Protocol I8Q-MC-GSEA(a)

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Oral Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3202328

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LY3202328

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

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3. Protocol Synopsis

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Oral Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3202328.

Rationale:

Cardiovascular (CV) disease remains one of the largest causes of morbidity worldwide and new treatments are needed. The principle aim of this single and multiple ascending dose study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of LY3202328 when administered orally as single doses to overweight, healthy subjects (Part A, single ascending dose [SAD] design) and as multiple doses to overweight, dyslipidemic subjects (Part B, multiple ascending dose [MAD] design). The data obtained in this study will help establish the doses and dosage regimen suitable for administration to dyslipidemic patient populations in future efficacy studies. In vitro testing showed some potential for LY3202328 to have mechanism-based inhibition of cytochrome P450 (CYP) 3A4; thus a drug-drug interaction (DDI) comparison arm has been included in Part B to investigate the effect of LY3202328 on the exposure of commonly used statins that are metabolized, at least in part, by CYP3A4. Additionally, the exploration of the degree of target inhibition (pharmacodynamic [PD] assessments) in dyslipidemic subjects will be assessed in Part B.

Objectives/Endpoints:

Objectives	Endpoints
Primary	To explore safety and tolerability of single and multiple doses of LY3202328 in statin-free, overweight, healthy subjects, or subjects with dyslipidemia.
Secondary	• To assess the PK characteristics of LY3202328 in statin-free, overweight, healthy subjects after single doses and in dyslipidemic subjects after multiple doses. • To evaluate the effect of food on the extent and rate of LY3202328 absorption. • To determine the effects of LY3202328 upon multiple dose administration on: o Fasting lipid profiles o Simvastatin and atorvastatin exposure.
Exploratory	• To explore the effects of LY3202328 on: o Post-prandial lipid profiles. o Fasting free fatty acids and β-hydroxybutyrate. o Fasting apolipoprotein (Apo) B100, ApoC3, proprotein convertase subtilisin/kexin type 9, lipoprotein (a), and insulin. o Body weight.

Summary of Study Design:

Study I8Q-MC-GSEA (GSEA) is a first-in-man, Phase 1, randomized, double-blind, placebo-controlled, ascending single- and multiple-oral dose study of LY3202328 in statin-free, overweight, healthy male and female subjects. This study will be conducted in 2 parts.

Part A, will comprise a SAD crossover design in statin-free, overweight, healthy male and female subjects, investigating the safety, tolerability, and PK of single doses of LY3202328 administered in the fasted state. In addition, one dose level will also be administered in the fed state to evaluate effects of food on the rate and extent of absorption.

Part B will comprise a MAD staggered parallel design in statin-free, overweight, dyslipidemic male and female subjects, investigating the safety, tolerability, and PK of multiple doses of LY3202328 and its effect on simvastatin and atorvastatin exposure.

Treatment Arms:
Part A: A total of 18 subjects will be enrolled in 2 cohorts. Cohort 1 will consist of 3 periods at dose levels 1, 10, and 100 mg, and Cohort 2 will consist of 3 periods at dose levels 3, 30, and 300 mg. A fourth dosing period will be added to either Cohort 1 or Cohort 2 to assess exposure differences when LY3202328 is administered in a fed state. Each cohort will consist of 9 subjects where subjects will receive either a single LY3202328 dose or a corresponding placebo in alternating ascending order.

In each cohort, 6 subjects will receive LY3202328 and 3 subjects will receive placebo. Subjects will be dosed in the fasted state in all periods except for subjects in the cohort that will return to repeat 1 dose level (planned 30 mg dose level) in the fed state to evaluate food effects on LY3202328 exposure. An additional potential cohort (not evaluated for food effect) will be reserved for the fourth dosing period at a higher dose level (600 mg). Escalation to this higher dose will only be made if exposure continues to increase between 100 and 300 mg dose levels and the safety profile supports dosing to a higher level.

Part B: A total of 40 subjects will be enrolled and divided evenly into 4 study periods (n=10 subjects per study period) to evaluate 4 dose levels of LY3202328 (Periods 5, 6, 7, and 8 at 5, 20, 100, and 300 mg, respectively, are planned).

Within each study period, 5 subjects will be stratified to the simvastatin DDI assessment and 5 subjects will be stratified to the atorvastatin DDI assessment. Within each stratum subjects will be randomly assigned 4:1 to receive LY3202328 or placebo so that 8 subjects will receive LY3202328 and 2 subjects receive placebo in each cohort. Subjects will receive a once daily (QD) dose of LY3202328 or placebo, to be administered in the morning in the fasted state for 29 total days. For DDI assessment, subjects will also receive a single atorvastatin or simvastatin dose a week prior to LY3202328 treatment initiation, and on Day 29 after initiation of LY3202328 dosing (coadministered with LY3202328). See Figure GSEA.1 for details.

The dose levels intended for study in Part B will be within the range of those tested in Part A. Specific dose levels will be selected after review of Part A data. Doses may range up to 300 mg or the maximum tolerated dose established in SAD Part A.

Number of Subjects:
Part A: It is planned that a total of 18 subjects will be enrolled in 2 cohorts with 9 statin-free, overweight, healthy subjects in each cohort.

Part B: It is planned that a total of 40 subjects will be enrolled in 4 cohorts with 10 statin-free, overweight, dyslipidemic subjects in each cohort.

Additional subjects may be enrolled to replace drop-outs or discontinued subjects, but are not required. Replacement subjects may complete any portion of the study as needed, i.e. any portion not completed by the discontinued subject.

Data Analysis:

Safety

The primary endpoint of this study is the number and severity of treatment-emergent adverse events, clinical laboratory abnormalities, changes in vital sign measurements, and other safety endpoints after administration of LY3202328 or placebo. Summary statistics will be provided by dose group and for all study subjects combined wherever appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Additional analysis will be performed if warranted upon review of the data.

Pharmacokinetics

The primary PK parameters for analysis will be maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) for LY3202328. The primary AUC metric will be calculated AUC from time zero to infinity ($AUC_{0-\infty}$) after single dose administration and AUC during one dosing interval ($AUC_{0-\tau}$) on day 28 after multiple dose administration. Pharmacokinetic parameter estimates (C_{max} and AUC) for LY3202328 will be evaluated to delineate effects of dose proportionality using a power model approach.

Drug-drug interaction assessment of the effect of LY3202328 coadministration on simvastatin and atorvastatin exposure will be conducted using ANOVA. Pharmacokinetic parameter estimates (C_{max} and AUC) for simvastatin and atorvastatin, administered alone or coadministered with LY3202328, will be compared. The ratios of statin exposure with and without LY3202328 coadministration at different dose levels of LY3202328 will be estimated, along with their confidence intervals.

The impact of food on the rate and extent of LY3202328 absorption will be assessed by calculating and summarizing the ratios of C_{max} and $AUC_{0-\infty}$, as well as the difference in the time to reach C_{max} (T_{max}), with and without food at the same dose level.

Review of PK may occur during the conduct of Part A and B to confirm exposure trends.

Pharmacodynamics

The PD assessments conducted in this study are typical and appropriate for Phase I single and multiple ascending dose evaluations of a novel therapeutic agent. The triglycerides concentrations will be analyzed to evaluate evidence of target engagement and intended pharmacological benefits.

Visual and tabular summarization of all PD measurements will be done. For the endpoints in the primary or secondary objectives, a statistical analysis will also be conducted.

Mixed effect model repeated measure would be the default method of analysis for PD endpoints with time-course data. For endpoints with only baseline and end-of-therapy measurements, ANCOVA will be the default, with baseline as a covariate. Other covariates may be a priori defined and included in the model.

Normality assumption will be tested using an appropriate visual or statistical method and, if it is violated, log transformation may also be performed on these data. The most sensitive analysis will be selected to test the effect of LY3202328 on the change from baseline in these PD data.

4. Introduction

Diacylglycerol acyltransferase 2 (DGAT2) plays a key role in processing fatty acids and secreting triglycerides (TG) from the liver. DGAT2 is responsible for catalyzing the formation of triacylglycerol from diacylglycerol and fatty acyl-coenzyme A. Despite the significant advancements made by statins in the treatment of dyslipidemia and cardiovascular (CV) disease, unmet need exists in a market projected to remain one of the largest causes of morbidity and mortality worldwide. DGAT2 inhibitor LY3202328 has the potential to offer value to patients, physicians, and providers through its expected diverse pharmacological profile to decrease TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), body weight, liver fat content, and improve glucose utilization. This broad pharmacological profile is expected to result in a reduction in CV events when added to or compared with statins or other standard-of-care therapies for these indications. A DGAT2 inhibitor also has the potential to treat other important metabolic diseases beyond dyslipidemia, including nonalcoholic fatty liver disease, and possibly Type-2 diabetes mellitus. Antisense oligonucleotide reduction of DGAT2 in liver and white adipose tissues for 18 weeks in LDL receptor (LDLr) knockout (KO) mice fed high-fat, cholesterol-enriched diets, reduced body weight (10%), total body fat (48%), plasma TG (70%), TC (52%), LDL-c (31%), and free fatty acids (FFA; 46%); and increased the glucose infusion rate needed to maintain glucose concentrations in a hyperinsulinemic-euglycemic clamp study by 70% (Manchem, 2010).

LY3202328 is a potent inhibitor of human DGAT2 with a half maximal inhibitory concentration (IC_{50}) of 124 nM in the primary enzyme assay and IC_{50} values of 197 nM and 47 nM in the HepG2 cell-based assay, with TG and apolipoprotein (Apo) B100 readouts, respectively. LY3202328 is highly selective compared to other acyl transferases in the TG synthesis pathway (IC_{50} >50 μM for DGAT-1, glycerophosphate acyltransferases-1 and -4, monoacylglycerol O-acyltransferases-2 and -3, as well as a general panel of enzymes and receptors), and it inhibits carbonic anhydrase with IC_{50} of 5 μM. LY3202328 demonstrated dose dependent inhibition of hepatic TG secretion in mice, with a median effective dose (ED_{50}) of 0.3 mpk when administered orally and a half maximal effective concentration (EC_{50}) of 142 ng/mL.

4.1. Study Rationale

There are many opportunities to address unmet need in the CV market. These include: 1) reducing residual CV event risk in patients already taking maximally-tolerated doses of statins; 2) providing predictable, robust lowering of both LDL-c and TG; 3) addressing common dyslipidemia co-morbidities such as obesity and diabetes; and 4) improving CV patient experience through decreased polypharmacy and a more acceptable mode of administration (oral versus injectable).

LY3202328 has the potential to offer a broad clinical profile that may result in a reduction in CV events when added to or compared to the standard of care. Further preclinical and Phase 1 studies will contribute to our understanding of the magnitudes of each clinical effect of LY3202328.

The principle aim of these dose-escalation studies is to evaluate the safety, tolerability, and pharmacokinetics (PK) of LY3202328 when administered orally as single doses to healthy subjects (Part A, single ascending dose [SAD] design) and as multiple doses to dyslipidemic subjects (Part B, multiple ascending dose [MAD] design). A food effect period will be performed in Part A to compare the exposure profile when LY3202328 is dosed in the fed or fasted state. The data obtained in this study will help establish the doses and dose regimen suitable for administration to dyslipidemic patient populations.

A drug-drug interaction (DDI) comparison arm will be included in Part B to investigate the effect of LY3202328 on the exposure of statins (i.e., simvastatin and atorvastatin). Additionally, the exploration of the degree of target inhibition (pharmacodynamic [PD] assessments) in dyslipidemic subjects will be assessed in Part B.

4.2. Background

LY3202328 is a low solubility, highly permeable molecule with high oral exposure in preclinical species. Oral bioavailability at the predicted human 80% maximal effective dose (ED_{80}) efficacious dose (13 mg once daily [QD]) is greater than 30% in preclinical species and is predicted to be 89% in humans. As the dose increases, exposures are expected to increase until reaching a plateau as absorption limitations are expected in humans for doses above 190 mg due to the solubility characteristics of the compound. In vivo, LY3202328 exhibits near linear increases in area under the plasma concentration-time curve (AUC) at doses up to 100 mg/kg with much lower than dose proportional increases in exposure above 100 mg/kg. The maximum plasma concentration (C_{max}) also increases with dose in a less than proportional manner. The time to reach C_{max} (T_{max}) is reached between 1 to 3 hours in most preclinical species. LY3202328 is eliminated predominantly by cytochrome P450 (CYP) 3A4 microsomal oxidation with <5% of dose excreted as parent by renal elimination. Based on in vitro data, LY3202328 is also a time-dependent inhibitor of CYP3A4 at high concentrations. However, lack of accumulation upon multiple dosing in vivo suggests that LY3202328 does not inhibit its own metabolism. These properties suggest a potential for DDIs with concomitantly administered CYP3A4 substrates (particularly those with a narrow therapeutic margin) or CYP3A4 inhibitors. Half-life in animal preclinical toxicology studies ranged from 3 to 12 hours, yet exposures in rat and dog toxicology studies showed no accumulation of LY3202328 after 28 days of repeat dosing. In humans, LY3202328 is projected to have a half-live of 6 to 8 hours. Human clinical dose projections based on Simcyp modeling of animal PK data predict a dose of 13 mg to achieve an average steady state concentration of 325 ng/mL (equivalent to a 24 hour AUC of 7.8 μg x h/mL) which is associated with 80% efficacy based on preclinical pharmacology studies (after correction for species difference in protein binding and receptor affinity).

In 28-day repeat dose Good Laboratory Practice (GLP) toxicology studies conducted at doses up to 500 mg/kg in rat and 250 mg/kg in dog (maximum feasible dose levels), no dose-limiting toxicities and no observable adverse effects were observed in either species. In rats administered 500 mg/kg, animals had minimal decreases in body weight gain (4%). Slight hypertrophy observed in liver centrilobular hepatocytes, adrenal zona fasciculata cells, and thyroid follicular cells correlated with minimal organ weight increases. These findings were consistent with

physiological adaptations to stress or minimal metabolic induction commonly observed in rodents. In dogs administered 250 mg/kg, there were infrequent emesis, liquid feces, and minor body weight loss (1%) with reduced food consumption. Rats and dogs administered 500 mg/kg and 250 mg/kg, respectively, had slight decreases in red blood cell mass (red blood cell count, hemoglobin concentration, and hematocrit) with evidence of regeneration based on higher absolute reticulocyte count. These effects observed in rats and dogs were not observed at the end of the 1-month reversibility phase of either study. The effects observed in rats and dogs were monitorable and there were adequate margins to the proposed clinical doses.

4.3. Benefit/Risk Assessment

The nonclinical safety information for LY3202328 adequately supports the transition from preclinical to clinical study. On the basis of the nonclinical data, LY3202328 is not considered to be a high-risk compound. This protocol reflects the fact that LY3202328 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 Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (2007). Any identified risks are considered to be monitorable and manageable at the planned dose range of 1 to 300 mg for LY3202328 in healthy subjects.

More information about the known and expected benefits and risks of LY3202328 can be found in Section 3.2 of the Investigator's Brochure (IB).

The sponsor, monitor, and investigator will perform this study in compliance with the protocol, good clinical practice (GCP), International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5. Objectives

5.1. Primary Objective

The primary objective of this study is to explore safety and tolerability of single and multiple doses of LY3202328 in statin-free, overweight, healthy subjects.

5.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the PK characteristics of LY3202328 in statin-free, overweight, healthy subjects after single and multiple doses.
- To evaluate the effect of food on the extent and rate of LY3202328 absorption.
- To determine the effects of LY3202328 upon multiple dose administration on:
    - Fasting lipid profiles
    - Simvastatin and atorvastatin exposure

5.3. Exploratory Objectives

The exploratory objective of this study is to explore the effects of LY3202328 on:

- Post-prandial lipid profiles.
- Fasting free fatty acids and β-hydroxybutyrate.
- Fasting ApoB100, ApoC3, proprotein convertase subtilisin/kexin type 9 (PCSK9), lipoprotein (a) (Lp[a]), and insulin.
- Body weight.

6. Study Design

6.1. Overall Design

Study I8Q-MC-GSEA (GSEA) is a first-in-man, Phase 1, randomized, double-blind, placebo-controlled, 2-part, ascending single- and multiple-oral dose study of LY3202328 in statin-free, overweight, healthy subjects (Part A) and in statin-free, overweight, dyslipidemic subjects with a statin DDI assessments (Part B).

This study will be conducted in 2 parts: Part A, a SAD study design at a single site and Part B, a MAD study design conducted in multiple sites.

Figure GSEA.1 illustrates the study design.

Part A: Single Ascending Dose

Cohort	N	Week 1	2	3	4	5	6	7	8	9
		Period 1		Period 2		Period 3			Period 4 (Food Effect)	
1	3	1 mg LY		10 mg LY		Placebo	D/C[a]			
	3	1 mg LY		Placebo		100 mg LY	D/C[a]			
	3	Placebo		10 mg LY		100 mg LY	D/C[a]			
2	3		3 mg LY		30 mg LY		Placebo		30 mg LY[b]	D/C[a]
	3		3 mg LY		Placebo		300 mg LY		Placebo[b]	D/C[a]
	3		Placebo		30 mg LY		300 mg LY		30 mg LY[b]	D/C[a]

Part B: Multiple Ascending Dose

Cohort	N	Week 3	4	5	6	7	8	9	10	11	12	13	14
3	10	Period 5											
		SS/AS[c]	5 mg LY or placebo[d]			SS/AS + 5 mg LY or placebo[e]	D/C[f]						
4	10			Period 6									
				SS/AS[c]	20 mg LY or placebo[d]			SS/AS + 20 mg LY or placebo[e]	D/C[f]				
5	10					Period 7							
						SS/AS[c]	100 mg LY or placebo[d]			SS/AS + 100 mg LY or placebo[e]	D/C[f]		
6	10							Period 8					
								SS/AS[c]	300 mg LY or placebo[d]			SS/AS + 300 mg LY or placebo[e]	D/C[f]

Abbreviations: AS = atorvastatin; CRU = clinical research unit; D/C = discharge (from the CRU); LY = LY3202328; N = number of subjects; SS = simvastatin.

a Discharge from the CRU will occur on Day 2 with Follow-up visits to occur on Days 3 and 5.

b LY3202328 or placebo will be administered with food.

c A single dose of simvastatin or atorvastatin will be administered on Day –7.

d Multiple doses of LY3202328 or placebo will be administered daily on Days 1 through 28.

e LY3202328 or placebo will be coadministered with simvastatin or atorvastatin on Day 29.

f Discharge from the CRU will occur on Day 30 with Follow-up visits to occur on Days 35 and 56.

Note: The doses for Part B are subject to change and will not exceed the maximum tolerated dose from Part A (starting as low as 5 mg and not to exceed 300 mg).

Figure GSEA.1. Study design for Protocol I8Q-MC-GSEA.

6.1.1. Part A: Single Ascending Dose with Food Effect Design

Part A will comprise a double-blinded, 2-staggered, alternating, 3- or 4-period sequence design of single ascending doses in statin-free, overweight (body mass index [BMI] 25.0 to 35.0 kg/m^2),

healthy male and female subjects, investigating the safety, tolerability, and PK of single doses of LY3202328 administered in the fasted state. One dose level will be repeated in the fed state using the same randomization as conducted in the fasted state to assess the effect of food on LY3202328 exposure.

A total of 18 subjects will be enrolled in 2 cohorts. Cohort 1 will consist of 3 periods at dose levels 1, 10, and 100 mg, and Cohort 2 will consist of 3 periods at dose levels 3, 30, and 300 mg. A fourth dosing period will be added to either Cohort 1 or Cohort 2 to assess exposure differences when LY3202328 is administered in a fed state. Each cohort will consist of 9 subjects where subjects will receive either a single LY3202328 dose or a corresponding placebo in alternating ascending order.

In each cohort, 6 subjects will receive LY3202328 and 3 subjects will receive placebo. Subjects will be dosed in the fasted state in all periods except for subjects in the cohort that will return for the fourth dosing period to repeat 1 dose level (planned 30 mg dose level) in the fed state to evaluate food effects on LY3202328 exposure. An additional potential cohort (not evaluated for food effect) will be reserved for the fourth dosing period at a higher dose level (600 mg). Escalation to this higher dose will only be made if exposure continues to increase between 100 and 300 mg dose levels and the safety profile supports dosing to a higher level.

Potential subjects will be screened to assess their eligibility to enter the study within 42 days prior to study entry (i.e., prior to Check in for Part A). Subjects will be confined at the clinical research unit (CRU) from Day –1 (the day before dosing) to Day 2 (24 hours postdose), and return on Days 3 and 5 (48 and 96 hours postdose, respectively) for follow-up assessments. Dosing in subsequent periods will be approximately 2 weeks after dosing in the prior period, with subjects dosed on Day 1 of Week 1, 3, or 5 (Cohort 1); Week 2, 4, or 6 (Cohort 2); and Week 8 (food effect period, Cohort 2).

Treatment of the cohorts in Part A will be staggered so that the appropriateness of escalation to the next dose level can be determined from the current dose level.

Safety assessments in Part A and Part B will include monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, physical examination findings, and 12-lead electrocardiogram (ECG) results. Escalation to the next dose period will be decided by the investigator in consultation with the sponsor's clinical research physician (CRP) at the dose escalation Data Review Meeting (DRM) as outlined in Section 7.3.1. The decision will be made based on safety data from each dosing period (Appendix 2). Pharmacokinetic and PD data are not required for the dose escalation decision; however, any drug concentration or PD data that becomes available prior to the DRM may be reviewed at the DRM. Interim analysis of PK will take place after collecting the 300 mg dose level samples to determine if a 600 mg dose level will be conducted. No interim analysis for PD is planned for the DRM.

6.1.2. Part B: Multiple Ascending Dose – Drug-Drug Interaction Design

Part B will comprise a double-blinded, MAD, staggered parallel design in dyslipidemic (TG: 150 to 499 mg/dL; LDL-c: 100 to 200 mg/dL), statin-free, overweight (BMI 27.0 to 40.0 kg/m^2), male and female subjects investigating the safety, tolerability, and PK of multiple doses of LY3202328 and the effect of LY3202328 on simvastatin and atorvastatin exposure.

A total of 40 subjects will be enrolled and divided evenly into 4 study periods (n=10 subjects per study period) to evaluate 4 dose levels of LY3202328 (Periods 5, 6, 7, and 8 at 5, 20, 100, and 300 mg, respectively, are planned).

Within each cohort, 5 subjects will be stratified to the simvastatin DDI assessment and 5 subjects will be stratified to the atorvastatin DDI assessment. Within each stratum subjects will be randomly assigned 4:1 to receive LY3202328 or placebo so that 8 subjects will receive LY3202328 and 2 subjects receive placebo in each cohort. Subjects will receive QD dose of LY3202328 or placebo in the morning in the fasted state for 29 total days. For DDI assessment, subjects will also receive a single atorvastatin or simvastatin dose a week prior to LY3202328 treatment initiation, and on Day 29 after initiation of LY3202328 daily dosing (coadministered with LY3202328).

The dose levels intended for study in Part B may change based upon data from Part A, but will range from as low as 1 mg and are not to exceed the highest dose evaluated in Part A. Any dose level used in Part B will not start until the safety data from the same or higher dose level in Part A has been reviewed by the safety committee responsible for dose escalation decisions.

Potential subjects will be screened to assess their eligibility to enter the study within 42 days prior to study entry (i.e., prior to Check in for Part B). For each cohort, subjects will be admitted to the CRU on Day –8 (the day before administration of a single dose of simvastatin or atorvastatin) and will be discharged 24 hours postdose (Day –6).

Subjects will be confined to the CRU from Day –2 to Day 2 (48 hours postdose) for initial dosing with LY3202328 and are required to return to the CRU for dosing and PK sampling the mornings of Days 7, 14, and 21. Prior to discharge from the CRU on Day 2, subjects will receive a labeled container with doses of LY3202328 that subjects will self-administer daily at home until the next morning visit at the CRU. Subjects will be instructed to take the drug QD in the morning in the fasted state and wait at least 60 minutes after the completion of dosing prior to commencing their breakfast. Subjects will be given diaries to record the time of their self-administered doses, whether the dose was administered with food or fasted, and the time of commencing the breakfast meal. Subjects must return the container (empty or not) and their diary at the next morning visit. Home dosing will be monitored via attempted phone calls when subjects will be reminded to take their medication and queried about the occurrence of AEs. Subjects should be instructed to take their dose at approximately the same time they received their first dose. Subjects will again be confined to the CRU on Day 27 (2 days before coadministration of LY3202328 or placebo with simvastatin or atorvastatin on Day 29) to Day 30 (24 hours post-coadministration of LY3202328 or placebo with simvastatin or

atorvastatin). Subjects will return to the CRU on Days 35 and 56 (168 and 672 hours postdose, respectively) for follow-up assessments.

The dose levels intended for study in Part B will be within the range of those tested in Part A. Specific dose levels will be selected after review of Part A data. Doses may range up to 300 mg or the maximum tolerated dose established in SAD Part A.

6.2. Number of Participants

Eighteen healthy males and female subjects may be enrolled in Part A where each subject is scheduled to receive 2 single doses of LY3202328 and 1 dose of placebo in ascending dose levels. Forty subjects may be enrolled in Part B (8 subjects will receive LY3202328 and 2 subjects will receive placebo in each of 4 dose level cohorts). Additional subjects may be enrolled to replace drop-outs or discontinued subjects, but are not required. Replacement subjects may complete any portion of the study as needed, i.e. any portion not completed by the discontinued subject with the goal to complete up to 18 subjects in Part A and up to 40 subjects in Part B. The decision to replace subjects will be discussed with the Sponsor prior to adding subjects.

6.3. End of Study Definition

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

6.4. Scientific Rationale for Study Design

The purpose of this study is to evaluate the safety, tolerability, PK, and degree of target inhibition (PD) of LY3202328 when administered orally as single doses to statin-free, overweight, healthy subjects (Part A) and as multiple doses (with a statin DDI assessment) to statin-free, overweight, dyslipidemic subjects (Part B).

For Part A, a standard single-dose, double-blind, randomized, placebo–controlled, SAD crossover design will be used. A randomization schedule for treatment sequence assignment will be used to reduce the potential for selection bias. For Part B, a double-blind, randomized, placebo–controlled, sequential MAD design will be used. The data obtained from this study will help establish the doses suitable for administration to patients with dyslipidemia and the possible existence of a DDI between LY3202328 and simvastatin and/or atorvastatin prior to studies in patient populations on stable treatment.

The selection of healthy subjects is appropriate and consistent with standard practices for an early phase clinical pharmacology study. The inclusion and exclusion criteria are chosen to select subjects who are known to be free from any significant illness. A placebo is included to enable characterization of AEs by serving as a negative control. LY3202328 is not anticipated to provide any benefit to the study subjects, and therefore the use of placebo will not deprive subjects of any benefit.

6.5. Justification for Dose

Human PK/PD modeling and preclinical absorption, disposition, metabolism, and excretion (ADME) profiles in rat, dog, and primate were used to predict that LY3202328 should achieve a sustained average ED_{80} concentration in man with an oral dose of 13 mg QD. This projected human dose compares favorably with the projected maximum absorbable dose of 190 mg determined using GastroPlus modelling of rat, dog, and monkey ADME profiles. In chronic lipid lowering studies, LY3202328 produced dose-dependent inhibition of LDL-c (61%), ApoB (53%), ApoC3 (43%), and PCSK9 (55%) in plasma, as well as liver TG (37%) in LDLr KO mice, and reduced liver TG (56%) in C57Bl/6 mice on a high fat diet. Finally, body surface area dose and predicted AUC exposure multiples are greater than 195x in GLP rat and dog toxicology studies relative to the predicted efficacy dose/exposure, and greater than 13x relative to the highest planned human dose of 300 mg. The proposed dose range for this first-in man-study of 1 to 300 mg of LY3202328 administered orally QD for up to 28 days was selected based on toxicology studies and modeling of PK/PD data from nonclinical studies of LY3202328, and the established margin of safety.

The nonclinical no-observed-adverse-effect level (NOAEL) doses and AUC values for LY3202328 following daily administration compared with planned human doses and projected human exposures are presented in Table GSEA.1.

Table GSEA.1. Margin of Safety for Oral Administration of LY3202328 Based on Administered Dose and Predicted Exposure

	Dose (mg)	Dose (mg/kg)	HED (mg/kg)	Dose Multiple[a]	AUC (µg•h/mL)[b]	Exposure Multiple[a]
Human[c]				–		–
Starting dose	1	0.0143	0.0143		0.6	
Efficacy dose	13	0.186	0.186		7.8	
Highest dose	300	4.29	4.29		114	
Rat NOAEL[d]		500	80.6		1710	
Starting dose				5600x		2850x
Efficacy dose				433x		219x
Highest dose				19x		15x
Dog NOAEL[e]		250	139		1520	
Starting dose				9700x		2533x
Efficacy dose				747x		195x
Highest dose				32x		13x

Abbreviations: AUC = area under the plasma concentration x time curve; HED = human equivalent dose based on body surface area; NOAEL = no-observed-adverse-effect level.

[a] Dose multiple is the dose in animal HED/human dose based on mg/kg^2 using Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, FDA/CDER, July 2005. Exposure multiple is the calculated as AUC in animals/predicted AUC in humans.

[b] Predicted human AUC over 24 hours upon repeat once daily dosing, based on predicted human pharmacokinetics mentioned in Section 5.1.8 of the Investigators Brochure. Note: human predicted AUC listed at a dose of 300 mg accounts for the expected absorption limitation, resulting in a maximum absorbable dose of 190 mg.

[c] Clinical dose based on 70-kg human.

[d] NOAEL determined in a 28-day repeat dose rat toxicity study. AUC is mean of male and female data at the end of the study (Study 8327-151).

[e] NOAEL determined in a 28-day repeat dose dog toxicity study. AUC is mean of male and female data at the end of the study (Study 8327-163).

7. Study Population

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

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

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

7.1. 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 healthy males or females, as determined by medical history and physical examination

- male subjects:
  - agree to use a reliable method of birth control during the study and 3 months following the last dose of the investigational product. Acceptable methods of birth control may include: 1) condom with spermicide; 2) Diaphragm with spermicide; or 3) female condom with spermicide.
- female subjects:
  - postmenopausal women include women with either:
    - spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa and not taking medications that induced amenorrhea (for example: oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy; or
    - spontaneous amenorrhea for 6 to 12 months and a follicle-stimulating hormone (FSH) level greater than 40 mIU/mL; or
    - women with a prior history of hysterectomy or bilateral oopherectomy have to be at least 40 year of age and FSH >40 mIU/mL.

[2] are at least 18 to 70 years old inclusive (for males), or 40 to 70 years old, inclusive (for females), at the time of study entry.

[3] are on a stable diet and exercise regimen for >3 months prior to screening.

[4] have a BMI of 25.0 – 35.0 (Part A) or 27.0 – 40.0 kg/m^2 (Part B) , inclusive, at screening.

[5] have a fasting TG between 150 and 499 mg/dL, inclusive, at screening (allowed but not required in Part A; required for Part B only).

[6] have a fasting LDL-c between 100 and 200 mg/dL inclusive, at screening (allowed but not required in Part A; required for Part B only).

[7] have clinical laboratory test results within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator. However, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase (ALP) have to be ≤1.5 × upper limit of normal (ULN); total bilirubin has to be within normal limit, unless in subjects with Gilbert's Syndrome; thyroid stimulating hormone (TSH) <ULN.

[8] estimated glomerular filtration rate ≥60 mL/minute/1.73m^2 with no proteinuria (defined as 1+ or greater on urine dipstick).

[9] are normotensive (defined as supine systolic blood pressure [BP] <150 mm Hg and diastolic BP <100 mm Hg). Subjects with controlled hypertension who are taking ACE-I (Lisinopril or captopril) or other antihypertensive agents not metabolized through the CYP3A4 may be considered. Blood pressure may be retested up to 2 additional times, under well-rested conditions.

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

[11] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[12] have given written informed consent approved by Chorus and the Ethical Review Board (ERB) governing the site.

7.2. Exclusion Criteria

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

[1] are taking a statin, any PCSK9 medications, or have started taking other TG lowering agents (e.g., niacin, fish oils) within the last 3 months. Subjects on stable background (>3 months) of non-statin TG lowering agents may be included in the study.

[2] are investigator site personnel directly affiliated with this study or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[3] are Chorus (Lilly) or CRO-site employees.

[4] are currently enrolled in a clinical trial involving an investigational product or off-label use of a drug or device, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[5] have participated (defined as last dose of study drug) in a clinical trial involving an investigational product or non-approved use of a drug within the last 30 days or within 5 half-lives, whichever is longer.

[6] have an abnormality in the 12-lead ECG, including corrected QT (QTc) interval with Bazett's correction >450 msec for men and >470 msec for women or an abnormality that, in the opinion of the investigator, increases the risks associated with participating in the study. ECGs may be repeated after 5 minutes resting quietly if the subject's heart rate is >75 bpm.

[7] have uncontrolled hypertension, or at screening a resting supine systolic BP of >150 mmHg or diastolic BP of >100 mmHg, confirmed after 5 minutes in the supine and resting state.

[8] have any current or prior history of significant cardiovascular disease, including acute myocardial infarction, unstable angina, congestive heart failure, cardiomyopathy or cardiomyositis. Subjects with clinically significant arrhythmia, including but not limited to atrial fibrillation, supraventricular/ventricular tachycardia, atrial-ventricular block, or sick sinus syndrome should also be excluded. Subjects with asymptomatic sinus arrhythmia, sinus bradycardia, or mild sinus tachycardia may be enrolled.

[9] show evidence of hepatitis C virus (HCV) and/or positive HCV antibody.

[10] show evidence of hepatitis B virus and/or positive hepatitis B surface antigen.

[11] have evidence of other chronic liver disease, including but not limited to chronic alcoholic disease, cirrhosis of any cause, or recent history (within 3 months of screening) of acute viral hepatitis or chronic autoimmune hepatitis. Subjects with history of biliary disease, including primary sclerosing cholangitis, must be excluded. Subjects with history of cholecystectomy longer than 6 months prior to visit 1 could be enrolled.

[12] have an alcohol intake that exceeds 7 units per week with no more than 3 units per day, or are unwilling to stop alcohol consumption for the duration of the study (1 unit = 12 ounces or 360 mL of beer; 5 ounces or 150 mL of wine; 1.5 ounces or 45 mL of distilled spirits).

[13] have a history of untreated endocrine illness such as diabetes mellitus, growth hormone insufficiency / acromegaly, adrenal gland, or thyroid illness.

[14] have been on medications or supplements for weight loss within 3 months of screening.

[15] have a history of active neuropsychiatric disease or are on pharmacological therapy for such conditions within 1 year of screening or have taken any antidepressants or antipsychotics within 3 months of screening for non-psychological indications.

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

[17] have had any major surgery within 30 days prior to screening or have planned elective surgeries to occur during the study.

[18] have a history or current presence of other cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, autoimmune, hematological (including any coagulopathy), neoplastic, or neurological disorders (Part B only) capable of significantly altering the absorption, metabolism, or elimination of drugs; or constituting a risk when taking the study medication; or of interfering with the interpretation of data. Basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease may be allowed.

[19] have been on medications that are known to inhibit CYP3A4 or P-glycoprotein (P-gp), or regularly consume grapefruit or grapefruit juice within 2 weeks of screening.

[20] are regular users of known drugs of abuse and/or show positive findings on urinary drug screening.

[21] are women who are pregnant or lactating.

[22] have donated blood of more than 500 mL within the last month, or have intention for blood donation during the study period.

[23] smoke >10 cigarettes per day or are unwilling to follow the CRU smoking rules.

[24] are unsuitable for inclusion in the study in the opinion of the investigator or sponsor.

[25] have proteinuria (defined as 1+ or greater on urine dipstick) at screening.

7.3. Lifestyle and Dietary Requirements

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

7.3.1. Meals and Dietary Restrictions

While confined at the CRU, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities. When not at the study site, subjects will be asked to take regular meals and avoid major deviations from their usual regimen and habits. Subjects are prohibited from consuming grapefruit or grapefruit juice during the entire duration of the study.

At required time points, subjects will be served high-fat/high-calorie lunch which must be consumed within 20-25 minutes. For subjects participating in the food effect period, a high-fat lunch will not be given. However, subjects will be required to consume a high-fat/high-calorie breakfast 30 minutes before study drug dosing. Both meals should be fully consumed by the subject.

A high-fat/high-calorie meal must contain approximately 60% fat, 20% carbohydrate, and 20% protein.

7.3.2. Caffeine, Alcohol, and Tobacco

Subjects will abstain from consuming alcohol-containing products for the duration of the study. Subjects are required to maintain their regular intake of caffeine- or xanthine-related beverages for the duration of the study.

While confined at the CRU, subjects are required to adhere to the CRU smoking and caffeine policy during the inpatient treatment days. Subjects should otherwise not intentionally change their consumption of tobacco- or caffeine-containing products during the study.

7.3.3. Activity

Subjects will refrain from strenuous exercise during the period of confinement at the CRU and will otherwise maintain their normal level of physical activity throughout the entire study (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

7.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened. Subjects who do not meet clinical laboratories inclusion/exclusion criteria may be reevaluated once. Screening of fasting triglycerides may be repeated for subjects with initial screening triglycerides of 140 to 150 mg/dl. The mean of the two values must be ≥ 150 mg/dl (following usual rounding rules) for inclusion.

8. Treatment

8.1. Treatment Administered

This study involves a comparison of LY3202328 to placebo when administered orally as a single dose in Part A and when administered in multiple doses both with and without a statin (simvastatin or atorvastatin) in Part B. Table GSEA.2 shows the treatment regimens.

In Part A, LY3202328 or placebo will be administered orally in the morning of Day 1 with approximately 240 mL of room temperature water in a sitting position. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

In Part B, all study drugs will be administered orally in the morning with approximately 240 mL of room temperature water. Simvastatin or atorvastatin will be administered on Day –7. LY3202328 or placebo will be administered QD on Days 1 to 29 while confined to the CRU (on Days 1 to 3, 7, 14, and 21) or at home. Simvastatin or atorvastatin will be coadministered with LY3202328 or placebo on Day 29 while subjects are confined to the CRU. Investigators should instruct subjects to store the LY3202328 or placebo capsules at home in the original container out of the reach of children at room temperature. Capsules should not be opened, crushed, or dissolved.

Table GSEA.2. Treatments Administered

Treatment Name	LY3202328	Placebo	Simvastatin	Atorvastatin
Dosage Formulation	HPMC capsule	HPMC capsule	Commercial	Commercial
Unit dose strength(s)/ Dosage Level(s)	1, 5, or 50 mg LY Part A: 1, 3, 10, 30, 100, or 300 mg Part B: 5, 20, 100 or 300 mg	Inactive	10 mg	10 mg
Route of Administration	Oral	Oral	Oral	Oral

Abbreviations: LY = LY3202328; HPMC = hydroxypropyl methylcellulose.

The investigator or designee is responsible for:

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

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

8.1.1. Packaging and Labeling

The drug product LY3202328 is supplied for clinical trial use as capsules and is composed of LY3202328 drug substance filled directly into hydroxypropyl methylcellulose capsules without additional ingredients. Each capsule is manufactured to contain LY3202328 equivalent to either 1, 5, or 50 mg of the free basic compound.

Placebo capsules look identical but contain no active ingredient and will be provided in similar packaging.

Simvastatin (Zocor®) and Atorvastatin (Lipitor®) will be obtained by the CRU as commercially available.

Clinical trial materials will be labeled according to the country's regulatory requirements and stored under ambient temperature conditions of 15°C to 30°C.

8.2. Method of Treatment Assignment

Subjects who meet all criteria for enrollment during Part A will be assigned to a randomization sequence number by the CRU on Day –1 within Cohort 1 (1, 10, and 100 mg) or Cohort 2 (3, 30, and 300 mg) that corresponds to 1 of the 3 treatment sequences in a 1:1:1 ratio so that 6 subjects receive LY3202328 and 3 subjects receive placebo, per dose level if all subjects are retained on study. The 30 mg dose level in Cohort 2 will be repeated in Period 4 to evaluate food effects on exposure.

Subjects who meet all criteria for enrollment during Part B will be stratified evenly to the simvastatin DDI assessment and the atorvastatin DDI assessment and assigned a randomization number on Day –7 of Part B for each cohort (Cohorts 3, 4, 5, and 6 at 5, 20, 100, and 300 mg, respectively, planned) in the order in which they were enrolled into the study. For each cohort, subjects will be randomly assigned 4:1 to receive LY3202328 or placebo within each stratum.

Randomization for Parts A and B will be performed in accordance with the randomization schedule generated by Chorus (or designee).

8.2.1. Selection and Timing of Doses

Study treatment will be administered as shown in the Schedule of Events (Appendix 2).

All doses in Parts A and B should be administered in the morning under fasted conditions (12 hours), except for food effect Period 4 in Part A, which will be administered in the fed state. All doses should be administered at approximately the same time on each day for Part B (on Days 2 to 29, within ±1 hour of dosing time of Day 1). In Part B, subjects will receive standard meals at appropriate times when confined to the CRU or during return visits for dosing. At least 60 minutes should separate the ingestion of the dose and the beginning of the breakfast meal while confined to the CRU and at home. Additionally, subjects will be asked to document time

of dosing and time of first meal in a diary and keep their standard diet when at home. A high-fat lunch meal will be administered 4 hours postdose in each period of Part A (with exception of Period 4) and on Days –1 and 28 in Part B to measure the post-prandial lipid profiles.

The actual time of all dose and initial meal administrations in the CRU will be recorded in the subject's case report form (CRF) and from the diary entries for the at-home dosings.

8.3. Blinding

Blinding will be maintained throughout the conduct of the study until all data are cleaned and the databased has been locked. Chorus may review interim unblinded data, the details of which will be included in the Blinding/Unblinding Plan. The simvastatin and atorvastatin dosing in Part B is planned to be an unblinded element of this study.

Emergency codes will be available to the investigator and pharmacy. A code, which reveals the treatment 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 Chorus 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. A subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Chorus CRP prior to unblinding a study subject's treatment assignment unless this could delay emergency treatment of the subject. If a study subject's treatment assignment is unblinded, Chorus must be notified immediately.

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

8.3.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the maximum tolerated dose (MTD) is determined. The highest dose level that is tolerated will be designated as the MTD. Doses in Part B will not exceed the MTD dose determined in Part A.

Safety data will be the primary criteria for the dose escalation. Dose escalation cannot occur without prior discussion and agreement between the investigator and the Chorus CRP.

Safety data, in particular AEs, serious adverse events (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, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for the next cohort. The magnitude of the dose escalation may be

reduced following DRM, but subsequent escalations cannot be increased by more than approximately 3 fold (a half-log increment).

For dose escalation decisions safety data from at least 6 subjects completing Day 5 procedures from each dosing period in Part A will be reviewed prior to escalating to the next dosing level. For Part B, safety data from at least 8 subjects completing Day 14 safety procedures will be reviewed prior to escalating to the next dosing level.

8.4. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer study treatment. All study treatments should be stored at the site 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).

Subjects will be given instructions and take home diary's to record dosing times and initiation of the first meal after dosing as described in Section 8.2.1.

8.5. Treatment Compliance

In Part A, LY3202328 or placebo will be administered at the CRU under the supervision of the investigator. As a result, subject compliance will be ensured.

In Part B, simvastatin and atorvastatin will be administered at the CRU under the supervision of the investigator. As a result, subject compliance will be ensured. LY3202328 or placebo will be administered at the CRU (on days of confinement) and subjects will also self-administer LY3202328 at home between study visits. Compliance will be assessed by subject diary entries, direct questioning, and enumeration of returned capsules.

Subjects who are significantly noncompliant in Part B will be discontinued from the study. The subject must take ≥80% of the intended dose to be deemed compliant with study drug administration. Similarly, a subject will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication (≥120% of the intended dose taken in a visit interval).

Study medication administration data and deviation(s) from the prescribed dosage regimen should be recorded in the subject's CRF.

8.6. Concomitant Therapy

Subjects on stable concomitant medication allowed by inclusion/exclusion criteria and/or through prior consultation with the Chorus Medical Monitor at the time of study entry should continue their regular, unchanged dose throughout the study. Subjects on oral or injectable diabetic medications are excluded from the study.

Drugs that are known inhibitors of CYP3A4 (e.g. Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) or P-gp are specifically excluded. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

If the need for concomitant medication arises for the treatment of minor AEs, the following medication may be administered by the investigator without consultation of Chorus CRP.

- Paracetamol as needed: <2000 mg/day.
- Topical medication for minor dermatological conditions.
- Stool softeners.

All additional medication used during the course of the study must be documented on the subject's CRF.

8.7. Treatment after the End of the Study

8.7.1. Continued Access to Investigational Product

LY3202328 will not be made available after conclusion of the study to subjects who participate in this study.

9. Discontinuation Criteria

9.1. Discontinuation from Study Treatment

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

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN along with one of the following criteria
  - total bilirubin level >2 × ULN or
  - prothrombin time >1.5 × ULN or
  - the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 × ULN
- ALP >2.5 × ULN and total bilirubin >2 × ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Subjects who discontinue the investigational product early for any reason will have the end-of-study procedures (Day 5 for SAD; Day 56 for MAD) performed as shown in the Schedule of Events (Appendix 2).

9.1.1. 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 Chorus 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 Chorus CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

9.2. 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.
- Significant noncompliance with study drug administration.
- 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 requests to be withdrawn from the study.
- Sponsor Decision
  - the sponsor decides study participation should be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Subjects who discontinue the study early will have end-of-study procedures (Day 5 for SAD; Day 56 for MAD) performed as shown in the Schedule of Events (Appendix 2).

9.3. 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.

10. Study Assessments and Procedures

Appendix 2 lists the Schedule of events, detailing the study procedures and their timing.

Appendix 3 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.

Investigators must document their review of each laboratory safety report.

10.1. Efficacy Assessments

Efficacy will not be assessed in this study. Pharmacodynamics will be assessed as described in Section 10.6.

10.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Chorus 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.

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.

After the informed consent form (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 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 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 administration is discontinued as a result of an AE, study site personnel must report this to Chorus or its designee via CRF or designated data transmission methods.

10.2.1. 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
- events considered significant by the investigator based upon appropriate medical judgment

Study site personnel must alert Chorus, 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 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 Chorus.

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.

10.2.1.1. 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 identifies as related to investigational product or procedure. United States 21 CFR 312.32, European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. The sponsor/designee 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.

10.2.2. Complaint Handling

Chorus/designee 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 (or drug delivery system) so that the situation can be assessed.

10.3. Treatment of Overdose

Refer to the IB (Section 7.3.9) and/or Product Label (LY and/or comparator) for details regarding an overdose of investigational product.

10.4. Safety

10.4.1. Laboratory Tests

For each subject, laboratory tests detailed in Appendix 3 should be conducted according to the Schedule of Events (Appendix 2). When collections for clinical laboratory tests are scheduled at the same time point as ECG collections, ECGs must be recorded prior to any blood sampling.

10.4.2. Vital Signs

For each subject, vital signs measurements should be conducted according to the Schedule of Events (Appendix 2) and following the study specific recommendations included in an Appendix or the Manual of Operations for the study.

Respiratory rate (collected at Screening and, for Part B only, Day -1, Hour -1), BP, pulse, and temperature should be measured after at least 5 minutes supine.

Orthostatic BP and pulse rate will be obtained from each subjects at all specified vital sign collection time points in Part A and on Day –1 through study discharge at specified vital sign collection time points in Part B. Supine BP and pulse rate will be measured after the subject has been supine for at least 5 minutes; standing BP and pulse rate will be measured in triplicate at 1, 2, and 3 minutes after the subject has been standing.

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

10.4.3. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Events (Appendix 2) and the study specific recommendations included in a Manual of Operations for the study that will be maintained that the CRU.

When ECG collections are scheduled at the same time point as any other tests the order of collection will be as follows:

1) ECGs.
2) vital signs.
3) any clinical laboratory, PK, PD, or biomarker blood sampling.

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 Chorus, or its designee, as an AE via CRF or designated data transmission methods.

In Part A, a 12-lead digital ECG will be collected from each subject as a single tracing during Screening and in triplicate (spaced approximately 1 minute apart) at all other specified ECG collection time points. In Part B, ECGs will be collected as a single tracing during Screening and Day -2. Twelve-lead ECGs will be collected in triplicate on Day –1 through study discharge at specified ECG collection time points.

Subjects must be supine for at least 5 minutes prior to ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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 finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if 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 collection. Any new clinically relevant finding should be reported as an AE.

10.4.4. Safety Monitoring

The Chorus CRP/scientist, or designee, will monitor safety data throughout the course of the study.

Chorus will review SAEs within time frames mandated by company procedures to meet local regulatory requirements. The Chorus CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate, and periodically review:

- trends in safety data
- AEs of special interest here.

If a study subject experiences elevated ALT or AST ≥3 × ULN or ALP/GGT/elevated total bilirubin ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities (see Appendix 5). To ensure subject safety and compliance with regulatory guidance, the investigator is to consult with the Chorus designated CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (Appendix 4).

If anemia (defined as a hemoglobin or hematocrit below normal reference range in the laboratory) develops during dosing, additional evaluation with a peripheral blood film, reticulocyte count, haptoglobin, indirect bilirubin, and LDH will be implemented.

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.

10.5. Pharmacokinetics

At the visits and times specified in the Schedule of Events (Appendix 2), serial venous blood samples of approximately 4 mL each will be collected to determine the plasma concentrations of LY3202328, simvastatin (Part B only), and atorvastatin (Part B only). Blood samples for PK characterization will be collected after single- and multiple-dose administration and follow-up visits in Parts A and B. Trough concentrations over multiple days during Part B will also be assessed.

Sample timing may be adjusted based on information gained during the study, while the total number of samples described in the Schedule of Events (Appendix 2) will be planned. Up to 2 additional PK samples may be collected per period if needed and with appropriate documentation of rationale for the additional samples.

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

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

Urine samples will be collected and pooled over the 24 hour dosing period to determine the urine concentrations and for the characterization of renal clearance of LY3202328 in Part A. Total urine output for the appropriate period post investigational product administration will be collected, pooled, and refrigerated. A predose urine sample will be collected to serve as a blank. The final urine sample will be collected at a time that coincides with a PK sample. At the end of the collection period (24 hours), the total urine volume will be recorded. Urine samples will be used to determine creatinine, quantification of LY3202328, and urine creatinine measurements. Approximately 20 mL of urine from the 24-hour urine collection will be stored for potential LY3202328 metabolite identification and other exploratory testing (10 mL each). Although not currently planned, urine sample collection may be added to Part B depending on results obtained from Part A.

Remaining plasma and urine PK samples may also be stored for LY3202328 metabolite identification.

At the visits and times specified in the Schedule of Events (Appendix 2) venous blood samples of approximately 4 mL each will be collected to determine serum creatinine measurements.

10.5.1. Bioanalysis

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

Concentrations of LY3202328, simvastatin, and atorvastatin will be assayed using validated analytical methods. Samples collected from placebo-treated subjects in each period are not planned for analyses. Simvastatin and atorvastatin analyses will only occur on samples collected during the 24 hour post dosing periods starting on Day –7 and Day 29.

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).

10.6. Pharmacodynamics

Pharmacodynamic blood samples of approximately 10 mL will be collected in Parts A and B as specified in the Schedule of Events (Appendix 2).

Plasma TG, TC, and high-density lipoprotein cholesterol (HDL-c) (to calculate LDL-c and non-HDL-c) will be assessed in the fasted state for the first 4 hours postdose and then again during the post-prandial period following a high-fat meal administration at 4 hours postdose in Part B. Changes in these PD markers from baseline (Day –1) and Day 28 will be assessed at each dose level to find at least 1 dose level that shows evidence of target engagement by a decrease in fasting or post-prandial lipids.

The lipid lowering ability of LY3202328 in subjects with a statin-free background will be quantified by TG, TC, and HDL-c (to calculate LDL-c and non-HDL-c) in Parts A and B, and by LDL-c ultracentrifugation methods in Part B only.

10.6.1. Exploratory Biomarker Analyses

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

Plasma samples for exploratory biomarker research will be collected at the times specified in the Schedule of Events (Appendix 2). Fasting LDL-c, FFA, β-hydroxybutyrate, ApoB100, ApoC3, PCSK9, and Lp(a) measured at baseline (Day –1), Day 28, and Follow-up will be evaluated in Part B.

Samples will be retained for a maximum of 1 year after the last subject visit, or until testing is complete after the last subject visit for the study at a facility selected by Chorus or its designee.

10.7. Pharmacogenomic/Stored Samples

A blood sample will be collected for pharmacogenetic analysis in Part A and Part B as specified in the Schedule of Events (Appendix 2) where local regulations allow.

DNA will be isolated from the pharmacogenetic sample to test genetic polymorphisms that may affect:

- the absorption, disposition, metabolism, or excretion of LY3202328;
- response to LY3202328;
- adverse reactions to LY3202328;
- unusual response to LY3202328 (either safety or PD response; genome-wide association studies may be used); and/or
- dyslipidemia-related gene polymorphisms.

Additionally, the samples obtained from the biomarker collections in Parts A and/or B will be stored and may be used as follows:

- plasma and serum for biomarker analysis to help explore and understand the mechanism of action of LY3202328 and/or dyslipidemia; and
- residue plasma samples from lipid collections may be stored for exploratory testing of other lipid pathways.

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 response to LY3202328 and to investigate genetic variants thought to play a role in dyslipidemia. 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 (DNA) or 5 years (plasma and serum) 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 Chorus 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 LY3202328 or after LY3202328 is commercially available.

11. Statistical Considerations and Data Analysis

11.1. Sample Size Determination

Part A (SAD): 9 statin-free, overweight, healthy subjects for Cohort 1 and 2 (each subject to receive investigational product at 2 active dose levels and placebo) and a possible additional cohort (each subject to receive investigational product at 1 active dose level [600 mg] or placebo). This sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK parameters, and is not powered on the basis of statistical hypothesis testing.

Part B (MAD): 10 statin-free, overweight, dyslipidemic subjects per cohort (8 subjects to receive active investigational product: 2 subjects to receive placebo) is a customary sample size for a Phase 1b MAD study evaluating safety, tolerability, and PK parameters, and is not powered on the basis of statistical hypothesis testing.

Additional subjects may be enrolled at any time if agreed to by the Sponsor to replace drop-outs or discontinued subjects with the goal to complete up to 18 subjects in Part A and 40 subjects in Part B. Replacements are not required. Replacement subjects for Part A may not be required to complete all periods.

11.2. Populations for Analyses

The study population will consist of up to 18 statin-free, overweight, healthy male and female subjects in Part A and up to 40 statin-free, overweight, healthy male and female subjects with dyslipidemia in Part B, aged 18 to 70 years old, inclusive, for males, or 40 to 70 years old, inclusive, for females. Two analysis populations will be used in this study:

- The Safety population will include all subjects who receive at least 1 dose of LY3202328.
- The PK population will include all subjects who receive LY3202328 (and simvastatin or atorvastatin in Part B) and have sufficient concentration data to obtain reliable estimates of the key PK parameters (C_{max} and AUC).

11.2.1. Study Participant Disposition

A subject disposition flow diagram will be prepared that will summarize the disposition of all subjects entered into the study, including the number of subjects entered and enrolled into the study, and the number who received at least 1 dose of study treatment. Subjects who discontinued from the study will be summarized by their reasons.

11.2.2. Study Participant Characteristics

Demographic and baseline information will be summarized using descriptive statistics. For continuous variables, the mean, standard deviation (SD), median, minimum, and maximum will be presented. For categorical variables, the number of subjects, frequency, and percentages will be presented. Individual subject demographics and baseline information will be presented in data listings.

Concomitant therapy used during the study period will be listed and summarized by dose group.

11.2.3. Treatment Compliance

Compliance will be ensured for administration of LY3202328 in Part A and administration of LY3202328, simvastatin and atorvastatin in Part B, as study drug will be administered at the CRU under the supervision of the investigator.

Treatment compliance for LY3202328 in Part B will be ensured on days of subject confinement to the CRU and study visits, but will be assessed by comparing returned pills with dispensed pills (the percentage of the actual number of capsules taken versus the number of capsules expected to be taken) for dosing days while not confined to the CRU.

Subjects who demonstrated significant noncompliance (<80% or >120% of the intended dose taken in a visit interval) will also be summarized.

Study medication administration data and deviation(s) from the prescribed dosage regimen should be recorded in the subject's CRF.

11.3. Statistical Analyses

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

Pharmacokinetic/PD and safety analyses will be conducted on the PK and Safety populations, respectively.

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

11.3.1. Safety Analyses

11.3.1.1. Clinical Evaluation of Safety

All LY3202328 and protocol procedure AEs will be listed, and, if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to study entry 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 current medical regulatory dictionary. Severity of the AE will be assessed according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007".

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

11.3.1.2. Statistical Evaluation of Safety

The primary endpoint of this study is the number and severity of treatment-emergent adverse events (TEAEs), clinical laboratory abnormalities, changes in vital sign measurements, and other safety endpoints after administration of LY3202328 or placebo. Summary statistics will be provided by dose group and for all study subjects combined wherever appropriate. For

continuous variables, summary statistics will include number of subjects, mean, median, SD, minimum, and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Additional analysis will be performed if warranted upon review of the data.

11.3.2. Pharmacokinetic Analyses

Pharmacokinetic parameter estimates for LY3202328, simvastatin (Part B only), and atorvastatin (Part B only) in plasma will be calculated by standard noncompartmental methods of analysis.

The primary PK parameters for analysis will be C_{max} and AUC. The primary AUC metric will be calculated AUC from time zero to infinity ($AUC_{0-\infty}$) on Day 1 (Parts A and B) and AUC during one dosing interval ($AUC_{0-\tau}$) on Day 28 of Part B of LY3202328 after single- and multiple-dose administrations (Parts A and B, respectively). If the half-life ($t_{1/2}$) was relatively long, $AUC_{0-\infty}$ may not be calculable for Day 1 of Part B, and would thus not be reported.

Other noncompartmental parameters, such as T_{max}, $t_{1/2}$, trough concentration (C_{trough}), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. Descriptive statistics of PK parameters will be presented with each dose.

Renal clearance of LY3202328 will be calculated as the ratio of amount excreted in urine/AUC. This will be compared to the unbound glomerular filtration rate, which is estimated using creatinine.

Pharmacokinetic parameter estimates (C_{max} and AUC) for LY3202328 will be evaluated to delineate effects of dose proportionality using a power model approach (Smith et al. 2000).

Drug-drug interaction assessment of the effect of LY3202328 coadministration on simvastatin and atorvastatin exposure will be conducted using ANOVA. Pharmacokinetic parameter estimates (C_{max} and AUC) for simvastatin and atorvastatin administered alone or coadministered with LY3202328 will be compared. The ratios of statin exposure with and without LY3202328 coadministration at different dose levels of LY3202328 will be estimated, along with their confidence intervals.

The impact of food on the rate and extent of absorption of LY3202328 will be assessed by estimating the ratio of C_{max} and $AUC_{0-\infty}$ in the fed and fasted state of at the same dose level. The ratio will be calculated within each subject, and then summarized for the group. Similarly, the difference in T_{max} between the fed and fasted will be calculated and summarized.

Other analyses, including PK modeling, may be conducted on the PK data.

11.3.3. Pharmacodynamic and Biomarker Analyses

The PD assessments conducted in this study are typical and appropriate for a Phase I single and multiple ascending dose evaluations of a novel therapeutic agent. The TG concentrations will be analyzed to evaluate evidence of target engagement and intended pharmacological benefits.

Visual and tabular summarization of all PD measurements will be done. For the endpoints in the primary or secondary objectives, a statistical analysis will also be conducted.

Mixed effect model repeated measure will be the default method of analysis for PD endpoints with time-course data. For endpoints with only baseline and end-of-therapy measurements, ANCOVA will be the default, with baseline as a covariate. Other covariates may be a priori defined and included in the model.

Normality assumption will be tested using an appropriate visual or statistical method, and, if it is violated, log transformation may also be performed on these data. The most sensitive analysis will be selected to test the effect of LY3202328 on the change from baseline in these PD data.

11.3.4. Interim Analyses

In Part A, interim analysis of PK will take place after collecting the 300 mg dosing group to determine if a 600 mg dose level will be conducted. In Part B, lipid assessments (triglycerides, LDLc, non-HDLc, and ApoB100) will be evaluated after completion of 20, 100, and 300 mg dose levels and reviewed by Chorus unblinded staff. No other interim analyses are planned for this study, however pharmacokinetic data may be reviewed at anytime it becomes available.

Select individuals may gain access to unblinded data, prior to the interim or final database lock, in order to initiate some analysis activities. In such a case, the individuals and unblinded data will be specified in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

12. References

1. Chorus. DGAT2 inhibitor LY3202328 investigator's brochure, 1st ed. Indianapolis, (IN); 2016.
2. European Medicines Agency. Committee For Medicinal Products For Human Use. Guideline on strategies to identify and mitigate risks for first-inhuman clinical trials with investigational medicinal products. September 2007. [Accessed 20 December 2015]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf.
3. Manchem P, Yu XX, Mullick A, Booten S, Murray S, Watts LM, Monia BP, Bhanot S. Antisense reduction of DGAT2 reduces body weight and improves dyslipidemia in high-fat high-cholesterol diet fed LDLr knockout mice. American Diabetes Association Annual Meeting 2010;448-PP.
4. Smith BP, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT, Forgue ST. Confidence interval criteria for assessment of dose proportionality. *Pharm Res.* 2000;17(10):1278-1283.

Appendix 1. Abbreviations and Definitions

Term	Definition
ADME	absorption, disposition, metabolism, and excretion
AE	adverse event: Any untoward medical occurrence in a 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
Apo	apolipoprotein
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	AUC from time zero to infinity
$AUC_{0-\tau}$	AUC during one dosing interval
blinding	A procedure in which one or more parties to the trial 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/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
BP	blood pressure
CL/F	apparent clearance
C_{max}	maximum plasma 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 trial-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 Chorus 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.
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
C_{trough}	trough concentration
CV	cardiovascular
CYP	cytochrome P450
DDI	drug-drug interaction
DGAT2	diacylglycerol acyltransferase 2
DRM	Data Review Meeting
ECG	electrocardiogram
ED_{80}	80% maximal effective dose
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
FFA	free fatty acids
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HDL-c	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial 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.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
KO	knockout
LDL-c	low-density lipoprotein cholesterol
LDLr	low-density lipoprotein receptor
Lp(a)	Lipoprotein (a)
MAD	multiple ascending dose(s)
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic
P-gp	p-glycoprotein
PK	pharmacokinetic
QD	once daily
QTc	corrected QT
SAE	serious adverse event
SAD	single ascending dose(s)
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 trial.
SD	standard deviation

SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TC	total cholesterol
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 to reach maximum plasma concentration
TG	triglyceride(s)
TSH	thyroid stimulating hormone
ULN	upper limit of normal
V/F	apparent volume of distribution

Appendix 2. Schedule of Events for Protocol I8Q-MC-GSEA

Appendix Table GSEA.1 Schedule of Events for Protocol I8Q-MC-GSEA: Part A (SAD)

Study Procedures[a]		Study Days															
Day	Screening[b]	C–1[c]	1												2	3	5
Hour			-0.5[s]	0	0.5	1	2	3	4	4.5	5	6	8	12	24	48	96
Administrative Procedures																	
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Medical history	X																
Safety Evaluations																	
Full physical examination[d]	X	X													X	X	X
Height & weight	X																
12-lead ECG[e]	X[e]	X		X[f]			X		X			X	X	X	X	X	X
Vital signs[g]	X	X					X		X				X		X	X	X
Clinical laboratory tests[h]	X			X[f]											X	X	X
Serum pregnancy test[i]	X	X															
Serum FSH test[i]	X																
Alcohol/drug screen	X	X															X
HIV/hepatitis screen	X																
Urine & serum creatinine		X															
AE monitoring	X	X															
Conmed monitoring	X	X															
Dosing/PK/PD/Pharmacogenomics																	
Serum TG, TC, HDL-c[j,k]				X[f,l]					X[m]	X	X	X	X		X[l,m]	X[l,m]	X[l,m]
Urine PK collection			X	X	X												
LY/placebo dosing				X[n]													
PK blood sample[k]				X[f]	X	X	X	X	X			X	X	X	X	X	X
Pharmacogenomic sample[o]			X														
Biomarker sample[p]			X												X		
Other																	
Confined at the CRU		X[q]															
Meal at the CRU		X							X[r]				X		X	X	X
CRU Visit	X															X	X

Abbreviations: AE = adverse events; C–1 = Check-in; CRU = clinical research unit; Conmed = concomitant medication; ECG = electrocardiogram; FSH = follicle stimulating hormone; HDL-c = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-c = low-density lipoprotein cholesterol; LY = LY3202328; PD = pharmacodynamic; PK = pharmacokinetics; TC = total cholesterol; TG = triglycerides.

[a] Refer to Section 10 of the protocol for details on study procedures.

[b] Screening to occur within 42 days of first study drug administration.

[c] Subjects will be admitted on Day –1 prior to dinner to control fasting times for Day 1 dosing.

[d] A full physical examination will be performed on the scheduled days. Symptom-driven physical examination may be performed at other times, at the investigator's discretion.

[e] Single 12-lead ECGs to be collected during Screening, triplicate ECGs (spaced approximately 1 minute apart) to be collected at all other time points. Subjects must be supine for at least 5 minutes prior to ECG collection. When ECG collections are scheduled at the same time point as any other tests, ECGs, followed by vital signs, must be recorded prior to any clinical laboratory, PK, PD, or biomarker blood sampling.

[f] Collection to occur prior to dosing.

[g] Vital signs to be measured include respiratory rate (Screening only), blood pressure, pulse rate, and temperature. Orthostatic blood pressure and pulse rate to be measured at all specified time points.

[h] Refer to Appendix 3 for the serum chemistry, hematology, and urinalysis clinical laboratory tests.

[i] Serum pregnancy tests to be performed on female subjects only; serum FSH tests to be performed on postmenopausal female subjects only.

[j] Serum TC, TG, and HDL-c will be measured; HDL-c will be used to calculate LDL-c and non-HDL-c.

[k] Any leftover plasma will be stored for residual or LY3202328 metabolite assessment, after all study related needs are met.

[l] Samples for serum chemistry will be obtained following a fast of at least 12 hours when a fasting lipid assessment is being performed at the same time. In case of dropouts or rechecks, subjects may not have fasted for 8 hours or 12 hours, as applicable, before the serum chemistry sample is taken.

[m] Sample collection to occur just prior to meal.

[n] LY3202328/placebo dosing will occur in the fasted state in all periods except the food effect period. Subjects being assessed for food effects on exposure will be given a high-fat/high-calorie meal prior to dosing during the food effect arm in Period 4.

[o] A blood sample from all randomized/enrolled subjects will be collected prior to Day 1 dosing.

[p] Biomarker plasma and serum collection (10 mL) should be sufficient for determination of ApoB48, lathosterol, lanosterol, desmosterol, among other biomarkers of interest.

[q] Subjects will be discharged following Hour 24 procedures (i.e., Day 2).

[r] A high-fat/high-calorie meal (containing approximately 60% fat, 20% carbohydrate, and 20% protein) will be given to subjects to 4 hours postdose for the post-prandial lipid assessment in all periods except for subjects in the food effect arm of Period 4.

[s] Assessments can be performed any time predose

Appendix Table GSEA.2 Schedule of Events for Protocol I8Q-MC-GSEA: Part B (MAD)

Study Procedures[a]		Study Days										
Day	Screening[b]	C–8[c]	–7									
Hour[d]			0[d]	0.5	1	2	3	4	6	8	12	24
Administrative Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Medical history	X											
Safety Evaluations												
Full physical examination[e]	X											
Height & weight	X											
Waist, neck, and hip circumference												
12-lead ECG[f]	X											
Vital signs[g]	X	X										X
Clinical laboratory tests[h,i]	X											
Fasting lipid panel[i]	X											
Serum pregnancy test[j]	X	X										
Serum FSH[j]	X											
Alcohol/drug screen	X	X										
HIV/hepatitis screen	X											
AE monitoring	X	X										
Conmed monitoring	X	X										
Dosing/PK/PD												
Simvastatin/atorvastatin dosing			X									
Simvastatin/atorvastatin PK blood sample			X	X	X	X	X	X	X	X	X	X
Other												
Confined at the CRU		X[k]										
Meal at CRU					X			X		X		X
Visit	X											

Appendix Table GSEA.2 Schedule of Events for Protocol I8Q-MC-GSEA: Part B (MAD) (continued)

Study Procedures[a]	**Study Days**									
Day	**C–2**[c]	**–1**								
Hour[d]		**-1**[y]	**0**[d]	**1**	**2**	**4**	**4.5**	**5**	**6**	**8**
Administrative Procedures										
Informed consent										
Inclusion/exclusion criteria	X									
Medical history										
Safety Evaluations										
Full physical examination[e]	X									
Height & weight		X								
Waist, neck, and hip circumference		X								
12-lead ECG[f]	X	X								
Vital signs[g]	X	X								
Clinical laboratory tests[h,i]		X								
Fasting lipid panel[i]		X								
Serum pregnancy test[j]	X									
Serum FSH[j]	X									
alcohol/drug screen	X									
AE monitoring	X									
Conmed monitoring	X									
Dosing/PK/PD										
Serum TG, TC, HDL-c[l]		X	X[m,n]	X	X	X[m]	X	X	X	X[m]
Fasting LDL-c, FFA, β-hydroxybutyrate, ApoB100[o]		X								
ApoC3, Lp(a), PCSK9, fasting insulin		X								
Pharmacogenomic sample[p]		X								
Biomarker sample[q]		X								
Other										
Confined at the CRU	X[k]									
Meal at CRU[r]	X					X[r]				X

Appendix Table GSEA.2 Schedule of Events for Protocol I8Q-MC-GSEA: Part B (MAD) (continued)

Study Procedures[a]	Study Days														
Day	1							2	3 to 6	7	8 to 13	14	15 to 20	21	22 to 27
Hour[d]	0	0.5	1	2	4	8	12	24/0	0	0	0	0	0	0	0
Safety Evaluations															
Full physical examination[e,h]	X														
Weight										X		X		X	
Waist, neck, and hip circumference										X		X		X	
12-lead ECG[f]					X			X		X		X		X	
Vital signs[g]	X				X			X		X		X		X	
Clinical laboratory tests[h,i]								X		X		X		X	
AE monitoring	X														
Conmed monitoring	X														
Dosing/PK/PD/Pharmacogenomics															
LY/placebo dosing at CRU	X							X		X		X		X	
LY/placebo dosing at home[t]									X		X		X		X
LY/placebo PK blood sample[s]	X[n]	X	X[m]	X	X[m]	X	X	X[m]		X[m,n]		X[m,n]		X[m,n]	
Serum TG, TC, HDL-c[l]										X[m,n]		X[m,n]		X[m,n]	
Fasting LDL-c, FFA, β-hydroxybutyrate, ApoB100[o]										X[m,n]		X[m,n]		X[m,n]	
ApoC3, Lp(a), PCSK9, fasting insulin												X[m,n]			
Biomarker sample[q]												X[m,n]			
Other															
Confined at the CRU	X														
Meal at CRU[u]			X		X	X		X		X		X		X	
Visit										X		X		X	

Appendix Table GSEA.2 Schedule of Events for Protocol I8Q-MC-GSEA: Part B (MAD) (continued)

Study Procedures[a]	Study Days														Follow-up	
Day	27	28											29	30	35[v]	56[v]
Hour[d]	0	–1[y]	0	0.5	1	2	4	4.5	5	6	8	12	24/0	48/0	168/0	336/0
Safety Evaluations																
Full physical examinations[e]	X															
Weight													X		X	X
Waist, neck, and hip circumference													X		X	X
12-lead ECG[f]					X		X				X		X		X	X
Vital signs[g]	X						X						X		X	X
Clinical laboratory tests[h,i]													X		X	X
Serum pregnancy test[j]	X															
alcohol/drug screen	X															
AE monitoring	X															
Conmed monitoring	X															
Dosing/PK/PD/Pharmacogenomics																
LY/placebo dosing at CRU			X										X			
Simvastatin/atorvastatin dosing at CRU													X			
LY/placebo PK blood sample			X[n]	X	X[m]	X	X[m]			X	X[m]	X	X[m,n]	X[m]	X[m]	X[m]
Simvastatin/atorvastatin PK blood sample													X[w]			
Serum TG, TC, HDL-c[l]		X	X[i,m,n]		X	X	X[m]	X	X	X	X[m]				X[m]	X[m]
Fasting LDL-c, FFA, β-hydroxybutyrate, ApoB100[o]			X[i,m,n]												X[m]	X[m]
ApoC3, Lp(a), PCSK9, fasting insulin			X[i,m,n]												X[m]	X[m]
Biomarker sample[q]			X[l]													X[m]
Other																
Confined at the CRU	X[x]															
Standardized meal at CRU[r]	X						X[r]				X		X	X	X	X
Within the CRU															X	X

Abbreviations: AE = adverse events; Apo = apolipoprotein; C –2, C –8 = Check‑in; CRU = clinical research unit; Conmed = concomitant medication; ECG = electrocardiogram; FFA = free fatty acid; FSH = follicle stimulating hormone; HDL-c = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-c = low-density lipoprotein cholesterol; Lp = lipoprotein; LY = LY3202328; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = pharmacodynamic; PK = pharmacokinetics; TC = total cholesterol; TG = triglycerides.

a Refer to Section 10 of the protocol for details on study procedures.

b Screening to occur within 42 days of first study drug administration.

c Subjects will be admitted on Day –8 (for simvastatin/atorvastatin dosing and PK), Day –2, and prior to dinner on Day 27, at the time indicated by the CRU.

d On Day –7 and –1, Hour 0 is defined as relative to Day 1 dosing time. On Days 1 to 28, Hour 0 is defined as the actual dosing time (for Days 2 to 28, within ±1 hour of dosing time of Day 1).

e A full physical examination with neurological assessments will be performed (predose) on the scheduled days. Symptom‑driven physical or neurological examination may be performed at other times, at the investigator's discretion.

f Single 12-lead ECGs to be collected during Screening and on Day –2. Triplicate ECGs (spaced approximately 1 minute apart) to be collected on Day–1. The decision to collect triplicate or single ECGs at all remaining time points will be made based on ECG data from Part A (triplicate ECGs are planned). Subjects must be supine for at least 5 minutes prior to ECG collection. When ECG collections are scheduled at the same time point as any other tests, ECGs, followed by vital signs, must be recorded prior to any clinical laboratory, PK, PD, or biomarker blood sampling.

g Vital signs to be measured include respiratory rate (Screening and Day –1, Hour –1 only) blood pressure, pulse rate, and temperature. Orthostatic blood pressure and pulse rate to be measured at all specified time points on from Day –1 to study discharge.

h Refer to Appendix 3 for the serum chemistry, hematology, and urinalysis clinical laboratory tests.

i Samples for serum chemistry will be obtained following a fast of at least 8 hours or 12 hours when a fasting simple lipid assessment (i.e., TC, TG and HDL-c) is will be performed at the same time. In case of dropouts or rechecks, subjects may not have fasted for 8 hours or 12 hours, as applicable, before the serum chemistry sample is taken. Lipid panel will also be assessed during the post-prandial lunch period on Days –1 and 28.

j Serum pregnancy tests to be performed on female subjects only; serum FSH tests to be performed on postmenopausal female subjects only.

k Subjects will be discharged following Hour 24 procedures (i.e., Days –6 and 2).

l Serum TC, TG, and HDL-c will be measured; HDL-c will be used to calculate LDL-c and non-HDL-c.

m Collection to occur just prior to meal.

n Collection to occur prior to the relative dosing time/prior to dosing.

o Low-density lipoprotein cholesterol for PD analysis will be evaluated by ultracentrifuge.

p A blood sample from all randomized/enrolled subjects will be collected prior to Day 1 dosing.

q Biomarker plasma and serum collection (10 mL) should be sufficient for determination of ApoB48, lathosterol, lanosterol, desmosterol, among other biomarkers of interest.

r A high-fat/high-calorie meal (approximately 60% fat, 20% carbohydrate, 20% protein) will be given to subjects to 4 hours postdose for the post-prandial lipid assessment.

s Any leftover plasma will be stored for residual or LY3202328 metabolite assessment, after all study related needs are met.

[t] Prior to release from the CRU, subjects will receive a properly labeled container with LY3202328 or placebo doses which will be self-administered by subjects at home until the next morning visit at the CRU. Subjects will be instructed to take the drug once daily in the morning in the fasted state and wait at least 60 minutes after the completion of dosing prior to commencing their breakfast. Subjects will be given diaries to record the time of their self-administered doses whether the dose was administered with food or fasted, and the time of commencing the breakfast meal. Subjects must return the container (empty or not) and their diary at the next morning visit. Home dosing will be monitored via attempted phone calls where subjects will be reminded to take their medication and queried about the occurrence of AEs. Subjects should be instructed to take their dose at approximately the same time they received their first dose.

[u] When confined in the CRU or during return visits for dosing, subjects will receive standard or high-fat meals at appropriate times. At least 60 minutes should separate the completion of ingestion of the dose and the beginning of the breakfast meal. While at home, subjects will be asked to keep their standard diet.

[v] Procedures to be performed at end of study or prior to early termination from the study. Subjects will be contacted for follow-up if the investigator deems necessary.

[w] Day 29 simvastatin/atorvastatin PK blood sample collection will follow the same schedule as Day –7 (predose [0], 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose).

[x] Subjects will be discharged on Day 30 after all assessments are completed.

[y] Assessments can be performed anytime predose.

Appendix 3. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]	Clinical Chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Magnesium
Cell Morphology	Glucose (fasting)
Absolute/relative/% counts of:	Blood urea nitrogen (BUN)
Neutrophils	Total cholesterol
Lymphocytes	Total protein
Monocytes	Albumin
Eosinophils	Total bilirubin
Basophils	Alkaline phosphatase (ALP)
Platelets	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis[a]	Creatinine
Specific gravity	Gamma-glutamyl transferase (GGT)
pH	
Protein	Additional tests (lipid panel, biomarker analyses)
Glucose	Apoliproprotein B100
Ketones	Apoliproprotein C3
Bilirubin	β hydroxybutyrate,
Urobilinogen	Free fatty acids (FFA)
Blood	Low-density lipoprotein cholesterol (LDL-c)
Nitrite	Lipoprotein (a)
	High-density lipoprotein cholesterol (HDL-c)
Ethanol testing[bc]	Insulin
Urine drug screen[bc]	Triglycerides (TG)
Hepatitis B surface antigen[b]	Proprotein convertase subtilisin/kexin type 9 (PCSK9)
Hepatitis C antibody[b]	
HIV[b]	
Pregnancy test (serum, in females only)	
Serum FSH (in postmenopausal females only)	
TSH (screening and Day 29 only)	
Serum and Urine Creatinine (Part A, Day -1 only)	

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells, TSH = Thyroid stimulating hormone.

a Results will be reported and/or validated by the Central Laboratory at the time of initial testing.

b Performed at screening only

c Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit.

Appendix 4. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the potential risks and benefits of participating in the study.
- 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 trial.

Ethical Review

The investigator must provide assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Chorus before the study may begin at the investigative site(s). Chorus 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
- ICFs
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance 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, (PPD , Chief Medical officer, Chorus) will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

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

Final Report Signature

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, Chorus or its representatives will do the following:

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

In addition, Chorus 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, Chorus, 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.

Study and Site Closure

Discontinuation of Study Site

Study site participation may be discontinued if Chorus, 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 Chorus judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 5. 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 Chorus or its designee CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serology[ab]**
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	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody (or anti-actin**
CPK	**antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Chorus-designated local laboratory.

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