Protocol I8D-MC-AZEB(a)

Effect of LY3314814 on the Pharmacokinetics of Rosuvastatin in Caucasian Healthy Subjects

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Confidential Information

LY3314814

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
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1. Protocol Synopsis

Title of Study:
Effect of LY3314814 on the Pharmacokinetics of Rosuvastatin in Caucasian Healthy Subjects

Rationale:
Rosuvastatin is a breast cancer resistance protein (BCRP; also known as ABCG2) substrate that is sensitive to BCRP activity in the gastrointestinal tract and liver. In vitro, LY3314814 has been characterized as a BCRP substrate and inhibitor. This study uses rosuvastatin as a substrate to evaluate whether LY3314814 is an inhibitor of BCRP activity in vivo.

Objectives/Endpoints:

Objectives	Endpoints
Primary The primary objective is to evaluate the effect of LY3314814 on the pharmacokinetics (PK) of rosuvastatin in healthy subjects.	The primary endpoint is the area under the drug concentration-time curve (AUC) from zero to infinity (AUC[0-∞]) of rosuvastatin administered alone and with LY3314814.
Secondary The secondary objectives are: • To assess the safety of LY3314814 when coadministered with rosuvastatin in healthy subjects; • To determine the effect of rosuvastatin on the PK of LY3314814.	Secondary endpoints include: • Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); • PK parameters of LY3314814 administered alone and with rosuvastatin: C_{max}, t_{max}, and AUC during a 24-hour dosing interval (AUC_{τ}).

Summary of Study Design:
Study I8D-MC-AZEB is a Phase 1, open-label, fixed-sequence, 2-period crossover study in Caucasian healthy male subjects and female subjects not of childbearing potential. Healthy males and females are as determined by medical history, physical examination, vital signs, clinical laboratory tests, and safety electrocardiograms. Subjects are to be 18 to 65 years of age, inclusive, with a body mass index between 19 and 32 kg/m^2, inclusive, at screening. Subjects with c.34AA, c.421AA, or c.34GA/ 421CA as well as c.521TC and c.521CC genotypes will be excluded from this study. Eligible subjects must lack evidence of significant active or previous neuropsychiatric disease, assessed by medical history, physical examination, and Columbia-Suicide Severity Rating Scale (C-SSRS).

Treatment Arms and Duration:
Subjects will receive a single oral dose of 20 mg rosuvastatin on Period 1 Day 1. In Period 2, subjects will receive oral doses of 50 mg LY3314814 once daily on Days 1 to 12 with a single 20-mg rosuvastatin oral dose coadministered on Day 8.

Number of Subjects:
Up to 42 subjects may be enrolled in order that 24 subjects complete the study.

Statistical Analysis:

Pharmacokinetic: Rosuvastatin administered alone (Period 1 Day 1) will represent the reference treatment and rosuvastatin coadministered with LY3314814 will represent the test treatment (Period 2 Day 8) for rosuvastatin PK analysis. Pharmacokinetic parameter estimates will be evaluated to delineate the effects of LY3314814 on rosuvastatin PK. Log-transformed AUC(0-∞) and C_{max} estimates for rosuvastatin will be analyzed using a linear mixed-effects analysis of variance model with treatment as a fixed effect and subject as a random effect. The ratios of geometric least squares means (ie, rosuvastatin + LY3314814 to rosuvastatin alone) will be calculated along with the 90% confidence interval (CI) for the ratios. The t_{max} for rosuvastatin will be analyzed using a nonparametric method; median differences of rosuvastatin + LY3314814 to rosuvastatin alone and the 90% CI for the median of differences will be calculated. A similar analysis will be performed to evaluate the effect of rosuvastatin on LY3314814, where LY3314814 administered alone (Period 2 Day 7) will be the reference treatment and LY3314814 coadministered with rosuvastatin will remain the test treatment (Period 2 Day 8). Additional analysis may be conducted if deemed appropriate.

Safety: All investigational product and protocol procedure adverse events 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. Each symptom will be classified by the most suitable term from the medical regulatory dictionary. The number of investigational product-related SAEs will be reported. Safety parameters that will be assessed include safety clinical laboratory parameters, vital signs, and C-SSRS. Orthostatic changes in vital signs will be assessed using change from supine to standing. The clinical laboratory parameters and C-SSRS data will be listed. Vital signs will be listed and summarized using standard descriptive statistics. Electrocardiograms will be performed for safety monitoring purposes and will not be presented. Additional analysis may be performed if warranted upon review of the data.

2. Schedule of Activities

Study Schedule Protocol I8D-MC-AZEB
Period 1

	Screening	Period 1							Comments
Procedure	Up to 45 days prior to enrollment	Day							
		-1	1	2	3	4	5	6	
Outpatient Visit	X								
Subject Admission to CRU		X							
Informed Consent	X								
Medical History	X								
Height and BMI	X								
Weight	X	X							
Drug and Alcohol Tests	X	X							
C-SSRS	X	X							
Estimated GFR	X								Estimated GFR will be calculated using the CKD-EPI equation.
Physical Exam		X							After screening exam on Period 1 Day -1, exams are to include only medical review and targeted examination, as appropriate.
Pregnancy Test		X							Pregnancy tests will be performed for all females.
Vital Signs (supine and orthostatic) (hours) [a]	X		P, 4, 8, 12	24	X	X	X	X	Vital signs include blood pressure and pulse rate. Body temperature will be obtained at screening and as clinically indicated. Sampling times are relative to the time of rosuvastatin administration (0 hour). Additional vital signs may be measured during each study period, if clinically indicated.
Clinical Lab Tests	X	X						X	See Appendix 2 for details. Results from sample on Period 1 Day -1 will be reviewed by the investigator prior to dosing on Period 1 Day 1. Tests may be repeated at the investigator's discretion.
OATP1B1, OATP521 T/TT, and BCRP Genotypes	X								Genotypes will be used to confirm subject eligibility. Subjects who meet all other screening eligibility criteria will return for a second screening visit, at least 21 days prior to enrollment, when samples will be collected for genotype analysis.
12-lead ECG	X	X							Additional ECGs may be obtained as clinically indicated.
Genetic Sample			P						Single sample for pharmacogenetic analysis.

	Screening	Period 1							Comments
Procedure	Up to 45 days prior to enrollment	Day							
		-1	1	2	3	4	5	6	
Rosuvastatin Administration			X						
Rosuvastatin PK Samples (hours) [a]			P, 1, 2, 3, 4, 5, 6, 8, 12	24	48	72	96	120	Sampling times are relative to the time of rosuvastatin administration (0 hour).
Biomarker Samples (hours) [a]			P, 1, 2, 3, 4, 5, 6, 8, 12	24	48	72	96	120	Samples for non-pharmacogenetic biomarker analysis.
AE Assessment	X	X							

Abbreviations: AE = adverse event; BCRP = breast cancer resistance protein; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; GFR = glomerular filtration rate; OATP = organic anion transporting polypeptide; P = predose; PK = pharmacokinetics.

[a] Specified times are approximate and actual times will be recorded. Actual sampling time should not exceed 1 hour prior to dosing for the predose sample or ±10% of the specified postdose sample time.

Study Schedule Protocol I8D-MC-AZEB
Period 2

	Period 2												Discharge/ Follow-up	Comments
Procedure	Day												≥7 days after final dose or ED	
	-1	1	2	3 to 5	6	7	8	9	10	11	12	13		
Outpatient Visit													X	
Subject Discharge from CRU												X		
Weight	X													
C-SSRS	X											X	X	
Physical Exam													X	After screening exam on Period 1 Day -1, exams are to include only medical review and targeted examination, as appropriate.
Pregnancy Test													X	Pregnancy tests will be performed for all females.
Vital Signs (supine and orthostatic) (hours) [a]		P, 4, 8, 12	24				P, 4, 8, 12	24	X	X	X	X	X	Vital signs include blood pressure and pulse rate. Body temperature will be obtained as clinically indicated. Sampling times are relative to the time of study drug administration (0 hour). Additional vital signs may be measured, if clinically indicated.
Clinical Lab Tests						X						X	X	See Appendix 2 for details. Results from sample on Period 1 Day 6 will be reviewed by the investigator prior to dosing on Period 2 Day 1. Tests may be repeated at the investigator's discretion.
12-lead ECG	X											X	X	Additional ECGs may be obtained if clinically indicated.
Rosuvastatin Administration							X							LY3314814 and rosuvastatin will be co-administered at the same time.

Procedure	Period 2												Discharge/ Follow-up	Comments
	Day												≥7 days after final dose or ED	
	-1	1	2	3 to 5	6	7	8	9	10	11	12	13		
LY3314814 Administration		X	X	X	X	X	X	X	X	X	X			
Rosuvastatin PK Samples (hours) [a]							P, 1, 2, 3, 4, 5, 6, 8, 12	24	48	72	96	120		Sampling times are relative to the time of rosuvastatin administration (0 hour). Samples may be collected at ED as applicable.
LY3314814 PK Samples (hours) [a]						P, 0.5, 1, 2, 3, 4, 8, 12	P, 0.5, 1, 2, 3, 4, 8, 12	P						Sampling times are relative to the time of LY3314814 administration (0 hour). Samples may be collected at ED as applicable.
Biomarker Samples (hours) [a]							P, 1, 2, 3, 4, 5, 6, 8, 12	24	48	72	96	120		Samples for non-pharmacogenetic biomarker analysis. Sampling times are relative to the time of rosuvastatin administration (0 hour). Samples may be collected at ED as applicable.
AE Assessment	X												X	

Abbreviations: AE = adverse event; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; P = predose; PK = pharmacokinetics.

[a] Specified times are approximate and actual times will be recorded. Actual sampling time should not exceed 1 hour prior to dosing for the predose sample or ±10% of the specified postdose sample time.

3. Introduction

3.1. Study Rationale

The breast cancer resistance protein (BCRP; also known as ABCG2) is an efflux transporter located in the small intestine, colon, and liver canalicular membrane (among other tissues), serving to limit the absorption of drugs from the gastrointestinal tract and to increase biliary secretion of drugs and their metabolites (Maliepaard et al. 2001). Certain BCRP substrates have been shown to have clinically significant drug interactions when administered with inhibitors of BCRP (International Transporter Consortium et al. 2010). Many of the substrates of BCRP are also substrates for other transporters or metabolizing enzymes, making it difficult to elucidate the clinical relevance of a putative BCRP substrate. A review by a consortium of pharmaceutical researchers recently suggested that oral rosuvastatin is likely the best available substrate to investigate the activity of a potential BCRP inhibitor, as its relatively low permeability makes it sensitive to BCRP activity in the gastrointestinal tract, and its relatively high biliary clearance make it sensitive to BCRP activity in the liver (Lee et al. 2015).

Rosuvastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor indicated for patients with primary hyperlipidemia, among other conditions. Rosuvastatin has a bioavailability of approximately 20%, reaching time of maximum observed drug concentration (t_{max}) approximately 3 to 5 hours after administration. Rosuvastatin pharmacokinetics (PK) are not impacted by the time of dose administration. Approximately 72% of total rosuvastatin clearance is hepatic, with the majority of this clearance occurring through biliary excretion; approximately 10% of an administered dose of rosuvastatin is metabolized. This metabolism primarily occurs via cytochrome P450 (CYP) 2C9. The half-life associated with the terminal elimination phase ($t_{1/2}$) is approximately 19 hours. Lee and colleagues (2015) note that rosuvastatin is a substrate for several transporters besides BCRP, including the hepatic uptake transporters organic anion transporting polypeptide (OATP) 1B1 and 1B3, as well as multidrug resistance associated protein 2 (also known as ABCC2; primarily involved in the efflux of drugs into bile or renal tubule). Genetic polymorphisms are known to influence the activity of these transporters. For example, various genetic polymorphisms of BCRP are found in humans; notably the c.34G>A and c.421C>A single nucleotide polymorphisms (SNPs) are associated with impaired BCRP activity and significantly increased systemic exposure of rosuvastatin (Furukawa et al. 2009, Wan et al. 2015, Keskitalo et al. 2009). Rosuvastatin area under the concentration-time curve (AUC) was 65% higher in carriers of the OATP1B1 (also known as SLCO1B1) c.521T>C SNP compared to subjects with the c.521TT genotype (Pasanen et al. 2007, Niemi et al. 2011). The c.1249G>A SNP in ABCC2 has been associated with a 2-fold increase in deferasirox exposure, and may therefore be expected to impact rosuvastatin PK (Cusato et al. 2015). Unlike many other BCRP substrates, however, rosuvastatin is neither metabolized by CYP3A to a clinically significant extent, nor is it a substrate for P-glycoprotein (Pgp; Crestor Prescribing Information).

LY3314814, also known as AZD3293, is a brain-permeable inhibitor of human beta-site amyloid precursor protein cleaving enzyme 1 being developed to slow disease progression in patients with early Alzheimer's disease (AD). In vitro, LY3314814 has been characterized as a BCRP

substrate and inhibitor (concentration of drug causing half-maximal inhibitory effect [IC_{50}] = 11.1 μM). Immediately following oral administration of 50 mg LY3314814, drug concentrations in gastric fluid are anticipated to exceed the in vitro IC_{50}, suggesting that there is a potential for inhibition at the level of the intestinal wall. Once absorbed, however, steady-state maximum observed drug concentration (C_{max}) following a regimen of 50 mg LY3314814 once daily (QD) (the highest dose being investigated in ongoing pivotal registration studies) is anticipated to be <10% of the IC_{50} for BCRP, suggesting a relatively low likelihood for LY3314814 to inhibit BCRP activity in other tissues. Of note, while LY3314814 has also been found to inhibit OATP1B1 and OATP1B3 in vitro, the LY3314814 IC_{50} for these transporters was high (≥40 μM), and unlikely to be clinically significant, as compared to BCRP. In vitro studies have also demonstrated that LY3314814 is not an inducer or inhibitor of CYP2C9 and would, therefore, not be expected to alter the metabolism of rosuvastatin. Based upon these data, rosuvastatin appears to be a reasonably specific substrate to evaluate whether LY3314814 is an inhibitor of BCRP activity in vivo.

3.2. Background

3.2.1. LY3314814 Clinical Experience

As of 21 June 2016, approximately 411 subjects/patients have been exposed to LY3314814 in completed clinical studies, including 399 healthy subjects and 12 patients with mild to moderate AD. Single doses ranging from 1 to 750 mg and multiple daily doses up to 150 mg were explored in the 10 completed clinical pharmacology studies. Two Phase 3 clinical trials testing daily doses of 20 and 50 mg LY3314814 are ongoing to evaluate the clinical efficacy of LY3314814 in patients with early AD (ClinicalTrials.gov identifiers: NCT02245737 and NCT02783573). One additional Phase 1 study (food effect) has completed with no additional safety concerns.

3.2.1.1. Clinical Pharmacokinetic Data

LY3314814 PK have been evaluated following single doses of 1 to 750 mg and at steady state from 15 to 150 mg. Following oral dosing, LY3314814 t_{max} is approximately 1 to 2 hours postdose and then follows a bi-exponential elimination profile. The LY3314814 $t_{1/2}$ is approximately 18 hours. Upon multiple dosing, exposure increases modestly with an accumulation ratio of approximately 1.46, based on area under the drug concentration-time curve (AUC). Steady state appears to be achieved 4 to 8 days following the initiation of dosing, consistent with LY3314814 $t_{1/2}$. Over the dose range from 15 to 150 mg, the AUC of LY3314814 increases in a dose proportional manner, although C_{max} appears to increase in a greater-than-proportional manner (a 3.3-fold increase in dose produced approximately a 4.2-fold increase in $C_{ss,max}$ values). No meaningful differences in PK have been observed between young and elderly healthy subjects, or between healthy subjects and patients with AD. Renal clearance was approximately 1.0 to 1.5 L/h (roughly 5% to 10% of apparent total body clearance), suggesting that renal clearance is a minor elimination pathway. LY3314814 is a substrate of CYP3A, as shown by drug interaction studies where strong inhibitors of CYP3A activity increased LY3314814 exposure by up to 2.85-fold. While LY3314814 was shown to be

a CYP3A inducer in vitro, clinical evidence suggests that there is no meaningful effect of LY3314814 on CYP3A activity. The effect of LY3314814 on Pgp activity has been studied in vitro and clinically. In vitro studies demonstrate that LY3314814 is a substrate and an inhibitor of Pgp. In clinical studies, LY3314814 increased dabigatran exposures by 15% when LY3314814 and dabigatran etexilate were administered at the same time, demonstrating that LY3314814 is a relatively weak inhibitor of Pgp. Since 21 June 2016, a food effect study was completed demonstrating that administration of 50 mg LY3314814 with food resulted in a modest (approximately17%) reduction in C_{max}, although AUC was not impacted, suggesting that food reduces the rate, but not the extent of absorption. The PK results for the major metabolite AZ13569724 mirrored those of the parent.

Additional information regarding LY3314814 PK may be found in the Investigator's Brochure (IB).

3.2.1.2. Clinical Safety Data

No clinically significant safety or tolerability concerns have been identified to date in the LY3314814 Phase 1 program up to the highest dose given (750-mg single dose; 150-mg daily dosing for up to 12 days). Across all 10 of the studies completed as of 21 June 2016, 2 serious adverse events (SAEs) were reported in 2 patients (severe ventricular tachycardia in a patient with a previously undisclosed cardiomyopathy, and cellulitis). Both SAEs occurred after 5 days of daily dosing and were judged by the investigator as not related to LY3314814.

The most frequent (occurring in 1% to 10% of healthy subjects) treatment-emergent adverse events (TEAEs) judged by the investigator to be related to study drug during LY3314814 treatment include headache, orthostatic hypotension, dizziness, constipation, back pain, rash, dry skin, lip dry, diarrhea, nausea, dermatitis contact, pruritus, and somnolence. The most common TEAEs judged by the investigator to be related to study drug in patients with mild to moderate AD include blurred vision, headache, and orthostatic hypotension. No clinical laboratory or electrocardiogram (ECG) safety concerns have been identified in the completed Phase 1 studies.

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the IB.

3.2.2. Rosuvastatin Clinical Safety Data

Full details of the known and expected benefits, risks, and reasonably anticipated AEs of rosuvastatin may be found the Crestor® Prescribing Information. The most frequent adverse reactions (rate >2%) are headache, myalgia, abdominal pain, asthenia, and nausea. Rosuvastatin may cause fetal harm when administered to a pregnant woman (Crestor Prescribing Information).

3.3. Benefit/Risk Assessment

No clinically significant safety or tolerability concerns have been identified in subjects to date for LY3314814 up to the highest dose given (750-mg single dose; 150-mg daily dosing for up to 12 days). The risk profile of LY3314814 remains supportive of further clinical development.

Hypopigmentation: Hypopigmentation of skin and haircoat has been observed in dogs. In completed Phase 1 studies with up to 6 weeks duration of exposure to LY3314814, no clinically significant hypopigmentation has been reported. Physical examinations and serial complete skin examinations will be performed by a dermatologist in clinical studies, as appropriate, and are defined in clinical protocols. If hypopigmentation is observed, patients may continue treatment.

Retinal effects: Adverse retinal changes were observed in preclinical studies, only at doses exceeding a maximum tolerated dose in rats (298-fold AUC-based multiple to 50-mg dose in humans). Adverse retinal changes were also observed in dogs at only the high dose in the 9-month study (211-fold AUC-based multiple to 50-mg dose in humans). In study I8D-MC-AZEO, 1 subject receiving LY3314814 and warfarin was noted to have asymptomatic small dot retinal hemorrhages on follow-up examination that resolved without intervention. Based on the large safety margins to adverse effects, the risk of adverse retinal effects occurring at the intended clinical doses of LY3314814 (up to 50 mg) is considered to be low. Ophthalmologic examinations are not planned for this study.

LY3314814 may increase rosuvastatin exposure. Crestor (rosuvastatin calcium) is marketed at doses up to 40 mg/day. Because this study is being conducted in healthy subjects who are not taking other drugs, and each subject will receive only a single dose of rosuvastatin on 2 occasions, a dose of 20 mg rosuvastatin is considered sufficient to appropriately characterize any potential drug-drug interaction, while minimizing any potential safety concerns that might be anticipated due to increased rosuvastatin exposure (Lee et al. 2015).

In this study, there is no anticipated therapeutic benefit for the subjects.

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of LY3314814 may be found in the IB.

4. Objectives and Endpoints

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

Table AZEB.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective is to evaluate the effect of LY3314814 on the PK of rosuvastatin in healthy subjects.	The primary endpoint is AUC from zero to infinity (AUC[0-∞]) of rosuvastatin administered alone and with LY3314814.
Secondary The secondary objectives are: • To assess the safety of LY3314814 when coadministered with rosuvastatin in healthy subjects; • To determine the effect of rosuvastatin on the PK of LY3314814.	Secondary endpoints include: • Incidence of TEAEs and SAEs; • PK parameters of LY3314814 administered alone and with rosuvastatin: C_{max}, t_{max}, and AUC during a 24-hour dosing interval (AUC_{τ}).
Exploratory The exploratory objective of this study is to evaluate the effect of genetic polymorphisms on the magnitude of the interaction between rosuvastatin and LY3314814.	Exploratory endpoints include key PK parameters of rosuvastatin: C_{max}, AUC(0-∞), and t_{max}.

5. Study Design

5.1. Overall Design

This is a Phase 1, open-label, fixed-sequence, 2-period crossover study to evaluate the PK of rosuvastatin administered alone and after 7 days of treatment with LY3314814 in Caucasian healthy male subjects and female subjects not of childbearing potential. Figure AZEB.1 illustrates the study design. All subjects will receive each of the following treatments:

Period 1: single oral dose of 20 mg rosuvastatin on Day 1.

Period 2: oral doses of 50 mg LY3314814 QD on Days 1 to 12 with a single 20-mg rosuvastatin oral dose coadministered on Day 8.

Period 2 will immediately follow Period 1, with no anticipated break between periods. Subjects will reside at the clinical research unit (CRU) for the duration of both study periods.

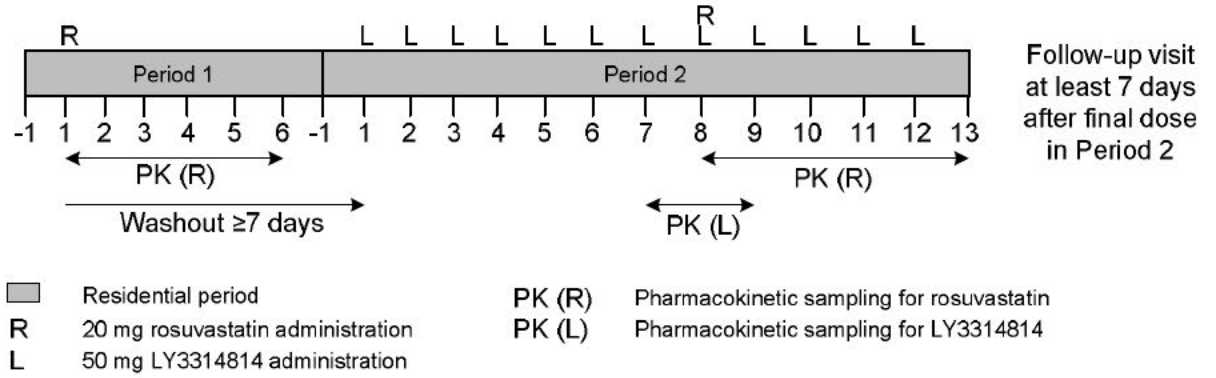

Figure AZEB.1. Illustration of study design for Protocol I8D-MC-AZEB.

Each subject will provide informed consent for study participation and will undergo a screening examination within 45 days prior to enrollment. Subjects who meet all other screening eligibility criteria will return for a second screening visit, at least 21 days prior to enrollment, when samples will be collected for genotype analysis.

In Period 1, subjects will be admitted to the CRU on Day -1. On the morning of Day 1, after an overnight fast of at least 8 hours, a single oral dose of 20 mg rosuvastatin will be administered and will be followed by a fast of at least 4 hours. Blood samples will be collected predose and up to 120 hours postdose (Day 6) for measurement of plasma rosuvastatin concentrations.

There will be a washout period of at least 7 days between the single dose of rosuvastatin on Day 1 in Period 1 and the first dose of LY3314814 on Day 1 in Period 2.

In Period 2, oral doses of 50 mg LY3314814 QD will be taken in the morning of Days 1 to 12. On the morning of Day 7, LY3314814 will be administered after an overnight fast of at least 8 hours and followed by a fast of at least 4 hours. On Day 8, after an overnight fast of at least 8 hours, a single oral dose of 20 mg rosuvastatin will be coadministered with 50 mg LY3314814 and will be followed by a fast of at least 4 hours. On Days 7 and 8, blood samples will be collected predose and up to 24 hours after the LY3314814 dose to determine plasma LY3314814

concentrations. Blood samples will be collected predose on Day 8 and up to 120 hours postdose (Day 13) for measurement of plasma rosuvastatin concentrations. Subjects will be discharged on Day 13 of Period 2 after all assessments have been completed. A follow-up visit will occur at least 7 days following the final LY3314814 dose in Period 2.

Safety and tolerability will be assessed throughout the study by means of vital sign measurements, clinical laboratory tests, ECGs, Columbia-Suicide Severity Rating Scale (C-SSRS), physical examinations (as indicated), and AE recording.

5.2. Number of Participants

Up to 42 subjects may be enrolled so that approximately 24 subjects complete the study.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study will be open-label. As the primary endpoints are objective rather than subjective, investigators and subjects do not need to be blinded.

Oral administration of LY3314814 has been chosen as this is the intended clinical route of administration. A fixed-sequence crossover design has been selected due to the long $t_{1/2}$ of rosuvastatin and LY3314814 (19 and 18 hours, respectively), as an increased study duration would be required if a 2-sequence crossover design was selected. The 7-day washout period after rosuvastatin administration in Period 1 is considered adequate to minimize potential PK carryover effects of rosuvastatin. In Period 2, LY3314814 will be administered for 7 days to allow adequate time to reach steady state prior to coadministration with rosuvastatin. Following coadministration, LY3314814 will continue to be administered QD during the rosuvastatin PK sample collection so any potential interaction due to LY3314814 can be determined. Based upon the available clinical PK data for LY3314814, the duration of this study is considered adequate to achieve the study objectives.

The selection of healthy subjects is appropriate and in keeping with standard regional practices for clinical pharmacology studies. The inclusion and exclusion criteria are chosen to select subjects who are known to be free from any significant illness and from any condition that could affect their safety or interfere with meeting the study objectives.

The human BCRP transporter is polymorphic. Subjects with the c.421C>A and c.34G>A polymorphisms, specifically the c.34AA, c.421AA, and c.34GA/ 421CA genotypes, will be excluded because these genetic polymorphisms are associated with impaired BCRP activity (Furukawa et al. 2009, Wan et al. 2015, Keskitalo et al. 2009). Because the activity of BCRP is impaired with these subjects, it would be anticipated that even complete inhibition of BCRP would not result in a substantial change in rosuvastatin exposure. Accordingly, excluding subjects with these polymorphisms will ensure that the “worst-case” interaction between LY3314814 and rosuvastatin will be evaluated in this study.

The human OATP1B1 transporter (also known as SLCO1B1) is also polymorphic. In order to evaluate worst-case interactions between LY3314814 and rosuvastatin, subjects with the c.521T>C polymorphism will be excluded from this study because this genetic polymorphism is associated with decreased transporting activity of OATP1B1 (Niemi et al. 2011) and higher plasma rosuvastatin concentrations (Crestor Prescribing Information).

The rate of c.34G>A and c.421C>A polymorphisms tend to be lower in Caucasian subjects than many other racial groups (Kim et al. 2010). Because of this, and due to other studies showing that rosuvastatin exposure in Asian subjects is approximately 2-fold that in Caucasian subjects (Crestor Prescribing Information), participation in this study will be limited to Caucasian subjects.

5.5. Justification for Dose

A dose of 50 mg LY3314814 administered orally QD was selected based on current clinical study data. LY3314814 doses up to 750 mg (highest planned dose) were well tolerated in the single ascending dose study. Multiple LY3314814 doses up to 150 mg QD for 12 days were also well tolerated. The 50-mg dose of LY3314814 selected for this study is the highest dose that is being used in the ongoing Phase 3 studies, and is the highest planned dose in Phase 3 studies.

Rosuvastatin is commonly administered to adults at an oral dose of 5 to 40 mg QD, with the majority of the clinical drug-drug interaction or pharmacogenetic studies conducted using a 10- or 20-mg dose (Crestor Prescribing Information; Lee et al. 2015). Rosuvastatin administered orally at a dose of 20 mg is suggested as a good clinical probe for both hepatic and intestinal BCRP function (Lee et al. 2015). Coadministration of rosuvastatin with LY3314814 may increase rosuvastatin exposure. Using calculations similar to those described by Elsby and colleagues (2016) and the assumption that LY3314814 will only inhibit BCRP in the intestine, it is estimated that LY3314814 may increase rosuvastatin exposures by approximately 70%. The 20-mg rosuvastatin dose selected for this study should provide adequate plasma rosuvastatin concentrations to address the study objectives with minimal risk for AEs.

6. 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, C-SSRS, and safety ECG.

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

Screening may occur up to 45 days prior to enrollment. Subjects who are not enrolled within 45 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. Subjects who meet all other screening eligibility criteria will return for a second screening visit, at least 21 days prior to enrollment, when samples will be collected for genotype analysis. Genotyping only needs to be conducted once, regardless of the 45-day screening window and any repeated assessments to confirm eligibility.

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

6.1. Inclusion Criteria

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

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

[1a] women not of childbearing potential may participate and include those who are:

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or

B. postmenopausal – defined as women over 50 years of age with an intact uterus who have not taken hormones or oral contraceptives within 1 year, who have had either spontaneous cessation of menses for at least 12 consecutive months, or 6 to 12 months of spontaneous amenorrhea with follicle-stimulating hormone level >40 mIU/mL consistent with menopause

[2] are Caucasian and may be of Hispanic ethnicity

[3] are 18 to 65 years old, inclusive, at the time of screening

[4] have a body mass index (BMI) of 19 to 32 kg/m^2, inclusive, at the time of screening

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

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

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

[8] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

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

[10] are Lilly employees, AstraZeneca employees, or Covance employees

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

[12] have participated, within the last 30 days, in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[13] have previously completed or withdrawn from this study or any other study investigating LY3314814, and have previously received the investigational product

[14] have known allergies to LY3314814, rosuvastatin, related compounds, or any components of the formulation, or history of significant allergic disease as determined by the investigator

[15] have a history of significant ophthalmic disease, which includes subjects with clinically significant eye abnormalities, particularly any eye problem involving the retina

[16] have vitiligo or any other clinically significant disorder of skin pigmentation as determined by the investigator

[17] have a history of previous or ongoing neuropsychiatric disease/condition including psychosis, affective disorder, anxiety disorder, borderline state, and personality disorder

[18] have acute suicidality, as evidenced by answering “yes” for Question 4 or Question 5 on the C-SSRS, indicating active suicidal ideation with any intent to act, at screening, Check-in, or at Period 2 Day -1

[19] have a history of suicidal behavior such that a determination of “yes” is made on the Suicidal Behavior section of the C-SSRS for “Actual Attempt,” “Interrupted Attempt,” “Aborted Attempt,” or “Preparatory Acts or Behavior”

[20] have a history of neurologic disease, including seizures, or clinically significant head injury

[21] have a history of use of antipsychotic drugs, or chronic use of antidepressant or anxiolytic drugs, prescribed as well as non-prescribed use

[22] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study, or have a history of significant dysrhythmias or atrioventricular (AV) block (including first degree AV block).

[23] have Fridericia-corrected QT interval of >470 msec for females or >450 msec for males

[24] have a history of prolonged QT syndrome

[25] have a clinically significant abnormal blood pressure or heart rate (supine) as determined by the investigator

[26] have c.34AA, c.421AA, or c.34GA/ 421CA genotypes as determined by genotyping

[27] have c.521TC and c.521CC genotypes as determined by genotyping

[28] have estimated glomerular filtration rate ≤59 mL/min/1.73 m^2

[29] have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels above the upper limit of normal (ULN) at screening or Check-in. Tests may be repeated at the investigator's discretion.

[30] history of myopathy

[31] have any medical conditions, medical history, or are taking any medication which are contraindicated in the Crestor (rosuvastatin) Prescribing Information

[32] have a history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data as determined by the investigator

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

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

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

[36] show evidence of hepatitis B and/or positive hepatitis B surface antigen

[37] are women of childbearing potential or who are pregnant or lactating

[38] are currently or have been smokers or users of tobacco- or nicotine-containing products within the 3 months prior to Check-in

[39] have donated more than 500 mL of blood, including plasma and platelets, within 1 month prior to Check-in

[40] use of any drugs or substances that are known strong inducers or inhibitors of CYP3A. Strong inhibitors of Pgp or inducers or inhibitors of BCRP are specifically excluded within 14 days prior to the first administration of study drug and during the study

[41] have used or intend to use any drug or dietary supplement that may affect rosuvastatin within 14 days prior to the first dose of rosuvastatin and/or during the conduct of the study

[42] have used or intend to use prescription medication, oral over-the-counter medication, or herbal preparations within 14 days prior to admission and during the study. If this situation arises, inclusion of an otherwise suitable subject may be at the discretion of the investigator.

[43] are unwilling to comply with the dietary requirements/restrictions during the study: (i) consume only the meals provided while resident in the CRU, and (ii) refrain from eating any food or drinking any beverages containing restricted foods, including grapefruits or grapefruit-containing products, Seville oranges or Seville orange-containing products, star fruits or star fruit-containing products, pomelo, or commercial apple juice or orange juice, within 7 days prior to the first dose of study drug until the final PK sample is collected

[44] unwilling to refrain from strenuous physical activity from 48 hours prior to the first dose and during the study

[45] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption from 48 hours prior to Check-in and during the study (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[46] are unwilling to refrain from consuming caffeine- or xanthine-containing food and drink within 48 hours prior to Check-in and while resident in the CRU

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

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Standardized meals will be provided during each subject's stay in the CRU.

Subjects will be required to fast overnight (at least 8 hours) prior to study drug doses that are followed by PK sample collection (Period 1 Day 1 and Period 2 Days 7 and 8). Fluids will be restricted from 1 hour prior to and until 1 hour after dosing with the exception of water required

for study drug administration. Water will be allowed ad libitum at all other times during the study. A standard meal will be given to the subjects no sooner than 4 hours after dosing on Period 1 Day 1 and Period 2 Days 7 and 8. On all other days when dosing is not followed by PK sample collection, study drug may be administered without regard to food and water. Meals will be provided as appropriate at all other times.

Subjects will refrain from consuming grapefruits or grapefruit-containing products, Seville oranges or Seville orange-containing products, star fruits or star fruit-containing products, pomelo, or commercial apple juice or orange juice within 7 days prior to the first dose of any study drug until the final PK sample is collected. If this situation arises, inclusion or ongoing participation of the subject may be at the discretion of the investigator, in consultation with the sponsor or designee.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects will refrain from consuming caffeine- or xanthine-containing food and drinks within 48 hours prior to Check-in. Caffeine- or xanthine-containing food and drinks will not be allowed while subjects are resident at the CRU.

Alcohol will not be permitted from 48 hours prior to Check-in and during the study.

Smoking will not be permitted throughout the study. Subjects will not have used any tobacco- or nicotine-containing products (including, but not limited to, cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 3 months prior to Check-in and during the entire study.

6.3.3. Activity

No strenuous exercise will be allowed for 48 hours prior to the first dose and during the study.

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

Table AZEB.2 shows the treatment regimens.

Tablets of LY3314814 and/or rosuvastatin will be administered orally with approximately 240 mL of room temperature water in the morning in a sitting position. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table AZEB.2. Treatments Administered

Treatment Name	Rosuvastatin	LY3314814
Dosage Formulation	20-mg tablet	50-mg tablet
Dosage Level	20 mg	50 mg
Route of Administration	Oral	Oral
Dosing Instructions	1 tablet taken on Period 1 Day 1 and Period 2 Day 8	1 tablet taken once daily on Period 2 Days 1 through 12

The investigator or designee is responsible for:

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

Note: In some cases, 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.

7.1.1. Packaging and Labeling

Each LY3314814 tablet is oval, biconvex, plain, dark tan, and film-coated. Tablets contain 50 mg LY3314814 and excipients and are provided in high-density polyethylene bottles.

Each rosuvastatin tablet is round, biconvex, pink, coated, and debossed with "CRESTOR" and "20" on one side (Crestor Prescribing Information). Tablets contain 20 mg rosuvastatin and excipients and are provided in bottles.

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

7.2. Method of Treatment Assignment

This study is not randomized. All subjects are to receive all treatments as described in Section 5.1.

7.2.1. Selection and Timing of Doses

Doses administered on the mornings of Period 1 Day 1 and Period 2 Days 7 and 8 will be preceded by an overnight fast of at least 8 hours and followed by a fast of at least 4 hours postdose. See Section 6.3.1 for meal and dietary restrictions. All doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Dose adjustments are not allowed for this study.

7.5. 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 in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Drugs that are known strong inducers or inhibitors of CYP3A, strong inhibitors of Pgp, or inducers or inhibitors of BCRP are specifically excluded. Drugs or dietary supplements that may affect rosuvastatin 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, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP). Occasional acetaminophen (paracetamol) up to a 2-gram total dose in a 24-hour period may be used at the discretion of the investigator. Any additional medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

Not applicable for this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

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

Subjects who discontinue treatment due to a hepatic event or abnormality of liver tests should have further clinical and laboratory monitoring and should have additional data collected. The process should be initiated by the investigator in consultation with the Lilly CRP/CP.

Subjects who discontinue the investigational product early will have early discontinuation procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

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

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

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

Subjects who discontinue the study early will have early discontinuation procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

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

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

Appendix 5 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.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

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 eCRF, the occurrence and nature of each subject's preexisting conditions. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

Any clinically significant findings from ECGs, labs, vital sign measurements, and other procedures should be reported as an AE to Lilly or its designee.

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

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

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- events considered significant by the investigator based upon appropriate medical judgment

Study site personnel must alert Lilly, 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 eCRF 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 eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations 312.32 and 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. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly will forward product complaints on LY3314814 to AstraZeneca in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

Complaints related to concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs
- communicating the product complaint within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint correspondence with the product.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3314814 or rosuvastatin is considered any dose higher than the assigned dose. There is no specific antidote for LY3314814. There is no specific treatment in the event of rosuvastatin overdose. In the event of an overdose, the subject should receive appropriate supportive care and any AEs should be documented.

Refer to the LY3314814 IB and Crestor Product Label for more information.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

For each subject, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Supine blood pressure and pulse rate should be measured after at least 5 minutes supine rest. Following the respective supine vital signs measurement, subjects will sit for approximately 1 minute and then standing blood pressure and pulse rate should be taken at 2 minutes, but no longer than 3 minutes, and at 5 minutes in a standing position.

If the subject feels unable to stand, supine and seated vital signs will be recorded.

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

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

9.4.3. Electrocardiograms

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood for safety or PK tests and before vital signs measurements. Subjects must be supine for at least 5 minutes before 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 investigator (or 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 to Lilly, or its designee, as an AE via eCRF.

9.4.4. Physical Examination

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

9.4.5. Body Weight

Body weight will be recorded as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.6. Columbia-Suicide Severity Rating Scale

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period (Posner et al. 2007a, 2007b). The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. Certified site personnel will administer the C-SSRS assessment and a corresponding self-harm supplement form as specified in the Schedule of Activities (Section 2) and as clinically indicated. If a self-harm event is reported, investigators will also complete the "self-harm follow-up" form. If the subject does not attend the discontinuation visit,

the C-SSRS and "self-harm supplement" form should still be completed if the site has become aware of a suicide-related thought or behavior by other communications. If a self-harm or suicidal-related event is considered serious by the investigator, it must be reported as an SAE via the procedures indicated in Section 9.2.1. If a clinically significant finding is identified, 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.

9.4.7. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or 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
- laboratory analytes
- AEs

If a study subject experiences elevated ALT ≥3 times ULN, ALP ≥2 times ULN, or elevated TBL ≥2 times ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days to confirm abnormality. If the abnormality persists or worsens, further clinical and laboratory monitoring should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

In the event a subject experiences a suspected drug-induced rash, the following procedures should be followed:

- The subject should be referred to a dermatologist for an expert opinion.
- A photograph of the rash should be taken.
- A blood sample should be drawn for PK analysis, if >12 hours since the last PK sample.

If treatment is discontinued due to a suspected drug-induced rash, the Lilly-designated medical monitor should be notified as soon as possible, even if the rash did not meet the definition of an SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the plasma rosuvastatin concentrations and samples of approximately 2 mL each will be collected to determine the plasma LY3314814 concentrations. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded.

9.5.1. Bioanalysis

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

Plasma rosuvastatin and LY3314814 concentrations will be assayed using validated liquid chromatography with tandem mass spectrometry methods.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein binding work.

9.6. Pharmacodynamics

Not applicable for this study.

9.7. Genetics

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3314814 or rosuvastatin, and particularly to investigate the effect of polymorphisms on the disposition of LY3314814 and rosuvastatin. Samples may be used to investigate genetic variants thought to play a role in AD. Assessment of variable response may include evaluation of AEs.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ethical review boards (ERBs) impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3314814 or after LY3314814 is commercially available.

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

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient 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.

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

Samples will be used for research on the drug target, disease process, variable response to LY3314814 or rosuvastatin, pathways associated with neurological disease, mechanism of action of LY3314814 or rosuvastatin, identification of LY3314814 metabolites, and/or research method, or for validating diagnostic tools or assay(s) related to neurological disease.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3314814 or after LY3314814 is commercially available.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 42 subjects may be enrolled in order that 24 subjects complete the study.

For rosuvastatin AUC, the intrasubject variability (coefficient of variation) was estimated to be 25.5% by assuming intrasubject variability comprised half of the total variability of 51% (CDER 2003); Martin et al. (2016) estimated the intrasubject variability of rosuvastatin AUC to be 21%. A sample size of 24 subjects will provide 92.3% probability that the estimated AUC geometric mean ratio will be within 0.15 of the upper and lower bounds of the 90% confidence interval (CI) in the log scale, which corresponds to approximately 0.162 in the natural scale.

While this study is not powered for the C_{max} geometric mean ratio to be within 0.15 of the upper and lower bounds of the 90% CI in the log scale, the C_{max} power calculations are described here to give the expected results context. For rosuvastatin C_{max}, the intrasubject variability was estimated to be 35.9% by assuming intrasubject variability comprised half of the total variability of 71.8% (CDER 2003); Martin et al. (2016) estimated the C_{max} intrasubject variability of rosuvastatin to be 34%. A sample size of 24 subjects will provide 19.6% probability that the estimated C_{max} geometric mean ratio will be within 0.15 of the upper and lower bounds of the 90% CI in the log scale.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

The subject's age, sex, weight, height, BMI, race/sub-race, tobacco/nicotine habits, or other demographic characteristics will be recorded and may be used in the PK and safety analyses as quantitative or classification variables.

10.3. Statistical Analyses

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

Pharmacokinetic analyses will be conducted on the full analysis set. This set includes all data from all subjects receiving at least one dose of the investigational product according to the treatment the subjects actually received. If a subject has an AE of vomiting that occurs at or before 2 times median t_{max} then that subject may be excluded from the PK summary statistics and statistical analysis. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. 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.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All investigational product 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 enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

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

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety clinical lab parameters, vital signs, and C-SSRS. Orthostatic changes in vital signs will be assessed using change from supine to standing. The clinical lab parameters and C-SSRS data will be listed. Vital signs will be listed and summarized using standard descriptive statistics. Electrocardiograms will be performed for safety monitoring purposes and will not be presented. Additional analysis may be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for rosuvastatin and LY3314814 will be calculated by standard noncompartmental methods of analysis. The primary PK parameter for analysis of rosuvastatin will be AUC(0-∞) following both doses. The C_{max} and t_{max} will also be reported. Other noncompartmental parameters, such as AUC from time zero to time t_{last} (AUC[0-t_{last}]), where t_{last} is the last time point with a measurable concentration; $t_{1/2}$; apparent clearance; and apparent volume of distribution, may be reported as appropriate.

The following PK parameters will be determined for LY3314814: C_{max}, t_{max}, and AUC_{τ}. Other noncompartmental parameters may be reported as appropriate.

10.3.2.2. Pharmacokinetic Statistical Inference

Rosuvastatin administered alone (Period 1 Day 1) will represent the reference treatment and rosuvastatin coadministered with LY3314814 will represent the test treatment (Period 2 Day 8) for rosuvastatin PK analysis. Pharmacokinetic parameter estimates will be evaluated to delineate the effects of LY3314814 on rosuvastatin PK.

Log-transformed AUC(0-∞) and C_{max} estimates for rosuvastatin will be analyzed using a linear mixed-effects analysis of variance model with treatment as a fixed effect and subject as a random

effect. The ratios of geometric least squares means (ie, rosuvastatin + LY3314814 to rosuvastatin alone) will be calculated along with the 90% CI for the ratios.

The t_{max} for rosuvastatin will be analyzed using a nonparametric method; median differences of rosuvastatin + LY3314814 to rosuvastatin alone and the 90% CI for the median of differences will be calculated.

A similar analysis will be performed to evaluate the effect of rosuvastatin on LY3314814, where LY3314814 administered alone (Period 2 Day 7) will be the reference treatment and LY3314814 coadministered with rosuvastatin will remain the test treatment (Period 2 Day 8).

Additional analysis may be conducted if deemed appropriate.

The effect of polymorphisms in genes coding for certain transporters (eg, ABCG2, ABCB1, ABCC2, SLCO1B3, NTCP, and SLCO2B1) on the magnitude of the interaction between rosuvastatin and LY3314814 may be explored. For each subject, the ratio of rosuvastatin exposures with and without concomitant LY3314814 exposures will be calculated. A graphical analysis of these ratios between subjects with and without SNPs of interest is intended. Additional analyses may be conducted as warranted.

An exploratory assessment of the effect of genetic polymorphisms in transporter enzymes on rosuvastatin PK may be conducted. The results of this study may be merged with the results of other studies of rosuvastatin to increase the likelihood of identifying the clinical significance of any particular polymorphism and reported elsewhere.

10.3.3. Interim Analyses

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

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Appendix 1. Abbreviations and Definitions

Term	Definition
AD	Alzheimer's disease
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the drug concentration-time curve
AUC_{τ}	area under the drug concentration-time curve during a 24-hour dosing interval
AUC(0-∞)	area under the drug concentration-time curve from zero to infinity
AUC(0-t_{last})	area under the drug concentration-time curve from time zero to time tlast, where t_{last} is the last time point with a measurable concentration
AV	atrioventricular
BCRP	breast cancer resistance protein
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all 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 Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.

CP	clinical pharmacologist
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-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
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
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration of drug causing half-maximal inhibitory effect
ICF	informed consent form
ICH	International Conference on Harmonization
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.
OATP	organic anion transporting polypeptide

open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
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.
SNP	single nucleotide polymorphism
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal elimination phase
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal

Appendix 2. 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	Glucose, random
Leukocytes (WBC)	Blood urea nitrogen
Cell Morphology	Total cholesterol
Absolute counts of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase
Eosinophils	Aspartate aminotransferase
Basophils	Alanine aminotransferase
Platelets	Creatinine
	Creatine phosphokinase
Urinalysis[a]	
Specific gravity	Ethanol testing[c]
pH	Urine drug screen[c]
Protein	Hepatitis B surface antigen[d]
Glucose	Hepatitis C antibody[d]
Ketones	HIV[d]
Bilirubin	Pregnancy test (females)[e]
Urobilinogen	FSH (females, if applicable)[d]
Blood	OATP1B1, OATP521 T/TT, and BCRP genotypes[f]
Nitrite	
Microscopic examination of sediment[b]	

Abbreviations: BCRP = breast cancer resistance protein; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; OATP = organic anion transporting polypeptide; RBC = red blood cells; WBC = white blood cells.

a Performed by local laboratory. Results will be validated by the laboratory at the time of initial testing.

b Test only if dipstick result is abnormal (ie, positive for blood, protein, or nitrites).

c Urine drug screen and ethanol testing will be performed by local laboratory at screening and at admission to the clinical research unit.

d Performed by local laboratory at screening only.

e Serum pregnancy tests will be performed at admission to the clinical research unit and at study follow-up or early termination. Tests will be performed by local laboratory.

f Performed by central laboratory.

Appendix 3. 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 give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonization (ICH) guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

This study will be conducted in accordance with:

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

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, 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 eCRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

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

Data Collection Tools/Source Data

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
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 = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by local laboratory.

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I8D-MC-AZEB Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	19.5	1	19.5
OATP1B1, OATP521 T/TT, and BCRP genotyping	10	1	10
Clinical laboratory tests[a]	12.5	5	62.5
Rosuvastatin pharmacokinetics[b]	2	31	62
LY3314814 pharmacokinetics[b]	2	20	40
Pharmacogenetics	10	1	10
Biomarker analysis	10	28	280
Total			484
Total for clinical purposes rounded up to nearest 10 mL			490

Abbreviations: BCRP = breast cancer resistance protein; OATP = organic anion transporting polypeptide.

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

[b] Including the 3 additional pharmacokinetic samples, if needed.

Appendix 6. Protocol Amendment I8D-MC-AZEB(a) Summary
Effect of LY3314814 on the Pharmacokinetics of Rosuvastatin in Caucasian Healthy Subjects

Overview

Protocol I8D-MC-AZEB "Effect of LY3314814 on the Pharmacokinetics of Rosuvastatin in Caucasian Healthy Subjects" has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall change and rationale for the change made to this protocol is as follows:

- The total sample size has been increased by 14 subjects to ensure that 24 subjects can complete the study. This increase takes into account the unanticipated withdrawal of 10 subjects and allowance for any additional withdrawals. The 10 subjects were withdrawn from the study early due to central laboratory errors in the genotyping results. Following enrollment based on the initial genotyping report, it was later determined the subjects did not meet the entry criteria based on the qualifying inclusive genotyping results reported.
- The wording in Section 9.4.2 (Vital Signs) has been updated to clarify the time spent in a standing position after which standing blood pressure and pulse rate should be measured for determining orthostatic changes.
- The wording in Section 6 has been updated to clarify that the genotyping does not need to be repeated for subjects who have other assessments repeated because they fall outside the 45-day screening window.

Revised Protocol Sections

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

1. Protocol Synopsis

Number of Subjects:

Up to ~~28~~ 42 subjects may be enrolled in order that 24 subjects complete the study.

5.2. Number of Participants

Up to ~~28~~ 42 subjects may be enrolled so that approximately 24 subjects complete the study.

6. Study Population

[…]

Screening may occur up to 45 days prior to enrollment. Subjects who are not enrolled within 45 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. Subjects who meet all other screening eligibility criteria will return for a second screening visit, at least 21 days prior to enrollment, when samples will be collected for genotype analysis. Genotyping only needs to be conducted once, regardless of the 45-day screening window and any repeated assessments to confirm eligibility.

9.4.2. Vital Signs

[…]

Supine blood pressure and pulse rate should be measured after at least 5 minutes supine rest. Following the respective supine vital signs measurement, subjects will sit for approximately 1 minute and then standing blood pressure and pulse rate should be taken ~~after~~ at 2 minutes, but no longer than 3 minutes, and at 5 minutes in a standing position.

10.1. Sample Size Determination

Up to ~~28~~ 42 subjects may be enrolled in order that 24 subjects complete the study.

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Approver: Scott W Andersen (AM\RM82091)
Approval Date & Time: 14-Mar-2017 15:49:13 GMT
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Approver: Juliet McColm (EMA\YE91063)
Approval Date & Time: 15-Mar-2017 09:01:29 GMT
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