3 for Cohorts J and K. A baseline PK profile will be collected on Day -2 for midazolam and atorvastatin in Cohort J and for simvastatin in Cohort K. A baseline PD profile, including oral glucose tolerance test (OGTT) and gastric emptying, will be collected on Day -1 for all cohorts in Part B. Beginning on the morning of Day 1 through Day 28, subjects will be administered either once daily (QD) or twice daily (BID) oral dose of LY3502970 or placebo, according to randomization. In case of BID dosing, the 2 doses will be separated by approximately 12 hours. On Day 27, midazolam will be coadministered with the morning dose of LY3502970 or placebo and atorvastatin administered 4 hours after midazolam in Cohort J. In Cohort K, simvastatin will be coadministered with the morning dose of LY3502970 or placebo on Day 27. Refer to Section 6.3.1 for pre- and postdose fasting restrictions. The PK, PD, and biomarker sampling and safety assessments will be performed according to the Schedule of Activities (Section 2.2). The PK or PD sampling schedules may be modified based on the available safety and PK data.

Subjects will remain at the CRU for the entire 4-week treatment period. The investigator or qualified designee will review all available inpatient safety data before discharging subjects from the CRU after the morning procedures are completed Day 29, provided they are deemed medically fit by the investigator. Subjects may be required to remain at the CRU as needed for safety follow-up based on clinical judgment of the investigator.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

5.1.2. Exploratory Food Effect Study in Healthy Subjects (Part C)

Part C may be initiated after the MTD is determined in Part A (SAD). Up to 12 subjects may be enrolled into 1 group (Cohort L). Subjects will receive a single oral dose of LY3502970 at a dose no higher than the MTD in Part A or B of the study, in each of 2 treatment periods. The dose will be determined by analysis of available PK, PD and safety data from Part A and Part B. Subject will be randomized to 1 of 2 treatment sequences (Table GZGA.2) comprised of 2 treatment arms:

- Fasted treatment: Dose administered with approximately 240 mL water following an overnight fast of at least 10 hours;

- Food-effect treatment: Dose administered with approximately 240 mL water following a meal consumed after an overnight fast of at least 10 hours.

Table GZGA.2. Treatment Sequences for Food Effect Study (Part C)

Sequence	Period 1	Period 2
1	Fasted	Meal
2	Meal	Fasted

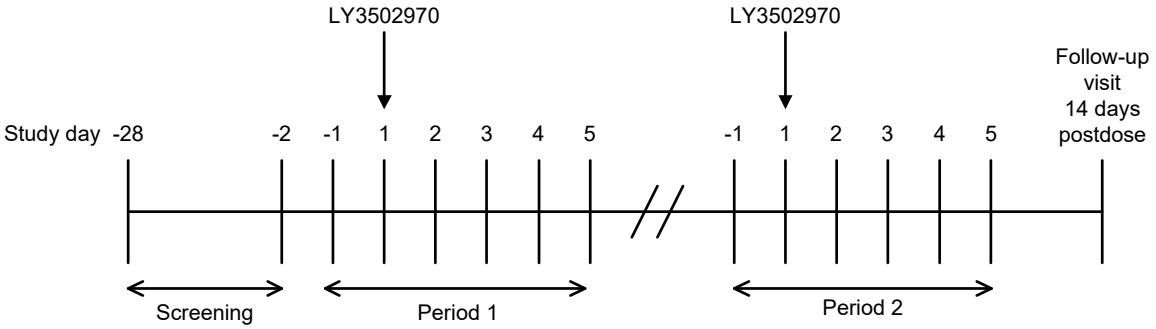
Figure GZGA.2 illustrates the study design for Part C. Subject eligibility will be determined at a screening visit. Eligible subjects will be admitted to the CRU on Day -1 in each period. On the morning of Day 1 in each period, a single oral LY3502970 dose will be administered, according to randomization, in either the fasted state or 30 minutes after the start of a meal. The PK, PD, and coproporphyrin biomarker sampling and safety assessments will be performed according to the Schedule of Activities (Section 2.3). The PK or PD sampling schedules may be modified based on the available safety and PK data.

In each period, subjects will remain in the CRU at least until completion of assessments on Day 4 and return for an outpatient visit on Day 5. Subjects may be required to remain at the CRU as needed for safety follow-up based on clinical judgment of the investigator, or to improve study procedure compliance, e.g., scheduling and transport reasons.

There will be a washout of at least 5 days between doses in Periods 1 and 2.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

Further details on fasting restrictions and meal requirements during each period are in Section 6.3.1.



There will be a washout period of at least 5 days between each dose.
In each period, subjects will remain in the clinical research unit at least until completion of assessments on Day 4 and return for an outpatient visit on Day 5.

Figure GZGA.2. Illustration of study design for Protocol J2A-MC-GZGA exploratory food effect study (Part C).

5.1.3. Exploratory LY3502970 Controlled-release Prototype Study in Healthy Subjects (Part D)

Part D may be initiated after the MTD is determined in Part A (SAD). It is planned that approximately 8 subjects may be enrolled into 1 group (Cohort M) and randomly assigned to LY3502970 controlled-release prototype (6 subjects) or placebo (2 subjects). Subjects will receive a single oral dose of LY3502970 at a dose no higher than the MTD in Part A or B of the study, in the treatment period. The dose will be determined by analysis of available PK, PD, and safety data from Part A and Part B.

Subject eligibility will be determined at a screening visit. Eligible subjects will be admitted to the CRU on Day -1. On the morning of Day 1, a single oral dose will be administered, according to randomization, after an overnight fast (at least 8 hours). The PK, PD, and coproporphyrin biomarker sampling and safety assessments will be performed according to the Schedule of Activities (Section 2.4). The PK or PD sampling schedules may be modified based on the available safety and PK data.

The investigator or qualified designee will review all available inpatient safety data before discharging subjects from the CRU after the morning procedures are completed Day 4, provided they are deemed medically fit by the investigator. Subjects may be required to remain at the CRU as needed for safety follow-up based on clinical judgment of the investigator, or to improve study procedure compliance, e.g., scheduling and transport reasons.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

5.1.4. Formulation Optimization (Part E)

Part E of the study may be initiated, at the earliest, after review of safety, tolerability, and available PK and PD data collected for Cohort K in Part B (refer to Section 10.3.7).

Approximately 20 subjects will be enrolled into Part E of the study to target 18 completers. All the subjects will receive LY3502970 once daily for 28 days. Dose titration will be every 6 days and will reach a maximum dose on Day 19. This dose will be no higher than the maximum dose tolerated in Part B.

At screening, subjects will be administered a Heidelberg pH capsule with approximately 240 mL of room temperature water to permit pH testing of the gastric environment. On the PK sampling days (Days 23 and 28), the Heidelberg pH capsule will be administered at least 30 minutes prior to LY3502970 dosing to allow stabilization. On Day 24, subjects will be randomized into 2 equal groups and assigned 2 different formulations of LY3502970 (see Section 7.1). From Day 24 to Day 28, the subjects will be administered the LY3502970 formulation as per their randomization. Refer to Section 6.3.1 for pre- and postdose fasting restrictions. The PK, PD, biomarker sampling, and safety assessments will be performed according to the Schedule of Activities (Section 2.5). The PK or PD sampling schedules may be modified based on the available safety and PK data.

Subjects will remain at the CRU for the entire 4-week treatment period. On Day 29, the investigator or qualified designee will review all available inpatient safety data before discharging subjects from the CRU after the morning procedures are completed, provided they are deemed medically fit by the investigator. Subjects may be required to remain at the CRU as needed for safety follow-up based on clinical judgment of the investigator.

Subjects will be discharged from the study after the review of all final safety assessments from the follow-up visit is completed by the investigator.

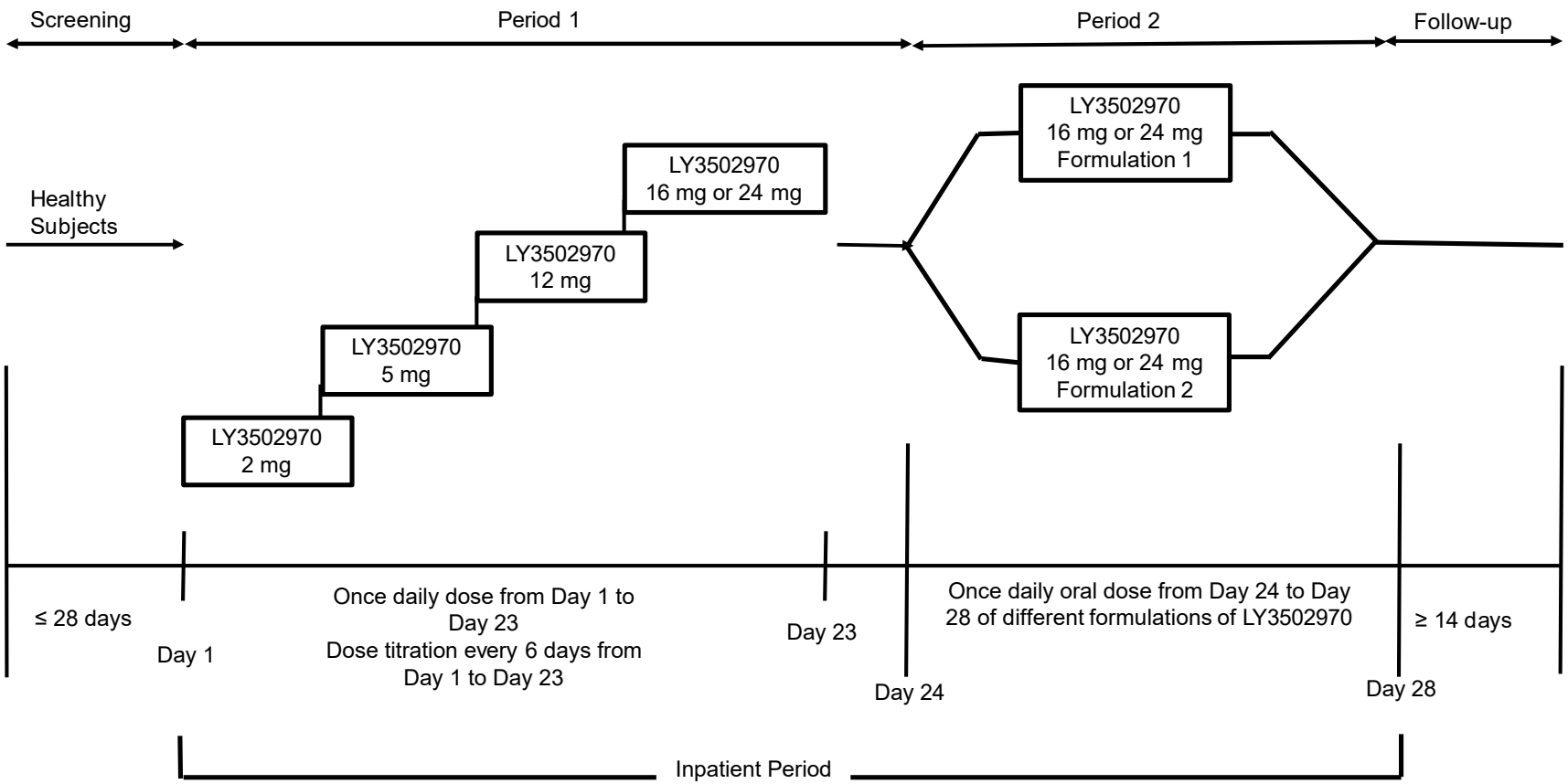


Figure GZGA.3. Illustration of study design for Protocol J2A-MC-GZGA exploratory formulation optimization study (Part E).

5.2. Number of Participants

Approximately 180 healthy subjects may be enrolled so that up to 146 subjects complete the study (48 in Part A, 60 in Part B, 12 in Part C, 8 in Part D, and 18 in Part E).

For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been finished.

In Part B, subjects discontinued from the study prior to Day 16 or receiving the planned third titration dose within a given cohort may be replaced. Subjects who discontinue after Day 16 or receiving the planned third titration dose within a given cohort will not be replaced.

Subjects withdrawn from the study due to safety reasons will not be replaced.

Refer to Section 7.4.1 for scenarios when dosing at the current level and further dose escalation will be discontinued. Refer to Sections 8.1 and 8.2 for circumstances for discontinuing a subject from investigational product and from the study, respectively.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

LY3502970 has not been previously administered to healthy subjects. A population of healthy subjects is selected to assess the safety and tolerability at the initial starting doses in humans, based upon the likelihood of less physiologic variability in the absence of the T2DM disease state, which may affect multiple organ systems, and in the absence of other confounding factors such as concomitant medications.

Safety and tolerability assessments will be made over all dose levels, including the monitoring of AEs (with special interest in incidence of nausea and/or vomiting), vital signs, body temperature, blood glucose levels, safety laboratory tests, liver panel tests, medical assessments, body weight, concomitant medication, triplicate ECGs, and telemetry cardiovascular monitoring (see Section 9.4.5). The decision to dose escalate in Parts A (SAD) and B (MAD) will be based primarily on safety and tolerability data (see Section 7.4.1).

Subjects and investigators are blinded to treatments in Parts A, B, and D to minimize bias during data collection.

Inclusion of placebo arms in Parts A, B, and D will also be used as a comparator to allow interpretation of PD, safety, and tolerability data.

A common obstacle to dose optimization of incretins is gastrointestinal tolerability. Adverse events such as nausea and vomiting are dose limiting, therefore dose titration may prove useful as a potential mitigation for these gastrointestinal effects. In Part B (MAD), LY3502970 multiple-dose regimens may be evaluated by dose titration in order to improve gastrointestinal tolerability and achieve higher exposures.

Although only a modest glucose-lowering effect is expected in healthy subjects due to LY3502970 action on glucose-dependent insulin secretion, a preliminary assessment of the PD effects of LY3502970 will be based on gastric emptying (acetaminophen test; Part B [MAD] only) and insulin response following OGTTs (Parts A, B, and D). The effect of LY3502970 on appetite sensations will be explored in Part B (MAD).

In vitro data indicate that LY3502970 may be an organic anion transporting peptide (OATP)1B1 inhibitor and CYP3A4 enzyme inhibitor. There are clinical study data indicating that coproporphyrins can differentiate between weak and strong OATP inhibitors (Lai et al. 2016); therefore, coproporphyrins 1 and 3 are being explored as potential biomarkers of OATP function. For this reason, plasma concentrations of coproporphyrin 1 and 3 will be measured during Parts A and B. Changes in coproporphyrin 1 and 3 levels may inform decision on the need to conduct a definitive clinical study to assess OATP-mediated drug-drug interactions (DDIs). The impact of LY3502970 on potential DDIs will be studied in Part B by collecting plasma midazolam, atorvastatin, and simvastatin concentrations in the absence and presence of plasma LY3502970 concentrations.

The exploratory food effect study (Part C) will be open-label as the PK endpoint is objective rather than subjective. The crossover design allows each subject to serve as his or her own control, thus reducing variability. A single dose administration for each study period is considered adequate to achieve the study objective. Since LY3502970 is predicted to have a half-life of approximately 12 hours, a washout period of at least 5 days was chosen to reduce the potential for detectable drug concentrations prior to the next dose administration. A standard meal has been selected to reflect the diet of the target population of patients with T2DM.

Part E will investigate the PK profile of 2 different formulations of LY3502970 with different amounts of excipients, after dose titration to a higher dose than could be investigated with single dosing in Part D. Gastric pH at the time of dosing will be assessed to provide additional information on the impact of gastric pH of the excipient.

5.4.1. Rationale for Excluding Sentinel Dosing

While recently published European Medicines Agency guideline (EMA 2017) recommends use of sentinel dosing in first-in-human studies, it also allows for flexibility in a proposed dosing approach based on the available scientific data and preclinical assessment of a given molecule.

Based on the risk assessment of the available data, LY3502970 does not present a high-uncertainty profile as per DeGeorge et al. (2018), which would necessitate inclusion of sentinel dosing approach. Namely, per DeGeorge, the following characteristics of the program would trigger a higher level of concern, none of which is the case with LY3502970:

- Lack of nonclinical pharmacology model in vivo that can reasonably predict intended and exaggerated pharmacologically active and excessive pharmacological responses in relation to measurable drug concentration in vivo and because the target is an endogenous human target, AND
- There are no clinically deployable biomarkers of target engagement/activity, AND

- Animal toxicity models are understood (or expected) to poorly reflect known human toxicity for the target, OR
- The types of toxicity that are known or can be anticipated are severe, likely irreversible, and without adequate prodromal signs.

Nonclinical pharmacology models exist for the prediction of intended and exaggerated pharmacology in conjunction with measurements of drug concentration. This includes nonhuman primates and a transgenic mouse model for human GLP-1 receptor. Based on the known pharmacological effects, clinically deployable biomarkers and assessments are well established for GLP-1RA, including gastrointestinal effects, decreased food consumption, and body weight loss. The nonclinical safety profile of LY3502970, as characterized in animal toxicology studies, reflects the established clinical toxicology of the compound, which consists primarily of exaggerated pharmacology and/or known class effects. The types of toxicities that are anticipated are mild, gradual in onset, transient, reversible and monitorable including potential off-target effects of low toxicologic impact in the hepatobiliary system that are also reversible and monitorable. In addition, local lymph node assays showed no skin sensitization potential of LY3502970. Furthermore, sentinel dosing with low-risk compounds, such as LY3502970, may lead to inability to interpret data due to false positive AE findings in the absence of data from all cohorts or placebo-treated subjects.

5.5. Justification for Dose

The planned total daily doses in this study (0.3 mg to 100 mg) have been selected to provide a full evaluation of the safety and tolerability of LY3502970, from a starting dose expected to have minimal to no pharmacological response up to doses 2- to 16-fold higher than the expected therapeutic dose range (6 to 50 mg once daily) projected based on preclinical pharmacological models. The planned LY3502970 doses also allow characterization of PK and preliminary assessment of PD effects in healthy subjects over a wide dose and exposure range, which will support dose selection for future clinical trials.

As described in Section 3.3, the LY3502970 nonclinical safety profile differs in a fundamental way between monkeys and rats based on on-target versus off-target activity, respectively. The findings in monkeys were based on exaggerated pharmacology or well-characterized class effects. Due to the exaggerated pharmacology, consisting of emesis, decreased food consumption, and body weight loss, dose levels in monkeys in toxicology studies were low and only provide small exposure multiples to human dose and exposure projections. As such, monkeys were considered the most sensitive species. In addition to the exaggerated pharmacology effects, the effects that define the NOAEL in monkeys consisted of effects on the cardiovascular system (increased PR interval), which were small in magnitude, isolated, well-tolerated, monitorable, reversible, and reflect a known GLP-1RA class effect of low toxicologic impact. Even though GLP-1RAs are known to minimally increase heart rate (2 to 4 beats per minute) or PR interval (2 to 3 milliseconds), as well as episodes of sinus tachycardia or first-degree atrioventricular block in humans, this class of drugs has actually proven to ultimately reduce major cardiovascular events in cardiovascular outcomes studies.

Rats represent a non-pharmacologically relevant species and do not display the dose-limiting gastrointestinal and subsequent body weight effects seen in monkeys. As a result, tolerability in rats is greater than monkeys and doses in the rat toxicology studies were higher (up to 74-fold higher) and provide an opportunity to assess off-target toxicity with LY3502970. The effects observed in rats were limited to small increases in serum bilirubin and bile acids without changes in associated toxicologically important biomarkers of hepatobiliary injury or liver pathology. These changes in bilirubin and bile acids are thought to be related to documented inhibition of liver transporters. These small changes, although used to define the NOAEL, did not represent toxicologically meaningful effects in the rats and while these changes inform the risk profile of LY3502970, if they occur in humans, are monitorable and reversible upon treatment cessation.

Based on projected human PK and PK/PD modeling of nonclinical data from monkey and humanized GLP-1 receptor mouse models, a starting dose of 0.3 mg may provide detectable LY3502970 exposure levels that are expected to demonstrate minimal to no pharmacological response in healthy subjects in Part A (SAD). This proposed starting dose is approximately 30-fold lower than the human equivalent doses based on the NOAEL doses in both rats and monkeys (Table GZGA.3). The proposed starting dose of 0.3 mg is approximately 3-fold lower than the maximum recommended clinical starting dose, which is calculated based on human equivalent dose multiple compared to the NOAEL in monkeys with a 10-fold safety factor (maximum recommended clinical starting dose = 0.87 mg). According to allometry-based projected human exposure, the area under the concentration versus time curve (AUC) exposure at the starting dose of 0.3 mg is expected to have >9-fold and >54-fold lower exposure multiple compared to the NOAEL AUC exposures from the monkey and rat repeat-dose studies, respectively (Table GZGA.3). Furthermore, the starting dose of 0.3 mg is predicted to achieve a C_{max} of approximately 45-fold and 93-fold lower exposure multiple compared to the NOAEL maximum observed concentration (C_{max}) from the monkey and rat repeat-dose studies, respectively (Table GZGA.3).

Table GZGA.3. Margin of Safety Based on Dose Multiples and Predicted Exposure Multiples for Oral Administration of LY3502970 Based on Administered Dose and Predicted Human Exposure to NOAELs in Rats and Monkeys

Species Dose level	Human Dose or HED (mg/m^2)	HED-based Dose Multiple MOS	AUC ($\mu g \cdot hr/mL$)	AUC Exposure Multiple MOS [d]	C_{max} ($\mu g/mL$)	C_{max} Exposure Multiple MOS [e]
Planned Human Starting Dose[a]						
0.3 mg (0.005mg/kg)	0.185		0.012 - 0.043		0.001 - 0.002	
Rat						
1.0 mg/kg NOAEL[b]	6	32×	2.34	195× - 54×	0.238	230× - 119×
Monkey						
0.45 mg/kg NOAEL[c]	5.4	29×	0.379	32× - 9×	0.076	76× - 38×

Planned Human Maximum Dose[a] 100 mg (1.67 mg/kg)	61.8		3.85 - 14		0.385 - 0.664	
Rat 1 mg/kg NOAEL[b]	6	0.1×	2.34	0.6× - 0.17×	0.238	0.6× - 0.36×
Monkey 0.45 mg/kg NOAEL[c]	5.4	0.1×	0.379	0.1× - 0.03×	0.076	0.2× - 0.11×

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; HED = human equivalent dose after body surface area conversion; MOS = margin of safety; NOAEL = no-observed-adverse-effect level.

[a] Assume human body weight = 60 kg for dose multiple. Assume human body weight = 70 kg for predicted human exposure. The human exposure AUC and C_{max} are presented as the range covering the prediction based on allometric/mechanistic scaled pharmacokinetic parameters from monkey and rat, respectively.

[b] Rat 28-day toxicology study TOX17-0065.

[c] Monkey 28-day toxicology study TOX17-0074.

[d] Projected AUC multiples to the range of projected human efficacious exposures.

[e] Projected C_{max} multiple to the range of projected human efficacious exposures.

The overall safety profile of LY3502970 can be assessed with respect to both the NOAELs and the highest dose levels administered to animals. The dose multiples and projected exposure multiples for oral doses of LY3502970 are presented in Table GZGA.3 compared to the NOAELs, and in Table GZGA.4 compared to the highest doses administered in animal studies. The NOAELs are acknowledged from the toxicology studies in rats and monkeys; however, as stated above the changes that define the adverse effect levels in the animals, including up to the highest dose given in both species, were low magnitude, rare or isolated, and not associated with detectable pathologic effects and were therefore considered of low risk to human subjects.

In Part A (SAD), the planned dose range is 0.3 mg to 100 mg. Dose levels are planned to increase in semilog intervals, but smaller intervals may be used (refer to Section 7.4.1). The higher dose levels in the proposed clinical dose scheme are anticipated to exceed the human equivalent dose (HED) levels for the NOAEL in both nonclinical species (Table GZGA.3; HED-based dose multiples for planned human maximum dose compared to the animal NOAEL dose is <1-fold). Dose levels ≥10 mg in this scheme exceed the HED for the NOAEL in rats and monkeys; however, dose levels ≥30 mg exceed the HED for the highest dose given to monkeys, but not rats. In the rat, the highest doses administered provide dose and exposure multiples to the highest clinical dose that are 22-fold and 7-fold respectively (Table GZGA.4). At these doses the effects in rats are limited to clinical chemistry and hematologic effects that will be monitored in the clinic. In the monkey, pharmacologically mediated effects on body weight and food consumption limited the ability to study higher dose levels. As such, the dose multiples and exposure multiples to the projected human high dose are <1-fold in the monkey (Table GZGA.4). As described previously, the cardiovascular effect, which was considered adverse in the monkey study, will be monitored carefully in the clinical program as will the clinical chemistry and hematologic effects observed in monkeys. Because the monkey data do not provide nonclinical safety data for the highest proposed clinical dose, the decision to proceed

to this dose will be based on the nature of the toxicology profile in the rat and careful review of the clinical safety and exposure data in the lower dose level cohorts.

Table GZGA.4. Dose Multiples and Predicted Exposure Multiples for Oral Administration of LY3502970 Based on Administered Dose and Predicted Human Exposure to Highest Doses in Rats and Monkeys

Species Dose level	Human Dose or HED (mg/m^2)	HED-based Dose Multiple MOS	AUC (µg·hr/mL)	AUC Exposure Multiple MOS[d]	C_{max} (µg/mL)	C_{max} Exposure Multiple MOS [e]
Planned Human Starting Dose[a]						
0.3 mg (0.005 mg/kg)	0.185		0.012 - 0.043		0.001 - 0.002	
Rat						
200 mg/kg[b]	1200	6486×	93.6	7800× - 2177×	6.26	6260× - 3130×
Monkey						
1.35 mg/kg[c]	16.2	87×	1.25	104× - 29×	0.22	220× - 110×
Planned Human Maximum Dose[a]						
100 mg (1.67 mg/kg)	61.8		3.85 - 14		0.385 - 0.664	
Rat						
200 mg/kg[b]	1200	22×	93.6	24× - 6.7×	6.26	16× - 9.4×
Monkey						
1.35 mg/kg[c]	16.2	0.3×	1.25	0.32× - 0.09×	0.22	0.6× - 0.33×

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum observed concentration; HED = human equivalent dose after body surface area conversion; MOS = margin of safety.

[a] Assume human body weight = 60 kg for dose multiple. Assume human body weight = 70 kg for predicted human exposure. The human exposure AUC and C_{max} are presented as the range covering the prediction based on allometric/mechanistic scaled pharmacokinetic parameters from monkey and rat, respectively.

[b] Rat 28-day toxicology study TOX17-0065.

[c] Monkey 28-day toxicology study TOX17-0074.

[d] Projected AUC multiples the range of projected human efficacious exposures.

[e] Projected C_{max} multiples to the range of projected human efficacious exposures.

The clinical dose range to be studied in Part B (MAD) will be selected based on safety, tolerability, PK, and PD data from Part A (SAD). The starting dose planned for Part B will be selected based on the MTD and glucose-lowering (PD) effect after single doses in Part A. The first MAD dose may initiate earlier if a dose to achieve an average glucose lowering of approximately 10 to 20 mg/dL during the OGTT is identified after reviewing the PK/PD response with interim analysis of the first 3 or more dose levels (refer to Section 10.3.8). The maximum planned total daily dose, 100 mg, is the same as the planned highest dose in Part A (SAD) in order to explore doses above the efficacious dose range. This planned maximum dose in Part B (MAD) may be revised based on SAD data or by achieving an MTD after repeated dosing in the MAD.

A duration of 4 weeks for Part B (MAD) allows for the evaluation of safety, tolerability, PK, and PD effects of LY3502970. Furthermore, it provides an opportunity to assess dose up-titration to higher exposures if needed to manage the gastrointestinal side effects and improved tolerability observed with other GLP-1RAs. This MAD study design is supported by available toxicology data.

In both Parts A and B, doses may be adjusted before each dose escalation based on safety, tolerability, and available PK and PD data.

6. Study Population

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

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

Screening may occur up to 28 days prior to enrollment. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. Part E subjects who are unable to swallow the Heidelberg pH capsule will be considered as screening failures.

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

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

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

[1a] male subjects:

- men, regardless of their fertility status, with non-pregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for 3 months following the last dose of investigational product (i.e., until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus)
    - men and their partners may choose to use a double-barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted however that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.)
    - periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the

duration of a trial, and withdrawal are not acceptable methods of contraception

- men with pregnant partners should use condoms during intercourse for the duration of the study and for 3 months following the last dose of investigational product (i.e., until the end of estimated relevant potential exposure in women of childbearing potential)
- men should refrain from sperm donation for the duration of the study and for 3 months following the last dose of investigational product (i.e., until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus)
- men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception

[1b] female subjects:

- women not of childbearing potential may participate and include those who are:
  - A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
  - B. postmenopausal – defined as either
    - i. a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
      - a. cessation of menses for at least 1 year, or
      - b. at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
    - ii. a woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
    - iii. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

[2] are between the ages of 18 and 65 years, inclusive, at screening

[3] have a body mass index of 20 to 40 kg/m^2, inclusive

[4] have hemoglobin A1c level of <6.5% at screening

[5] have safety laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

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

[7] are reliable, willing to make themselves available for the duration of the study, willing to follow study procedures (including swallowing the Heidelberg pH capsule in Part E), and willing to remain in the CRU for approximately 4 weeks (Parts B and E)

[8] are able and willing to give signed informed consent approved by Lilly and the ethical review board (ERB) governing the CRU

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

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

[10] are Lilly employees

[11] are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[12] have participated, within 30 days of screening, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

[13] have previously completed or withdrawn from this study

[14] have known allergies to LY3502970, GLP-1 analogs, related compounds or any components of the formulation, acetaminophen (Part B), or history of significant atopy

[15] have an abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG (QT) data analysis, such as a corrected QT interval using Fridericia's formula (QTcF) >450 msec, PR 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 (Note: the QTcF and PR criteria are applicable at screening only)

[16] have an abnormal blood pressure and/or pulse rate as determined by the investigator

[17] have a significant history of or current cardiovascular (eg, myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism), respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data

[18] have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase or lipase (>1.5-fold the upper limit of normal [ULN]) or gastrointestinal disorder (eg, relevant esophageal reflux or gall bladder disease) or any gastrointestinal disease which impacts gastric emptying (e.g., gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs or dipeptidyl peptidase-IV inhibitors

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

[20] have a serum calcitonin level of:

(a) ≥20 ng/L at Visit 1, if estimated glomerular filtration rate ≥60 mL/min/1.73m^2

(b) ≥35 ng/L at Visit 1, if estimated glomerular filtration rate <60 mL/min/1.73m^2

[21] have a history of malignancy within 5 years prior to screening

[22] have a history of a chronic liver disease, such as, but not limited, to Chronic Hepatitis or Gilbert's syndrome

[23] have serum triglyceride ≥5 mmol/L (442.5 mg/dL) at screening

[24] have evidence of significant psychiatric disorder(s) as determined by the investigator

[25] show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies

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

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

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

[29] are women of childbearing potential

[30] are women who are lactating

[31] have been treated with prescription drugs that promote weight loss (eg, Saxenda® [liraglutide], Meridia® [sibutramine], Sanorex® [mazindol], Adipex-P® [phentermine], BELVIQ® [lorcaserin], Mysimba® [naltrexone/bupropion]), similar other body weight loss medications including over-the-counter medications (eg, Alli®), oral antidiabetic drugs used off-label for weight management, any appetite suppressant (eg, food or supplements), or any other method that stops feeling hungry within 3 months prior to screening

[32] intend to use over-the-counter or prescription medication 7 and 14 days before planned dosing, respectively, apart from occasional intake of vitamin/mineral supplements, allowable antiemetics, and acetaminophen 14 days before the first dose. Refer to Section 7.7 for additional concomitant therapy restrictions regarding acetaminophen. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the investigator (refer to Section 7.7). The following medications are excluded, except atorvastatin, midazolam, and simvastatin when coadministered with LY3502970 in Part B of the study:

- drugs that reduce gastrointestinal motility including, but not limited to, anticholinergics, antispasmodics, 5-hydroxytryptamine-3 receptor antagonists, dopamine antagonists, and opiates
- lipid-lowering drugs, such as statins (eg, atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin)

[33] have donated blood of more than 450 mL or more in the last 3 months or any blood donation within the last month from screening and check-in on Day -1 (Parts A, C, and D) or Day -2 (Part B)

[34] regularly use known drugs of abuse and/or show positive findings on drug screening

[35] have a history of alcohol abuse

[36] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (females up to 65), or are unwilling to stop alcohol consumption 24 hours prior to dosing until discharge from the CRU (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)

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

[38] use of any drugs or substances that are known strong inducers or inhibitors of cytochrome P450 (CYP)3A is specifically excluded within 14 days prior to the first administration of study drug and during the study.

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

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Parts A (SAD) and D (controlled-release): Standard meals will be provided as appropriate in the CRU. Subjects will be required to fast overnight for at least 8 hours before taking an oral dose of study drug and for each study day when clinical safety laboratory and PD samples are taken and OGTTs are administered. Subjects will be administered study drug with approximately 240 mL of room temperature water. No food will be allowed for at least 4 hours postdose. Fluids will be restricted from 1 hour prior to and until 1 hour after dosing, except for the water required for dose administration. Water may be consumed freely at all other times.

Part B (MAD): Standard meals will be provided as appropriate in the CRU. Subjects will be required to fast overnight for at least 8 hours before:

- OGTTs are administered;
- Taking an oral dose of study drug (LY3502970, midazolam, atorvastatin, or simvastatin) that is followed by PK and PD sample collections;
- Collection of safety laboratory, liver panel, lipid panel, and nonpharmacogenetic samples.

No food will be allowed for at least 4 hours post LY3502970 morning dose on days when OGTTs are administered or when dosing is followed by PK and PD sample collections. In Cohorts J and K, subjects should avoid food for at least 2 hours after a dose of atorvastatin or simvastatin. Subjects will be administered study drug (LY3502970) with approximately 240 mL of room temperature water. Fluids will be restricted from 1 hour prior to and until 1 hour after LY3502970 dosing, except for the water required for dose administration. Midazolam will be diluted in 50 to 100 mL of water. Subjects will be encouraged to drink the midazolam solution completely in ≤2 minutes, followed by approximately 50 to 100 mL of water to rinse the cup/glass. The rinse should be consumed in ≤10 minutes. Water may be consumed freely at all other times.

On all other days, study drug may be administered without regard to food and water.

Part C (food effect): Standard meals will be provided as appropriate in the CRU.

Fasted treatment: Following an overnight fast of at least 10 hours, subjects will be administered study drug with approximately 240 mL of room temperature water. No food will be allowed for at least 4 hours postdose. Fluids will be restricted from 1 hour prior to and until 1 hour after dosing, except for the water required for dose administration.

Food-effect treatment: Following an overnight fast of at least 10 hours, subjects will start a standardized meal 30 minutes prior to administration of the study drug. Subjects will consume this entire meal in 30 minutes or less; however, the study drug will be administered 30 minutes after the start of the meal. The study drug should be administered with approximately 240 mL of

room temperature water. No further food will be allowed for at least 4 hours postdose. Fluids will be restricted from 1 hour prior to and until 1 hour after dosing, except for fluid provided with the meal and water required for dose administration.

The total caloric content will be approximately 500 calories. The macronutrient composition of the meals should be targeted to provide approximately 50% of the calories from carbohydrate, 30% of the calories from fat, and 20% of the calories from protein.

Part E (formulation optimization): Standard meals will be provided as appropriate in the CRU. Subjects will be required to fast overnight for at least 8 hours before:

- OGTTs are administered;
- Taking an oral dose of LY3502970 that is followed by PK and PD sample collections;
- Collection of safety laboratory, liver panel, lipid panel, and nonpharmacogenetic samples.

No food will be allowed for at least 4 hours after LY3502970 dose on days when OGTTs are administered or when dosing is followed by PK and PD sample collections. Subjects will be administered LY3502970 with approximately 240 mL of room temperature water. Fluids will be restricted from 1 hour prior to and until 1 hour after LY3502970 dosing, except for the water required for dose administration and Heidelberg pH capsule administration. Water may be consumed freely at all other times.

On all other days, study drug may be administered without regard to food and water.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects will be allowed to maintain their regular caffeine consumption throughout the study period.

No alcohol will be allowed at least 24 hours before each CRU admission and each outpatient visit and throughout the duration of each CRU visit. Between CRU visits, daily alcohol should not exceed 3 units for males and 2 units for females (a unit is defined in Exclusion Criterion [36], Section 6.2).

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

6.3.3. Activity

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

6.4. Screen Failures

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

Individuals who meet the criteria for enrollment in Part A (SAD), but are unable to enroll due to non-medical reasons (eg, scheduling conflicts), may be re-screened up to 2 times and enrolled in Parts B, C, D, or E. The interval between re-screenings should be at least 2 weeks. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Subjects that are unable to swallow the capsule would be recorded as screening failures.

7. Treatment

7.1. Treatment Administered

LY3502970 or placebo will be administered orally with room temperature water of each dosing day in a sitting position. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Refer to Section 6.3.1 for water volumes for dose administration and fasting requirements around dosing.

Table GZGA.5. Treatments Administered

Treatment Name	LY3502970	LY3502970 Controlled-release	Placebo	Atorvastatin	Midazolam	Simvastatin
Dosage Formulation	Capsule	Capsule	Capsule	Tablet	Syrup	Tablet
Unit Dose Strength(s)/ Dosage Level(s)	Extemporaneous preparation 0.3 mg to 100 mg	Extemporaneous preparation Dose to be determined	Matching placebo	40 mg	200 µg	20 mg
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling

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

LY3502970 will be supplied as a spray-dried solid dispersion consisting of 30% LY3502970/70% polyvinylpyrrolidone-vinyl acetate and will be combined with sodium bicarbonate for extemporaneous preparation at the CRU for Part A, B, and C. Part E will evaluate the LY3502970 solid dispersion combined with sodium bicarbonate or magnesium hydroxide. For Part D, the LY3502970 solid dispersion filled directly into capsule shells with no other excipients to be evaluated as a controlled-release prototype.

Instructions for extemporaneous preparation of the study drug will be provided by the sponsor.

Matching placebo for the LY3502970 capsules will be sourced centrally. Midazolam, atorvastatin, and simvastatin will be sourced locally by the site.

The proposed range of capsule strengths to be prepared is listed in Table GZGA.5.

For any specific cohort/dosing period, the total number of capsules administered will be the same for all subjects, regardless of whether assigned to placebo or LY3502970. However, the number of capsules may vary between dosing periods and cohorts.

7.2. Method of Treatment Assignment

The randomization tables for Parts A, B, C, D, and E will be prepared by the statistician for the study and provided to the CRU pharmacists or pharmacy staff involved in dose preparation. The allocation and dispensing of the study drug will be fully documented and verified by a second person. Detailed records of the amounts of the study drug received, dispensed, and remaining at the end of the study will be maintained by the CRU pharmacist.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day for multiple doses. The actual time of all dose administrations will be recorded in the subject's case report form (CRF).

7.3. Blinding

For Parts A, B, and D, the dosing for LY3502970 and placebo will be subject- and investigator-blind; Part C will be open-label; Part E will be subject and investigator blind. To preserve the blinding of the study, all study site personnel, except pharmacy staff who prepare and dispense study medication, will be blinded to treatment allocation.

Blinding will be maintained throughout the conduct of the trial until all data are cleaned to an acceptable level of quality and locked.

The site pharmacist who prepares and dispenses study medication will receive a randomization table with treatment codes to enable preparation of blinded placebo doses. The pharmacist will assign treatment.

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

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The

subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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

7.4. Dose Modification

Dose levels or increments, sampling schedule, and length of CRU stay may be adjusted in view of emerging safety, tolerability, PK, or PD data during the study. Dose increments may be reduced (but not increased), a dose level may be repeated, or a lower dose may be administered. Doses in Part B may be given QD or BID. Dose escalations will not exceed a half-log (approximately 3-fold) increase in dose. The timing of the sampling may be adjusted, but the number of samples will not increase. The duration of the CRU stay or the duration of safety follow-up may be increased (for example, if the half-life of LY3502970 is longer than anticipated) but not decreased. These changes must be appropriately documented and communicated by the sponsor to the investigator. Because these adjustments to timings or dose levels are allowable changes permitted by the protocol, they would not require a protocol amendment.

7.4.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is determined or stopping criteria have been met. The highest dose level that is tolerated will be designated as the MTD.

Safety and tolerability data will be the primary criteria for the dose escalation. In addition, if available at the time of dose-escalation decision, PK or PD results will be used as supporting data for dose escalation, but such data are not required. No dose escalation can occur without prior discussion and agreement between the investigator and sponsor.

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

After review of these data (see Section 10.3.7), escalation to the next dose level will be made by the investigator and sponsor. The magnitude of the dose escalation may be reduced (as low as 2-fold from the previous dose) following data review, but subsequent escalations cannot be increased by more than approximately 3-fold (a half-log increment) or dose levels may be repeated.

Based on tolerability and PK data, a dose-titration regimen (QD or BID dosing) may be evaluated in Part B.

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

1) One treatment-related SAE (unless due to anticipated pharmacology of LY3502970).
2) Two or more clinically significant events (CSE), defined as moderate to severe symptoms, clinical signs, and clinical laboratory findings that could cause harm to health and would preclude further dosing of a patient/subject who experiences this effect. CSEs will be determined by the investigator or suitable designee and may include findings that do not fulfill the criteria for SAEs.
3) ≥40% of subjects in a dose level experience a symptomatic hypoglycemic episode with blood glucose 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 LY3502970 administration.
4) Two or more subjects on active drug develop persistent (>1 week) symptoms suggestive of acute pancreatitis. Refer to algorithm for the monitoring of pancreatic events in Appendix 5.

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

Dosing may continue, if deemed appropriate by the investigator, at doses lower than those resulting in termination of the escalation.

7.5. Preparation/Handling/Storage/Accountability

Refer to Section 7.1.1 for extemporaneous preparation.

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

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product 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.

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

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Refer to exclusion criteria in Section 6.2 for excluded medications and treatments.

In general, concomitant medication should be avoided; however, acetaminophen (1 g, maximum of 2 g in 24 hours) may be administered at the discretion of the investigator for treatment of headaches, etc. No start of new concomitant therapy apart from occasional intake of vitamin/mineral supplements, allowable antiemetics, and acetaminophen, will be permitted for over-the-counter or prescription medication 7 and 14 days, respectively, before the first dose of LY3502970 through the final post study follow-up visit.

In the case of mild intercurrent illness during the study, concomitant treatment with acetaminophen may be allowed at the discretion of the investigator. This will be recorded in the CRF. **However, concomitant treatment with acetaminophen should not be allowed after midnight prior to the gastric-emptying test and throughout the day of the gastric-emptying test.**

Because LY3502970 may be associated with nausea and vomiting, symptomatic care (eg, antiemetic drugs [except 5-hydroxytryptamine 3 antagonists] and antacids) can be used as per usual standard of care, but should be avoided if possible.

Signs and symptoms of dehydration should be evaluated and, if present, appropriately managed.

Similarly, antidiarrheal agents are allowed to be prescribed if the subject reports an AE of diarrhea.

Drugs that are known strong inducers or inhibitors of CYP3A are specifically excluded.

If the need for concomitant medication (other than acetaminophen; i.e., nonsteroidal anti-inflammatory drugs) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly CP or CRP. Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

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

Refer to Section 9.4.6.1 and Appendix 4 for the monitoring of hepatic safety.

In addition, discontinuation of the investigational product for abnormal pancreatic tests **should be considered** by the investigator when a subject meets the following condition:

- lipase and/or amylase are confirmed to be ≥3× ULN. Please refer to algorithm for the monitoring of pancreatic events in Appendix 5.

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP/CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP/CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- 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
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study
    - if the subject, 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
- Subject Decision
    - the subject, or legal representative, requests to be withdrawn from the study

8.3. Subjects Lost to Follow-up

A subject 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 subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

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

Appendix 6 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the subject to discontinue the investigational product before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

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

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

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

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF.

9.2.1. Serious Adverse Events

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

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

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

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

Although all AEs are recorded in the CRF after signing informed consent, SAE reporting to the sponsor begins after the subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the subject summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

Subjects should 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.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3502970 is considered any dose higher than the dose assigned through randomization. Treatment for overdose is supportive care.

Refer to the IB for LY3502970.

9.4. Safety

9.4.1. Laboratory Tests

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

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

9.4.2. Physical Examination

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

9.4.3. Vital Signs

For each subject, vital signs measurements should be conducted according to the Schedule of Activities (Section 2). Additional vital signs may be measured during each study period if warranted.

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

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, subjects should be supine

for approximately 5 minutes and stand for at least 3 minutes. If the subject feels unable to stand, supine vital signs only will be recorded.

Body temperature will be measured, as specified in the Schedule of Activities (Section 2), and as clinically indicated.

9.4.4. Body Weight

Weight will be measured as indicated in the Schedule of Activities (Section 2). Subjects will be weighed in light clothing at approximately the same time in the morning before dosing and after an overnight fast and evacuation of bowel and the bladder, if possible. During the treatment period, weight will be measured twice on each scheduled occasion, with the subject stepping off the scale between measurements. Both 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.

9.4.5. Electrocardiograms

This study includes single ECGs, triplicate ECGs, and telemetry collected according to the Schedule of Activities (Section 2).

Electrocardiograms must be recorded before collecting any vital signs or blood samples. Any ECGs coinciding with meal times should be collected prior to eating. Subjects 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.

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

Single and Triplicate ECGs

For each subject, single 12-lead digital ECGs will be collected at screening and follow-up and/or early discontinuation. All single ECGs recorded should be stored at the investigational site.

At time points indicated in the Schedule of Activities (Section 2), consecutive replicate 12-lead digital ECGs will be collected in triplicates at approximately 1 minute intervals.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (eg, palpitations, near syncope, syncope) to determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed

and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point. Any new clinically relevant finding should be reported as an AE.

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

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

Telemetry

Telemetry will be monitored in Part A (SAD) and, based on telemetry results from Part A, may be considered in Part B.

For each subject, local ECG telemetry will be performed according to the Schedule of Activities (Section 2). Local telemetry is for safety monitoring purposes and will be monitored by the clinical staff. The telemetry system has standard alarms to alert the clinical staff to any detected abnormalities, for example, cardiac arrhythmias and prolongation of QT interval, during which additional 12-lead ECGs may be obtained at the investigator's discretion. Electrocardiograms may also be performed in the event of technical or logistical impediments to the use of telemetry.

9.4.6. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes including ALT, AST, TBL, amylase, and lipase
- adverse events, including AEs of special interest (nausea, vomiting, and diarrhea) and reported and adjudicated pancreatitis

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

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

9.4.6.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP,

TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

- elevation of serum ALT to ≥3× ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.4.6.2. Pancreatic Safety

Further diagnostic assessments will be recommended whenever lipase and/or amylase are confirmed to be ≥3× ULN at any visit post treatment sequence allocation even if the subject is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Appendix 5) and, if pancreatitis is suspected, the case will be further defined during an adjudication process. Any subject who develops symptoms of pancreatitis must not receive further administration of LY3502970.

9.4.7. Glucose Monitoring

Blood glucose will be monitored for safety according to Schedule of Activities (point of care safety glucose samples; Section 2).

9.4.7.1. Hypoglycemia Reporting

The subject's blood glucose concentrations for safety assessment will be monitored during the inpatient part of the study, using a validated method (eg, glucose analyzer) available at the site.

Investigator review of glucose results clinically indicative of hypoglycemia is required. Hypoglycemic events (PG ≤70 mg/dL [3.9 mM] or blood glucose ≤63 mg/dL [3.5 mM]) should be appropriately recorded in the CRF. The following hypoglycemia definition should be applied for reporting in the CRF and evaluating hypoglycemic events:

- **Documented Glucose Alert Level (Level 1), PG ≤70 mg/dL (3.9 mmol/L):**
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (3.9 mmol/L)
  - **Unspecified hypoglycemia:** an event during which PG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycemia

- **Documented Clinically Significant Hypoglycemia (Level 2) PG <54 mg/dL (3.0 mmol/L):**
  - **Symptomatic hypoglycemia:** an event during which typical symptoms of hypoglycemia are accompanied by PG <54 mg/dL (3.0 mmol/L)
  - **Asymptomatic hypoglycemia:** an event not accompanied by typical symptoms of hypoglycemia but with PG <54 mg/dL (3.0 mmol/L)
  - **Unspecified hypoglycemia:** an event during which PG <54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded
- **Severe hypoglycemia (Level 3):** an event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the subject has an altered mental status and cannot assist in his/her care, is semiconscious or unconscious, or experienced coma with or without seizures, and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (≤70 mg/dL [3.9 mmol/L]).
- **Severe hypoglycemia requiring medical attention:** a severe hypoglycemic event when subjects require therapy by health care providers (emergency medical technicians, emergency room personnel, etc.).

Other Hypoglycemia:

- **Nocturnal hypoglycemia:** any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking.
- **Relative hypoglycemia:** an event during which typical symptoms of hypoglycemia, which do not require the assistance of another person, are accompanied by PG >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold.
- **Overall (or total) hypoglycemia:** this optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is counted only once in this category.
- **Probable symptomatic hypoglycemia:** an event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by PG ≤70 mg/dL (3.9 mmol/L).

9.4.8. Nausea, Vomiting, and Diarrhea

Nausea, vomiting, and diarrhea events are considered AEs of special interest and will be recorded as AEs in the CRF. For each event assessment of severity, duration and investigator's opinion of relatedness to study drug and protocol procedure will be captured.

9.4.9. Gastric pH Evaluations

At the time points specified in the Study Schedule (Section 2.5), subjects will be administered a Heidelberg pH capsule with approximately 240 mL of room temperature water to permit pH testing of the gastric environment. This will occur before LY3502970 dosing. On the PK sampling days (Days 23 and 28), the Heidelberg pH capsule will be administered at least 30 minutes prior to dosing to allow stabilization. The pH will be measured from 30 minutes prior to dosing until 1 hour after dosing.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of LY3502970, midazolam, atorvastatin, simvastatin, and relevant midazolam, atorvastatin, and simvastatin metabolites. A maximum of 3 samples for LY3502970 concentrations may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

In Part A, urine samples will be collected at the times specified in the Schedule of Activities (Section 2) for the characterization of renal clearance. Total urine output for the appropriate period post investigational product administration will be collected, pooled, and refrigerated. At the end of the collection period, the total urine volume will be recorded. Urine samples will be used to determine the amount of LY3502970 and creatinine excreted during each collection interval.

At the visits and times specified in the Schedule of Activities, venous blood samples will be collected to determine serum creatinine measurements.

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

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

9.5.1. Bioanalysis

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

Concentrations of LY3502970, midazolam, atorvastatin, simvastatin, acetaminophen, coproporphyrin 1, coproporphyrin 3, and any relevant metabolites will be assayed using a validated liquid chromatography tandem mass spectrometry method. Analyses of samples collected for LY3502970 concentrations from placebo-treated subjects are not planned. It is planned that samples collected from both LY3502970- and placebo-treated subjects will be analyzed for midazolam, atorvastatin, simvastatin, coproporphyrin 1, and coproporphyrin 3 and any relevant metabolites.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time,

samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein-binding work.

9.6. Pharmacodynamics

Preliminary assessment of LY3502970 PD will be evaluated based on:

- fasting glucose,
- fasting insulin,
- glucose and insulin during the OGTT,
- body weight (see Section 9.4.4),
- lipids (including fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol),
- acetaminophen during gastric emptying (Part B only), and
- appetite analysis.

Additional exploratory PD analysis may be analyzed as deemed appropriate. Nonpharmacogenetic samples will be collected to enable potential exploratory biomarker analyses related to LY3502970 mechanism of action, diabetes, and diabetic complications, including obesity (see Section 9.8.2).

At the visits and times specified in the Schedule of Activities (Section 2), samples will be obtained for the measurement of PD. The timing of PD samples is intended to assess pharmacologic effects of LY3502970. The sampling times may be modified at the discretion of the sponsor, but the total number of the samples or total blood volume will not increase.

The sample(s) will be stored for up to a maximum of 2 years after the last subject visit for the study at a facility selected by the sponsor.

9.6.1. Glucose Samples

Serum concentrations of glucose from the clinical laboratory samples and glucose only samples, according to the Schedule of Activities (Section 2), will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

9.6.2. Insulin Samples

Serum concentrations of insulin collected according to the Schedule of Activities (Section 2) will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

9.6.3. Oral Glucose Tolerance Test (Part B)

Glucose and insulin will be measured in an OGTT to assess effects of LY3502970 on glycemic control, disposition index, and insulin sensitivity. The schedule for OGTTs is indicated in the Schedule of Activities (Section 2).

Subjects shall maintain their regular carbohydrate intake 3 days before the scheduled OGTT. Subjects shall fast for approximately 8 hours overnight before administration of the OGTT. A 75-gram glucose dose will be given orally. Subjects should consume the glucose load within 5 minutes. If a subject develop symptoms of hypoglycemia, bedside blood glucose concentration may be measured and the subject will be treated per investigator discretion. Blood samples will be drawn for assessment of glucose and insulin at times indicated in the Schedule of Activities (Section 2).

9.6.4. Lipid Panel Samples

Samples for lipid panel tests collected according to the Schedule of Activities (Section 2), will be assayed using validated analytical methods. Refer to Appendix 2 for details regarding the lipid panel tests. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

9.6.5. Gastric Emptying (Part B)

Acetaminophen is a well-established marker for the rate and extent 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-time profile of acetaminophen, specifically, decreasing its C_{max} and t_{max} without altering the extent (total drug amount) absorbed. A dose of approximately 1 g acetaminophen is considered to be sufficient for bioanalytical detection.

Acetaminophen to assess gastric emptying will be administered as indicated in the Schedule of Activities (Section 2). The acetaminophen dose should be given soon after the 75-g glucose dose for the OGTT.

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

9.6.6. Appetite Analysis

To explore the effects of LY3502970 on meal intake and appetite sensation, subjects in Part B (MAD) 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. These measurements shall be performed according to the Schedule of Activities (Section 2).

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

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

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

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to LY3502970 and to investigate genetic variants thought to play a role in T2DM and diabetes complications, including obesity. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3502970 or after LY3502970 is commercially available.

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

9.8. Biomarkers

9.8.1. Coproporphyrins

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of coproporphyrin 1 and coproporphyrin 3. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

9.8.2. Nonpharmacogenetic Biomarkers

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

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

Samples will be used for research on the drug target; disease process; variable response to LY3502970; pathways associated with T2DM, obesity, or diabetes complications; mechanism of action of LY3502970; and/or research methods, or for validating diagnostic tools or assay(s) related to T2DM, obesity, or diabetes complications.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3502970 or after LY3502970 or is commercially available.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size for Parts A through E of the study was chosen to provide sufficient data for evaluating safety, PK, and/or PD parameters, as well as primary objectives of this study.

For details regarding the number of subjects planned for each part, refer to Section 5.2.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

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

10.3. Statistical Analyses

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

Pharmacokinetic and PD analyses will be conducted on data from all subjects who receive at least one dose of the investigational product and have evaluable PK and PD data, respectively. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Analyses will be fully detailed in the statistical analysis plan (SAP).

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The number of investigational product-related SAEs will be reported.

Details regarding the analysis of AEs of special interest will be described in the SAP.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized, using standard descriptive statistics. Additional analysis will be performed, if warranted, upon review of the data.

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

Vital signs will be summarized with respect to observed values and change from baseline (Day 1, predose) values by treatment at each time point using descriptive statistics. For change from baseline values, a mixed-model repeated-measure model with treatment, time (of measurement), and treatment-by-time interaction as fixed effects, subject as random effect, and baseline as covariate will be used to determine the effects of LY3502970. Least squares means as well as 90% confidence intervals (CIs) will be reported.

The ECG parameters and changes from baseline, including the PR, QT, RR, and QTcF intervals, QRS duration, and heart rate, will be summarized. The number and percentage of subjects with a maximum increase from baseline in QTcF interval will be summarized for each treatment group according to the following categories: >30 msec and >60 msec. In addition, the number and percentage of subjects with QTcF postdose values will be summarized by treatment group according to the following categories: >450 msec; >480 msec; and >500 msec. Analyses may be performed to determine the effects of PK parameters on QTcF.

Additional analysis will be performed, if warranted, upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3502970 will be calculated by standard noncompartmental methods of analysis. The primary parameters for analysis will include C_{max}, AUC, and t_{max}. Other parameters, such as half-life, apparent clearance, renal clearance, and apparent volume of distribution, may be reported. If deemed necessary, additional model-based analysis may be performed.

All PK parameters will be listed and summarized using descriptive statistics.

The PK parameters for midazolam, atorvastatin, simvastatin, and their metabolites will also be analyzed using standard noncompartmental methods of analysis.

Renal clearance of LY3502970 will be calculated as the ratio of amount excreted/AUC. This will be compared to the unbound glomerular filtration rate, which is estimated using creatinine.

10.3.2.2. Pharmacokinetic Statistical Inference

Parts A (SAD) and B (MAD): For single- and multiple-dose parts of the study, PK dose proportionality of LY3502970 will be assessed separately. Log-transformed C_{max} and AUC estimates 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.

The parameter t_{max} will be analyzed using a nonparametric method.

Exploratory Part B (DDI): The primary PK parameter estimates for midazolam, atorvastatin, and simvastatin and their metabolites will be compared between Day -2 (baseline) and Day 27 (presence of LY3502970). Log-transformed C_{max} and AUC estimates will be evaluated. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

Exploratory Part C (food effect): The primary PK parameter estimates will be compared between the reference fasted treatment and food-effect treatment. Log-transformed C_{max} and AUC estimates will be evaluated in a linear mixed-effects model. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

Exploratory Part D (controlled-release): The primary PK parameter estimates will be compared between the controlled-release prototype formulation (Part D) and the corresponding dose level from Part A. Log-transformed C_{max} and AUC estimates will be evaluated. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

Exploratory Part E (formulation optimization): The primary PK parameter estimates will be compared between reference formulation, and test formulations 1 and 2. Log-transformed C_{max} and AUC estimates will be evaluated in a linear mixed-effects model. The treatment differences will be back-transformed to present the ratios of geometric least squares means and the corresponding 90% CIs.

10.3.3. Pharmacodynamic Analyses

Inferences will be sought regarding the ability of LY3502970 over a range of doses to reduce fasting or dynamic glucose together with the effects on insulin.

10.3.3.1. Pharmacodynamic Parameter Estimation

Fasting glucose and insulin concentrations and AUC for glucose and insulin during an OGTT will be presented. The AUC for glucose and insulin during an OGTT will be calculated using the trapezoidal rule. The AUC as well as derived parameters or observed concentration at specific time points for each subject on the study day will also be baseline-adjusted. The concentrations on Day -1 will be used as baseline.

Acetaminophen will be used to assess the effect of LY3502970 on gastric emptying in Part B. The concentration-time profiles of acetaminophen will be presented for Days -1, 1, and 28. Acetaminophen PK parameter estimates will be calculated by standard noncompartmental analysis methods and summarized using descriptive statistics. Key parameters for analysis will

include C_{max}, AUC, and t_{max} of acetaminophen. Other parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Body weight and change from baseline body weight will be summarized by visits.

10.3.3.2. Pharmacodynamic Statistical Inference

The PD parameters from each part of the study will be analyzed separately. The PD parameters from placebo-treated subjects within each part of the study will be pooled for the final analysis. The PD parameters may be transformed before statistical analyses, if deemed necessary. Absolute values and change from baseline in each parameter will be analyzed using mixed-effects models to evaluate treatment effects as well as treatment comparisons. The main comparisons will be between each LY3502970-treated group and placebo group.

Least squares means as well as 90% CIs will be reported. The parameter t_{max} of acetaminophen will be analyzed using a nonparametric method. All PD parameters, including the baseline-corrected parameters, will be summarized and tabulated by treatment group and day. Summary statistics will be provided. The individual observed and mean time profile of the postdose PD parameters will be plotted by treatment group.

Additional analysis will be performed, if warranted, upon review of the data.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD modeling may be evaluated to characterize the exposure-response relationships between LY3502970 concentrations and various PD endpoints, provided data are sufficient.

10.3.5. Appetite Analyses

The study assessment will be the overall appetite score as measured according to the 0- to 100-mm VAS. Descriptive statistics will be used to summarize the baseline, postdose time points, and absolute change from baseline in overall appetite score by treatment group. Details will be provided in the SAP.

10.3.6. Biomarker Analyses

Plasma concentrations of coproporphyrin 1 and coproporphyrin 3 will be listed and summarized, using standard descriptive statistics. Parameter estimates for coproporphyrin 1 and coproporphyrin 3 will be calculated by standard noncompartmental methods. Parameters, including $C_{predose}$, C_{max}, t_{max}, and AUC, will be summarized using descriptive statistics.

Additional analysis may be performed, if warranted, upon review of the data.

10.3.7. Data Review During the Study

Access to the data is scheduled to occur after every dosing session during Parts A and B of the study. The purpose of these reviews is to guide SAD and MAD escalation decisions; initiation of the MAD portion of the study; dose selections; and PK and PD sample collection schemes. The investigator will remain blinded and the Lilly sponsor team will be unblinded throughout the study.

For SAD and MAD escalation decisions, the review will include data collected through Day 5 for Part A or Day 15 for Part B for at least 5 subjects receiving LY3502970 in the preceding dose level. The investigator and sponsor will make the determination regarding dose escalation based upon their review of the safety and tolerability data. Although not mandated, available PK and PD data may also be reviewed.

For the decision to initiate Part B (MAD), the review will include safety, tolerability, and available PK and PD data collected, at the earliest, up to Day 5 for Cohort C in Part A. Part B may be initiated if data from Part A indicates an approximately 10 to 20 mg/dL glucose-lowering effect at a tolerated dose.

10.3.8. Interim Analyses

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject 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
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/or his staff and the subject are not.
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CSE	clinically significant event

CYP	cytochrome P450
ECG	electrocardiogram
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
GLP-1RA	glucagon-like peptide-1 receptor agonist
HED	human equivalent dose
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
MAD	multiple-ascending dose
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
non-investigational product	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
OATP	organic anion transporting peptide
OGTT	oral glucose tolerance test
randomize	The process of assigning subjects to an experimental group on a random basis.
PD	pharmacodynamic(s)

PG	plasma glucose
PK	pharmacokinetic(s)
QTcF	corrected QT interval using Fridericia's formula
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
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.
SUSARs	suspected unexpected serious adverse reactions
SAE	serious adverse event
SAP	statistical analysis plan
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.
SUSARs	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time of maximum observed concentration
ULN	upper limit of normal
VAS	visual analog scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Differential WBC absolute counts of:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Platelets

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

Serology[a,d]
- Hepatitis B surface antigen
- Hepatitis B core antibody
- Hepatitis C antibody
- HIV

Hemoglobin A1c[a,d]

Calcitonin[a,d]

Clinical Chemistry[a]
- Sodium
- Potassium
- Bicarbonate
- Chloride
- Calcium
- Phosphorus
- Magnesium
- Glucose, fasting
- Blood urea nitrogen
- Uric acid
- Total protein
- Albumin
- Amylase
- Lipase
- Creatinine

Lipid Panel[b]
- Total cholesterol
- Triglycerides
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol

Liver Panel[b]
- Total bilirubin
- Direct bilirubin
- Indirect bilirubin
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Gamma-glutamyl transferase

Ethanol testing[a,e]

Urine drug screen[a,e]

Pregnancy test[a,f]

Follicle-stimulating hormone[a,d,g]

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

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

[a] Performed at local laboratory.

[b] Performed at local laboratory for screening and at central and local laboratories for all other time points.

[c] If clinically indicated, per investigator's discretion.
[d] Performed at screening only.
[e] Urine drug screen and ethanol level will be performed at screening and may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.
[f] For females only: serum pregnancy tests will be performed at screening and follow-up.
[g] For females with spontaneous amenorrhea for 6 to 12 months, if needed, to confirm postmenopausal status.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

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

Recruitment

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

Ethical Review

The investigator or appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonization (ICH) guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Site

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Red blood cells	Prothrombin Time
White blood cells	Prothrombin Time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase	**Anti-nuclear antibody[a]**
Aspartate aminotransferase	**Alkaline Phosphatase Isoenzymes[a]**
Gamma-glutamyl transferase	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
Creatine phosphokinase	

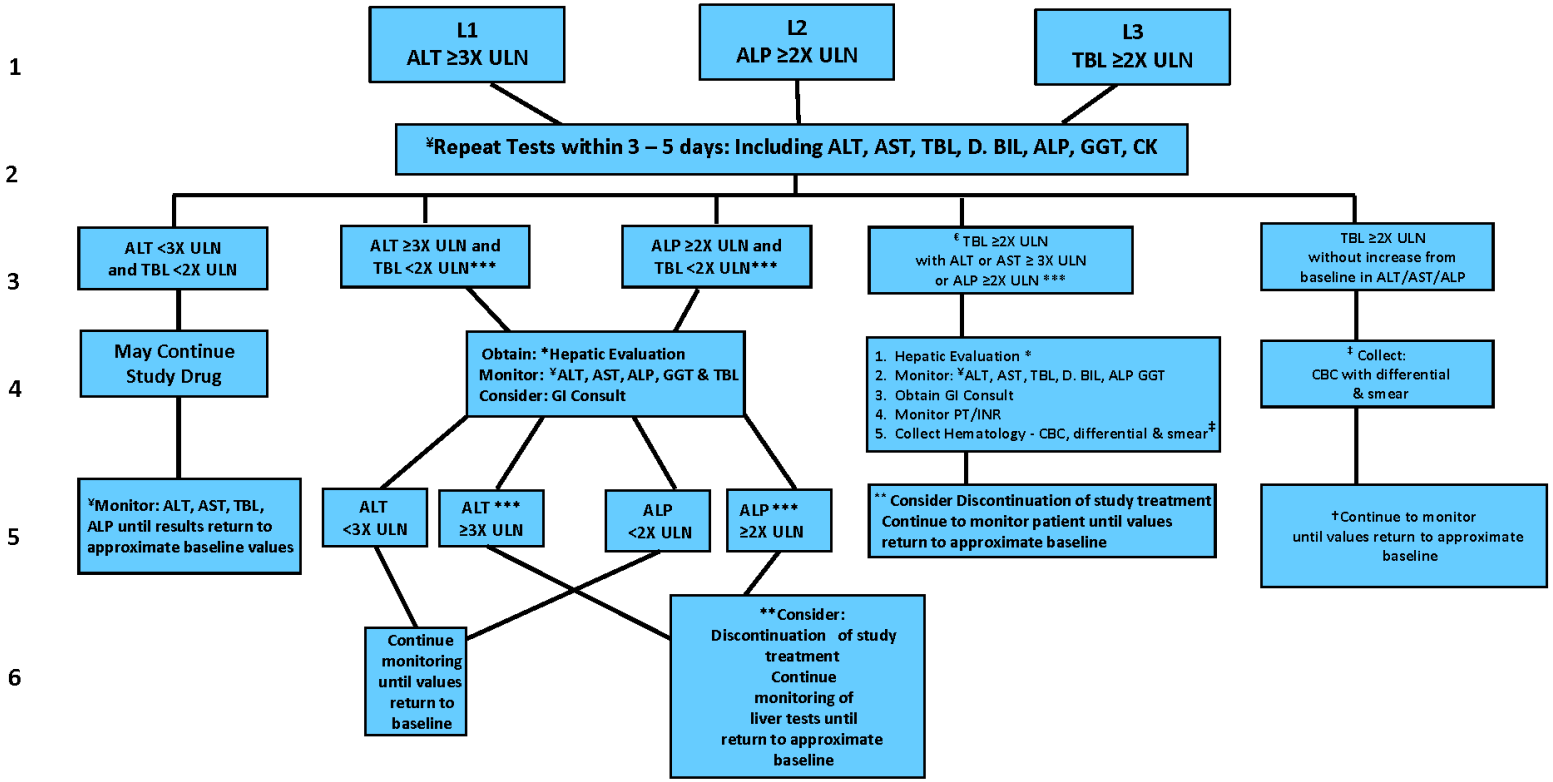
Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

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

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

Hepatic Safety Monitoring Algorithm:**
For subjects with no known liver disease, and normal or near normal baseline liver tests
(ALT <2X ULN, TBL <1.5X ULN, ALP <1.5X ULN)

If at any point during monitoring, a condition at the 3rd row of the algorithm is met, then proceed down that branch of the algorithm



* Hepatic Evaluation – see on the next page

** This flow chart is designed to assist in timely collection of data which will aid in assessment and monitoring of liver injury during a clinical trial. It is not designed to recommend specific discontinuation rules. See next page for background information on hepatic discontinuation.

*** Refer to the protocol instructions regarding potential eCRF completion

¥ These tests are all included in the hepatic chemistry panel.

€ The combination of ALT≥3X ULN AND TBL≥ 2X ULN may suggest a Hy's Law case when occurring in the absence of significant cholestasis and no other cause of liver injury

‡ Testing for serum haptoglobin level may be considered when differential and smear are not available

† Isolated elevation of TBL (predominantly indirect) may be due to Gilbert's syndrome. In these cases fluctuation in TBL levels may be a part of the patient's normal pattern

* Hepatic Evaluation:

- Obtain history and conduct a physical examination. Determine if symptoms or signs of liver disease are present (e.g. flu-like symptoms, nausea, vomiting, fever, confusion, right upper quadrant discomfort or tenderness, jaundice, fatigue, poor appetite, increased abdominal girth, itching).
- Obtain blood samples for laboratory analysis of ALT, AST, CK, TBL, D. BIL, ALP, GGT, viral serology for HAV, HBV, HCV, HEV and autoimmune serology (see below). Utilize the hepatic evaluation kit from the central lab, if available. Fractionated bilirubin is determined for the differential diagnosis of non-hepatic etiologies such as hemolysis, and Gilbert's syndrome. An elevated unconjugated (indirect) bilirubin with normal aminotransferases during fasting is likely to be Gilbert's syndrome, when TBL is less than 3 mg/dL. In patients with elevated ALP of unclear origin consider testing for ALP isoenzymes.
- Complete the hepatic safety data collection as described in the protocol.
- Recommend viral serology tests during monitoring of a clinical study includes: HBs Ag, HBs Ab, HBc Ab, HAV Ab (IgG and IgM), HCV Ab, and HEV Ab (IgG and IgM).
- Recommended serology tests for autoimmune hepatitis includes: ANA, ASMA (or anti-actin antibody.)

Clinical Background Regarding Hepatic Discontinuation
for Subjects with no known liver disease, and normal or near normal baseline liver tests
(ALT <2X ULN, TBIL <1.5X ULN, ALP <1.5X ULN) (Based on current FDA's Guidance on Drug Induced Liver Injury)

- **Increases in blood levels of aminotransferases (ALT and AST) to more than 3x upper limit of normal (ULN) are commonly observed during clinical trials. Such increases are often self limiting despite continuation of the drug and rarely progress to severe drug induced liver injury (DILI).**
- **Reversible asymptomatic increase in aminotransferase-levels during drug treatment is a nonspecific phenomenon (often called "adaptation") and is not a reliable predictor of the drug's potential to cause severe DILI.**
- **Therefore, discontinuation of a study drug upon finding of an elevated ALT or AST of >3x ULN (but <8x ULN) is often unnecessary, and will not permit learning whether adaptation occurs.**
- **On the other hand, rising bilirubin level (TBL) or prolongation of prothrombin time (PT or INR) may indicate a significant liver injury and, when caused by a drug, are considered to have stronger predictive power of the drug's potential to cause severe DILI.**
- **Hy's Law: The combination of drug related elevation of ALT ≥3x ULN and TBIL ≥2x ULN, in the absence of significant cholestasis (i.e. ALP <2X ULN), and in the absence of other causes of liver injury, is known collectively as a "Hy's Law," and is considered highly predictive of a drug's ability to cause severe DILI.**
- **Based on these considerations, the FDA has recommended using the following criteria as hepatic discontinuation rules. These criteria are also recommended by the Lilly Liver and GI Safety Advisory Committee for use in Lilly development programs, in subjects with no known liver disease and normal or near normal baseline liver tests (ALT< 2x ULN, TBIL <1.5x ULN, ALP <1.5x ULN):**
  - **ALT or AST >8x ULN**
  - **ALT or AST >5x ULN for more than 2 weeks**
  - **ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5**
  - **ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)**
- **Although there are currently no specific recommendations in the FDA guidance regarding discontinuation in patients with elevated ALP, it is recommended to consider discontinuation in a patient with ALP elevation which meets one of the following criteria and is deemed to be of liver origin and drug related**
  - **ALP >3x ULN**
  - **ALP >2.5x ULN and TBL > 2x ULN**
  - **ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)**
- **Whenever possible, the decision to discontinue the investigational product for abnormal liver tests should be made by the investigator in consultation with the Lilly designated medical monitor**

Glossary

Acronym	Name
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
ASMA	Anti smooth-muscle antiboy
AST	Aspartate aminotransferase
CBC	Complete Blood Count
CK	Creatine kinase
D. BIL	Direct Bilirubin
GGT	Gamma glutamyl transpeptidase (or transferase)
GI	Gastro Intestinal, Gastroenterology
HAV	Hepatitis A virus
HAV Ab	Hepatitis A virus antibody
HBc Ab	Hepatitis B core antibody
HBs Ab	Hepatitis B surface antibody
HBV	Hepatitis B virus
HBs Ag	Hepatitis B surface antigen
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HEV	Hepatitis E virus
HEV Ab	Hepatitis E virus antibody
IgG	Immunglobulin G
IgM	Immunglobulin M
PT/INR	Prothrombin time/ International Normalized Ratio
TBL	Total Bilirubin
ULN	Upper Limit of Normal

Appendix 5. Pancreatic Monitoring Tests for Treatment-Emergent Abnormality

GLP-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 LY3502970 on the exocrine pancreas, amylase and lipase values will be monitored in all current and future clinical trials with LY3502970.

Additional monitoring will be requested for amylase or lipase values ≥3× ULN at any visit after randomization, even in asymptomatic subjects (see figure below). Lipase and amylase may also be obtained at any time during the clinical trials for any subject suspected of having symptoms suggestive of pancreatitis (such as severe gastrointestinal 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:

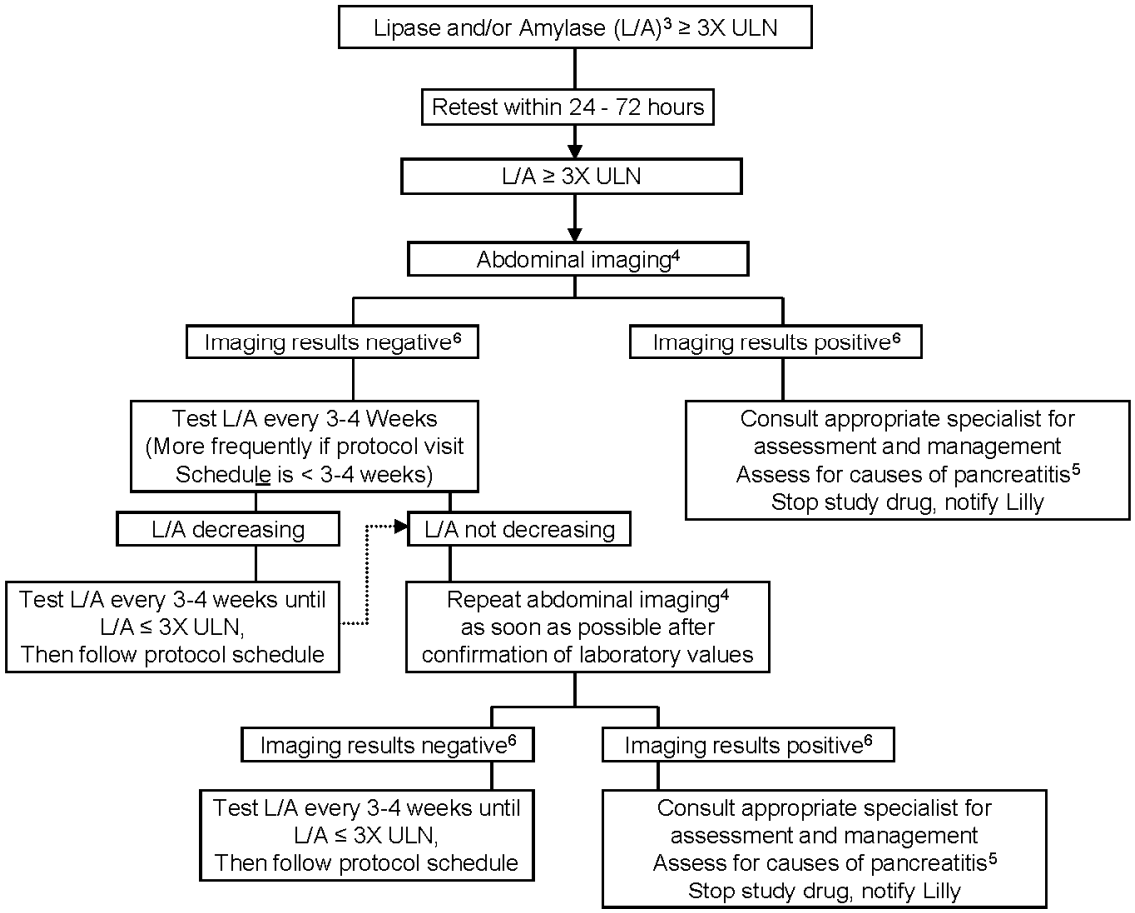
- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3× ULN
- characteristic findings of acute pancreatitis on computed tomography scan or magnetic resonance imaging

Most subjects with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back in approximately half the cases. The pain is often associated with nausea and vomiting. However, experience with GLP-1 agonists has demonstrated that some subjects asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase. For subjects considered by investigators to be asymptomatic for pancreatitis, but whose value(s) for lipase and/or amylase are ≥3× ULN, an algorithm is in place to follow these subjects safely and to quickly reach/or not a diagnosis of pancreatitis.

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

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

Follow this algorithm when the value(s) for serum lipase and/or amylase are ≥ 3X ULN.



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

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

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

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

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

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

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Appendix 6. Blood Sampling Summary

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

Protocol J2A-MC-GZGA Sampling Summary for Part A

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Serum pregnancy test	3.5	1	3.5
Safety laboratory tests[a]	6.5	3	19.5
Liver panel[a]	3	3	9
Lipid panel	3	2	6
Insulin	3	6	18
Glucose	3	6	18
LY3502970 pharmacokinetics	2	12	24
Serum creatinine	2.5	4	10
Insulin (OGTT)	3	10	30
Glucose (OGTT)	3	10	30
Coproporphyrins	3	12	36
Pharmacogenetics	10	1	10
Total			243.5
Total for clinical purposes rounded up to nearest 10 mL			250

Abbreviations: OGTT = oral glucose tolerance test.

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

Protocol J2A-MC-GZGA Sampling Summary for Part B

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Safety laboratory tests[a]	6.5	5	32.5
Serum pregnancy test	3.5	2	7
Liver panel[a]	3	5	15
Lipid panel	3	3	9
Insulin	3	11	33
Glucose	3	11	33
LY3502970 pharmacokinetics	2	33	66
Midazolam pharmacokinetics (Cohort J)	1	18	18
Atorvastatin pharmacokinetics (Cohort J)	2	16	32
Simvastatin pharmacokinetics (Cohort K)	2	22	44
Insulin (OGTT)	3	15	45
Glucose (OGTT)	3	15	45
Coproporphyrins (Cohorts G – I)	3	30	90
Coproporphyrins (Cohorts J – K)	3	8	24
Acetaminophen pharmacokinetics	2	32	64
Pharmacogenetics	10	1	10
Nonpharmacogenetics biomarkers			
Plasma	2	4	8
Serum	2.5	4	10
P800 plasma	2	4	8
Total for Cohorts G through I			505
Total for Cohort J			489
Total for Cohort K			483
Total for clinical purposes rounded up to nearest 10 mL			490 - 510

Abbreviations: OGTT = oral glucose tolerance test.

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

Protocol J2A-MC-GZGA Sampling Summary for Part C

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Serum pregnancy test	3.5	1	3.5
Safety laboratory tests[a]	6.5	7	45.5
Liver panel[a]	3	3	9
Insulin	3	18	54
Glucose	3	18	54
LY3502970 pharmacokinetics	2	36	72
Coproporphyrins	3	36	108
Pharmacogenetics	10	1	10
Total			385.5
Total for clinical purposes rounded up to nearest 10 mL			390

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

Protocol J2A-MC-GZGA Sampling Summary for Part D

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Serum pregnancy test	3.5	1	3.5
Safety laboratory tests[a]	6.5	3	19.5
Liver panel[a]	3	3	9
Insulin	3	6	18
Glucose	3	6	18
LY3502970 pharmacokinetics	2	12	24
Insulin (OGTT)	3	10	30
Glucose (OGTT)	3	10	30
Coproporphyrins	3	12	36
Pharmacogenetics	10	1	10
Total			227.5
Total for clinical purposes rounded up to nearest 10 mL			230

Abbreviations: OGTT = oral glucose tolerance test.

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

Protocol J2A-MC-GZGA Sampling Summary for Part E

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Serum pregnancy test	3.5	3	10.5
Safety laboratory tests[a]	6.5	5	32.5
Liver panel[a]	3	7	21
Lipid panel	3	5	15
Insulin	3	12	36
Glucose	3	12	36
LY3502970 pharmacokinetics	2	45	90
Pharmacogenetics	10	1	10
Nonpharmacogenetic biomarkers			
Plasma	2	4	8
Serum	2.5	4	10
P800 plasma	2	4	8
Total			306.5
Total for clinical purposes rounded up to the nearest 10 mL			310

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

Appendix 7. Protocol Amendment J2A-MC-GZGA(f) Summary
A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Healthy Subjects

Overview

Protocol J2A-MC-GZGA, A Single- and Multiple-Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3502970 in Healthy Subjects, has been amended. The new protocol is indicated by Amendment (f) and will be used to conduct the study in place of any preceding version of the protocol.

This amendment is considered nonsubstantial.

The overall changes and rationale for the changes made to this protocol are as follows:

- Amended the Schedule of Activities in Part B for administering simvastatin (Cohort K).
- Amended the Schedule of Activities in Part E to remove baseline OGTT and all OGTT data collection during treatment in Part E.
- Amended the Schedule of Activities in Part E to address that study drug administration will be done from Days 1 to 28.
- Amended the Schedule of Activities in Part E to address that 8 hour insulin and glucose samples are collected on Days 13 and 24.
- Amended the Schedule of Activities in Part E to remove frequently sampled insulins on Day 24 as OGTT was removed. Predose, 8 and 24 hour remained.
- Amended Section 7.1.1 to include text regarding the formulations used in Part E.
- Other minor grammatical and formatting edits and re-numbering were made, but these do not otherwise affect the content of this protocol. These changes may not be reflected in the Revised Protocol Sections.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Study Schedule for Part B – Cohorts J and K: Multiple-Ascending Dose for Weeks 3, 4, 5, and 6

Procedure	Treatment									Follow-up		Comments
	Week 3			Week 4				Week 5	Week 6			
Day	15	16	17 to 21	22	23 to 27	28	29	32 ±1	35 ±1	42 ±2	ED[b]	
Administer simvastatin (Cohort K)					X (Day 27)							Simvastatin will be coadministered with either LY3502970 or placebo on Day 27 ~~Administer simvastatin 4 hours after LY3502970 dose on Day 27~~ (Cohort K). ~~In case of BID dosing, to be administered with the morning dose.~~

2.5. Study Schedule for Exploratory Part E – Formulation Optimization

Study Schedule for Part E: Titration Periods 1 and 2

Procedure	Screening	Baseline		Treatment					Comments
				Titration Period 1			Titration Period 2		
Day	-28 to -3	-2	-1	1	2	3 to 6	7	8 to 12	
~~OGTT (hour)[a]~~			~~X~~						~~Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.~~
~~OGTT – glucose sample (hour relative to glucose dose)~~			~~0, 0.5, 1, 1.5, 2~~						~~Sampling times may be adjusted after review of preliminary data.~~

Study Schedule for Part E: Titration periods 3, 4, and test period

Procedure	Treatment											Follow-up		Comments
	Titration Period 3			Titration Period 4		Test Period								
Day	13	14	15 to 18	19	20 to 23	24	27	28	29 ±1	32±1	35±1	40 ±2	ED[b]	
Weight[a]	Predose			Predose		X			X			X	X	Weight will be measured in a consistent way (see Section 9.4.4).
Administer study drug	X	X	X	X	X	X	X	X						Study drug will be administered from Days 1 to 28. See Section 5.1.4.
Insulin sample (hour)[a]	Predose, 8	24[c]		Predose		Predose, ~~0, 0.5, 1, 1.5, 2,~~ 8, 24[c]	~~24~~[e]					X	X	Except for the 8-hour samples on Days 13~~15~~ and 24~~28~~, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
Glucose sample (hour)[a]	Predose, 8	24[c]		Predose		Predose, 8, 24[c]	~~24~~[e]					X	X	Except for the 8-hour samples on Days 13~~15~~ and 24~~28~~, subjects will be required to fast for at least 8 hours before each blood sample is drawn.
VAS for appetite[a]	Predose			Predose		X						X		
LY3502970 PK samples (hour)[a]	Predose			Predose, 0.5, 1, 2, 4, 6, 8, 12, 16, 24[c] ~~(Day 19)~~	Predose, 0.5, 1, 2, 4, 6, 8, 12, 16 (Day 23)	24[c]		Predose, 0.5, 1, 2, 4, 6, 8, 12, 16	24, 36	96 ± 24	168 ± 24			Sampling times may be adjusted after review of preliminary data.
~~OGTT (hour)[a]~~						~~2~~								~~Subjects will be required to fast for at least 8 hours before OGTT. Times may be adjusted after review of preliminary data.~~

~~OGTT glucose sample (hour relative to glucose dose)~~						~~0, 0.5, 1, 1.5, 2~~								~~Sampling times may be adjusted after review of preliminary data.~~

7.1.1. Packaging and Labeling

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

~~LY3502970 will be supplied as a spray-dried solid dispersion consisting of 30% LY3502970/70% PVP-VA (polyvinylpyrrolidone-vinyl acetate) and will be combined with sodium bicarbonate for extemporaneous preparation at the CRU for Part A. For Parts B and C, LY3502970 solid dispersion may be supplied either in combination with sodium bicarbonate or by itself. The controlled-release prototype for Part D will consist of the solid dispersion filled directly into capsule shells with no other excipients. For Part E, LY3502970 solid dispersion will be combined with sodium bicarbonate, calcium carbonate, or magnesium hydroxide.~~

LY3502970 will be supplied as a spray-dried solid dispersion consisting of 30% LY3502970/70% polyvinylpyrrolidone-vinyl acetate and will be combined with sodium bicarbonate for extemporaneous preparation at the CRU for Part A, B, and C. Part E will evaluate the LY3502970 solid dispersion combined with sodium bicarbonate or magnesium hydroxide. For Part D, the LY3502970 solid dispersion filled directly into capsule shells with no other excipients to be evaluated as a controlled-release prototype.

Appendix 6. Blood Sampling Summary

Protocol J2A-MC-GZGA Sampling Summary for Part B

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Safety laboratory tests[a]	6.5	5	32.5
Serum pregnancy test	3.5	~~1~~2	~~3.5~~7
Liver panel[a]	3	5	15
Lipid panel	3	3	9
Insulin	3	11	33
Glucose	3	11	33
LY3502970 pharmacokinetics	2	33	66
Midazolam pharmacokinetics (Cohort J)	1	18	18
Atorvastatin pharmacokinetics (Cohort J)	2	16	32
Simvastatin pharmacokinetics (Cohort K)	2	22	44
Insulin (OGTT)	3	15	45
Glucose (OGTT)	3	15	45
Coproporphyrins (Cohorts G – I)	3	30	90
Coproporphyrins (Cohorts J – K)	3	8	24
Acetaminophen pharmacokinetics	2	32	64
Pharmacogenetics	10	1	10
Nonpharmacogenetics biomarkers			
Plasma	2	~~4~~5	8~~10~~
Serum	2.5	~~4~~5	10~~12.5~~
P800 plasma	2	~~4~~5	8~~10~~
Total for Cohorts G through I			505~~508~~
Total for Cohort J			489~~492~~
Total for Cohort K			483~~486~~
Total for clinical purposes rounded up to nearest 10 mL			490 - 510

Abbreviations: OGTT = oral glucose tolerance test.

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

Protocol J2A-MC-GZGA Sampling Summary for Part E

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	29.5	1	29.5
Serum pregnancy test	3.5	3	10.5
Safety laboratory tests[a]	6.5	5~~6~~	32.5 ~~39~~
Liver panel[a]	3	7	21
Lipid panel	3	5	15
Insulin	3	12 ~~17~~	36 ~~48~~
Glucose	3	12	36
LY3502970 pharmacokinetics	2	45	90
~~Glucose (OGTT)~~	~~3~~	~~10~~	~~30~~
Pharmacogenetics	10	1	10
Nonpharmacogenetic biomarkers			
Plasma	2	4	8
Serum	2.5	4	10
P800 plasma	2	4	8
Total			306.5 ~~355~~
Total for clinical purposes rounded up to the nearest 10 mL			310 ~~360~~

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

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