Protocol I8D-MC-AZEP(d)

An Absolute Bioavailability Study of LY3314814 in Healthy Subjects Using an Intravenous Tracer Method

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An Absolute Bioavailability Study of LY3314814 in Healthy Subjects Using an Intravenous Tracer Method

LY3314814

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1. Protocol Synopsis

Title of Study:
An Absolute Bioavailability Study of LY3314814 in Healthy Subjects Using an Intravenous Tracer Method

Rationale:
Absolute bioavailability data are required by regulatory agencies in some geographical areas. Knowledge of absolute bioavailability is helpful in the interpretation of pharmacokinetic (PK) data, and may be helpful in the design of clinical pharmacology studies.

Objectives/Endpoints:

Objectives	Endpoints
Primary The primary objective is to estimate the absolute bioavailability of LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour intravenous (IV) infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814(+)-Camsylate (referred to as [$^{13}C_4{}^{15}N_3$]-LY3314814 from this point forward) in healthy subjects.	The primary endpoint is LY3314814 absolute bioavailability, as calculated based on the ratio of the dose-adjusted area under the drug concentration-time curve (AUC) from zero to infinity (AUC[0-∞]) of LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814.
Secondary The secondary objectives are: • To assess the safety of LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 in healthy subjects; • To characterize the PK parameters of LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 in healthy subjects.	Secondary endpoints include: • Incidence of treatment-emergent adverse events (AEs) and serious AEs; • LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814 PK parameters: AUC(0-∞), AUC from time zero to time t_{last} (AUC[0-t_{last}]), where t_{last} is the last time point with a measurable concentration, maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), and half-life associated with the terminal elimination phase ($t_{1/2}$).

Summary of Study Design:
Study I8D-MC-AZEP is a Phase 1, single-center, open-label, single-period study to determine the absolute bioavailability of LY3314814 in healthy male and female subjects not of childbearing potential.

Treatment Arms and Duration:
On Day 1, following an overnight fast of at least 8 hours, subjects will receive a single oral dose of 50 mg LY3314814 and at approximately the same time an IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 will be started. The infusion will run for 2 hours.

Number of Subjects:
Up to 8 subjects may be enrolled and dosed to ensure that at least 6 subjects complete and have evaluable PK data.

Statistical Analysis:
Pharmacokinetic: To quantify the absolute bioavailability of LY3314814, a mixed-effect analysis of variance model will be applied to the log-transformed dose-adjusted AUC of LY3314814 obtained after oral dosing and that of the IV administered [$^{13}C_4{}^{15}N_3$]-LY3314814. The model will contain formulation (oral or IV) as a fixed effect and subject as a random effect. The absolute bioavailability will be expressed as the ratio of the least-squares geometric means of the formulations (oral : IV) along with its corresponding 90% confidence interval. The PK parameter estimates for LY3314814, and [$^{13}C_4{}^{15}N_3$]-LY3314814 will be summarized using appropriate descriptive statistics. Additional analysis may be conducted if deemed appropriate.

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. Each symptom will be classified by the most suitable term from the medical regulatory dictionary. The number of investigational product-related serious AEs will be reported. Safety parameters that will be assessed include clinical lab parameters, vital signs, and electrocardiograms. The clinical lab parameters will be listed. Vital signs will be listed and summarized using standard descriptive statistics. Electrocardiograms and physical examinations 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-AZEP

	Screening	Day							FU or ED	Comments
Procedure	Up to 28 days prior to enrollment	-1	1	2	3	4	5	6	≥7 days after postdose or ED	
Outpatient Visit	X					X	X	X	X	
Subject Admission to CRU		X								
Subject Discharge from CRU					X					
Informed Consent	X									
Medical History	X									
Height and BMI	X									
Weight	X	X								
Drug and Alcohol Tests	X	X								
Estimated GFR	X									Estimated GFR will be calculated using the Modification of Diet in Renal Disease equation.
Physical Exam	X							X	X	After screening exam, exams are to include only medical review and targeted examination, as appropriate.
Pregnancy Test (if applicable)	X	(X)							X	Serum pregnancy tests will be performed at screening and at follow-up or early discontinuation for all females (if applicable). A urine pregnancy test (X) may be performed upon admission and may be repeated during the study at the investigator's discretion.
Vital Signs (supine) (hours) [a]	X		P, 2, 4, 8, 12	24	X	X	X	X		Sampling times are relative to the time of oral dose administration (0 hour).
Clinical Lab Tests	X	X						X	X	See Appendix 2 for details. Follow-up sample is only if clinically indicated.
12-lead ECG (hours) [a]	X	X			X			X	X	Sampling times are relative to the time of oral dose administration (0 hour).

	Screening	Day							FU or ED	Comments
Procedure	Up to 28 days prior to enrollment	-1	1	2	3	4	5	6	≥7 days after postdose or ED	
Genetic Sample			P							Single sample for pharmacogenetic analysis.
LY3314814 Oral Administration (hours)			0							Dosed in the morning following an overnight fast of ≥8 hours.
[$^{13}C_4{}^{15}N_3$]-LY3314814 IV Administration (hours)			0-2							Infusion to start at approximately the same time as the oral dose and run for 2 hours.
PK Samples (hours) [a]			P, 0.25, 0.5, 1, 1.5, 2*, 2.5, 3, 4, 8, 12	24	48	72	96	120		Sampling times are relative to the time of oral dose administration (0 hour). Labeled and non-labeled drug assessments will be conducted on the same sample at each time point. During the infusion of [$^{13}C_4{}^{15}N_3$]-LY3314814 and for at least 4 hours post-infusion, the PK blood samples will be taken from the arm contralateral to the infusion site. *The 2-hour sample will be collected immediately prior to the end of IV infusion.
AE Assessment	X	X							X	

Abbreviations: [$^{13}C_4{}^{15}N_3$]-LY3314814 = [$^{13}C_4{}^{15}N_3$]-LY3314814(+)-Camsylate; AE = adverse event; BMI = body mass index; CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; GFR = glomerular filtration rate; IV = intravenous; P = predose; PK = pharmacokinetics.

[a] Specified times are target and actual times will be recorded. All attempts should be made to ensure that the actual sampling time does 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

Absolute bioavailability data are required by regulatory agencies in some geographical areas. Knowledge of absolute bioavailability is helpful in the interpretation of pharmacokinetic (PK) data, and may be helpful in the design of clinical pharmacology studies.

3.2. Background

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) (defined as the continuum of mild cognitive impairment due to AD and mild dementia of the Alzheimer's type).

3.2.1. *Clinical Experience*

As of 28 November 2016, approximately 429 subjects/patients have been exposed to LY3314814 in completed Phase 1 trials, of which 417 were healthy subjects and 12 were patients with AD. Single oral doses ranging from 1 to 750 mg and multiple daily doses up to 150 mg were explored in 11 completed clinical pharmacology studies.

An additional Phase 1 trial (I8D-MC-AZEB) evaluating the effect of LY3314814 on rosuvastatin in healthy subjects and 3 Phase 3 trials (Study I8D-MC-AZET, Study I8D-MC-AZES, Study I8D-MC-AZFD) evaluating daily doses of 20 mg and 50 mg LY3314814 in patients with mild cognitive impairment and mild AD dementia, are currently ongoing.

LY3314814 has not previously been administered as an intravenous (IV) dose.

3.2.1.1. Clinical Pharmacokinetic Data

LY3314814 PK have been evaluated following single oral doses of 1 to 750 mg and at steady-state from 15 to 150 mg. Following oral dosing, LY3314814 time of maximum observed drug concentration (tmax) is approximately 1 to 2 hours postdose and then follows a bi-exponential elimination profile. The LY3314814 half-life associated with the terminal elimination phase (t1/2) 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 t1/2. Over the dose range from 15 to 150 mg, the PK of LY3314814 appears dose proportional. 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 5% to 10% of total body clearance), suggesting that renal clearance is a minor elimination pathway. A food effect study was completed demonstrating that administration of 50 mg LY3314814 with food resulted in a minimal (approximately 17%) reduction in maximum observed drug concentration (Cmax), although AUC was not impacted. These results suggest that food reduces the rate, although not the extent, of absorption. The PK results for the major metabolite AZ13569724 mirrored those of the parent.

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. LY3314814 co-administration resulted in minor changes in exposure of the sensitive CYP3A4 substrate midazolam, suggesting that there is no clinically-meaningful effect of LY3314814 on CYP3A activity.

In vitro data suggests that LY3314814 is a substrate and inhibitor of Pgp. A regimen of 50 mg LY3314814 once daily increased dabigatran mean AUC from zero to infinity (AUC[0-∞]) and C_{max} by 15% and 17%, respectively, when a single 150-mg dose of dabigatran etexilate (P-glycoprotein [Pgp] substrate) was administered at the same time as LY3314814 in healthy subjects. These data suggest that LY3314814 is a relatively modest inhibitor of Pgp.

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 the 11 completed studies as of 28 November 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 were judged by the investigator as not related to LY3314814.

In completed studies, the most frequent treatment-emergent adverse events (TEAEs) reported by healthy subjects and patients with AD during LY3314814 treatment or wash-out (occurring in 1% to 10% of subjects) periods include headache, orthostatic hypotension, dizziness, constipation, back pain, rash, dry skin, diarrhea, nausea, and pruritus. In general, there have been no clinical laboratory or ECG safety concerns identified in the completed Phase 1 studies. Safety reviews of the ongoing Phase 3 trials are completed by an Independent Data Monitoring Committee (IDMC) which meets quarterly. The recommendations of the IDMC at all meetings thus far for each study have been to continue without any modification.

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

3.3. Benefit/Risk Assessment

Study AZEP will include standard safety assessments, including spontaneous reporting of AEs, clinical laboratory tests, 12-lead ECGs, vital signs and physical examinations. Additionally, there are exclusion criteria in the protocol designed to prevent enrollment of subjects who may be at increased risk of potential adverse effects.

Potential risks of LY3314814 identified from non-clinical studies or completed phase 1 studies include, but are not limited to, elevated liver enzymes, QT-prolongation in overdose, hypopigmentation of skin or hair, rash, retinal changes, and potential interactions with other drugs, including simvastatin, and strong CYP3A inducers or inhibitors, strong Pgp inducers or inhibitors, and BCRP inhibitors or inducers. Of note, no LY3314814-related effects on male

reproductive potential were identified in rats. No additional safety signals or potential risks have been identified to date during Phase 3 development.

Overall, in the opinion of the sponsor, Study AZEP has been carefully designed to safeguard participants against potential risks. Although no benefit is expected for the healthy subjects participating in this study, the information obtained from this study will benefit the development of this molecule and patients with AD who may use this molecule for therapeutic benefit in the future, for whom there are currently no approved disease-modifying treatments.

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 AZEP.1 shows the objectives and endpoints of the study.

Table AZEP.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective is to estimate the absolute bioavailability of LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour intravenous (IV) infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814(+)-Camsylate (referred to as [$^{13}C_4{}^{15}N_3$]-LY3314814 from this point forward) in healthy subjects.	The primary endpoint is LY3314814 absolute bioavailability, as calculated based on the ratio of the dose-adjusted AUC(0-∞) of LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814.
Secondary The secondary objectives are: • To assess the safety of LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 in healthy subjects; • To characterize the PK parameters of LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814 following simultaneous administration of a single oral dose of 50 mg LY3314814 and a 2-hour IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 in healthy subjects.	Secondary endpoints include: • Incidence of TEAEs and SAEs; • LY3314814 and [$^{13}C_4{}^{15}N_3$]-LY3314814 PK parameters: AUC(0-∞); AUC from time zero to time t_{last} (AUC[0-t_{last}]), where t_{last} is the last time point with a measurable concentration; C_{max}; t_{max}; and half-life associated with the terminal elimination phase ($t_{1/2}$).

5. Study Design

5.1. Overall Design

This is a Phase 1, single-center, open-label, single-period study to estimate the absolute bioavailability of LY3314814 in healthy male and female subjects not of childbearing potential.

Each subject will provide informed consent for study participation and will undergo a screening examination within 28 days prior to enrollment.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 and will remain resident in the CRU for at least 48 hours after the start of infusion, followed by outpatient visits on Days 4, 5, 6, and 7 (follow-up visit). On Day 1, following an overnight fast of at least 8 hours, subjects will receive a single oral dose of 50 mg LY3314814 and at approximately the same time an IV infusion of approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 will be started. The infusion will run for 2 hours. Blood samples will be collected predose and up to 120 hours postdose to measure LY3314814, and [$^{13}C_4{}^{15}N_3$]-LY3314814 concentrations. During the infusion and for at least 4 hours post-infusion, the PK blood samples will be taken from the arm contralateral to the infusion site. A follow-up visit will occur at least 7 days postdose.

Safety and tolerability will be assessed throughout the study by means of vital sign measurements, clinical laboratory tests, ECGs, physical examinations (as indicated), and AE recording.

5.2. Number of Participants

Up to 8 subjects may be enrolled and dosed to ensure that at least 6 subjects complete and have evaluable PK data.

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 endpoint is objective rather than subjective; therefore, investigators and subjects do not need to be blinded.

The label or tracer method allows simultaneous oral and IV dosing which provides less variability in the absolute bioavailability estimate, and ensures the systemic clearance is equivalent for the IV and oral doses.

The IV dose of [$^{13}C_4{}^{15}N_3$]-LY3314814 will be administered at a constant rate of infusion over 2 hours duration, so that the end of the IV dose occurs approximately at the t_{max} of the LY3314814 oral dose.

5.5. Justification for Dose

An oral dose of 50 mg LY3314814 was selected based on current clinical data. LY3314814 doses up to 750 mg were well tolerated in the single ascending dose study. The 50-mg dose of LY3314814 selected for this study is the highest dose that is being used in the ongoing Phase 3 studies.

The approximate 100-µg dose of [$^{13}C_4{}^{15}N_3$]-LY3314814 to be delivered intravenously is 0.20% of the 50-mg oral dose and is expected to have minimal impact on exposure and tolerability. This small fraction of the oral dose obviates the need for toxicology studies with IV administration. In addition, the IV dose is within the anticipated sensitivity that can be achieved using liquid chromatography-tandem mass spectrometry (LC/MS/MS) for the tracer. The 2-hour infusion duration is intended to align the oral and IV t_{max} (at 2 hours).

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

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 inclusion criteria at screening and/or enrollment:

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

[1a] female subjects:

women not of childbearing potential may participate and include those who are:

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

ii. postmenopausal – defined as women over 50 years of age with an intact uterus who have had 12 months of natural (spontaneous) amenorrhea without an alternative medical cause and a serum follicle-stimulating hormone level >40 mIU/mL

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

[3] have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at the time of screening

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

[5] have venous access sufficient to allow for blood sampling and IV administration of the investigational product as per the protocol

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

[7] 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:

[8] 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.

[9] are Lilly employees, AstraZeneca employees, or employees of third-party organizations involved with the study that require exclusion of their employees

[10] 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

[11] have participated, within the last 3 months, 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.

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

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

[14] have a history of significant ophthalmic disease, which includes subjects with clinically significant eye abnormalities, particularly any eye problem involving the retina, as determined by the investigator

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

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

[17] have a history of neurologic disease, including seizures (with the exception of febrile infantile seizures), or clinically significant head injury

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

[19] 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)

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

[21] have a personal or family history of prolonged QT syndrome

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

[23] have estimated glomerular filtration rate ≤59 mL/min

[24] 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

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

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

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

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

[29] are women who are pregnant or lactating

[30] have donated blood of more than 500 mL within 1 month prior to Check-in

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

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

[33] use of any drugs or substances that are known strong inducers or inhibitors of cytochrome P450 (CYP) 3A, strong inhibitors or inducers of P-glycoprotein (Pgp), or inhibitors of breast cancer resistance protein (BCRP) are specifically excluded within 14 days prior to the administration of study drug and during the study

[34] 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 consuming any restricted food or beverages within 7 days prior to the study drug administration until the final PK sample is collected

[35] are unwilling to refrain from strenuous physical activity from 72 hours prior to dosing and during the study

[36] 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 while resident in the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[37] are unwilling to refrain from consuming caffeine- or xanthine-containing food and drink from 24 hours prior to Check-in and while resident in the CRU

[38] 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*

Subjects will be required to fast overnight (at least 8 hours) prior to study drug administration on Day 1. Fluids will be restricted from 1 hour prior to and until 1 hour after oral dosing, with the exception of water required for study drug administration. Otherwise, water will be freely available at all times. A standard meal will be given to the subjects no sooner than 4 hours after the oral dose. 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, poppy seeds, or commercial apple juice or orange juice within 7 days prior to dosing 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 24 hours prior to Check-in until discharge from the CRU.

Alcohol will not be permitted from 48 hours prior to Check-in until discharge from the CRU.

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 physical activity will be allowed for 72 hours prior to dosing and during the study.

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

This study involves a comparison of a single 50-mg oral dose of LY3314814 administered concurrently with an IV formulation containing approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 infused over 2 hours. Table AZEP.2 shows the treatment administered.

On Day 1, 1 tablet of LY3314814 will be administered orally with approximately 240 mL of room temperature water in the morning in a sitting position.

On Day 1, approximately 100 µg [$^{13}C_4{}^{15}N_3$]-LY3314814 will be administered as an IV infusion over 2 hours at an approximate rate of 15 mL/hour, in the semi-recumbent position. The IV infusion will be initiated at approximately the same time as the oral dose is administered.

Table AZEP.2. Treatments Administered

Treatment Name	LY3314814	[$^{13}C_4{}^{15}N_3$]-LY3314814[a]
Dosage Formulation	50-mg tablets	Solution
Dosage Level	50 mg	100 µg
Route of Administration	Oral	Intravenous infusion
Dosing Instructions	1 tablet taken on Day 1	2-hour infusion

[a] Dosage information and administration instructions for [$^{13}C_4{}^{15}N_3$]-LY3314814 will be provided in a separate pharmacy manual.

The investigator or designee is responsible for:

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

Note: In some cases, 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 will be provided in high-density polyethylene bottles.

Information regarding the [$^{13}C_4{}^{15}N_3$]-LY3314814 solution for IV infusion will be provided in a separate pharmacy manual.

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

7.1.2. *Retention Samples*

Samples of LY3314814 will be retained and stored according to the storage conditions listed on the product label by the site (or facility approved by Lilly) for at least 5 years following the date on which the last application or supplemental application to the Food and Drug Administration (FDA) is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the study.

7.2. Method of Treatment Assignment

All subjects will receive the same treatment; this study will not be subject to randomization.

7.2.1. *Selection and Timing of Doses*

Doses will be administered on the morning of Day 1, preceded by an overnight fast of at least 8 hours and followed by a fast of at least 4 hours post-oral-dose. See Section 6.3.1 for meal and dietary restrictions.

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.

7.4.1. *Special Treatment Considerations*

7.4.1.1. Premedication for Infusions

Premedication for the infusion is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator.

7.4.1.2. Management of Infusion Reactions

The risk of an infusion reaction is anticipated to be small; however, because this is the first administration of IV [$^{13}C_4{}^{15}N_3$]-LY3314814, all subjects should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that a significant infusion reaction occurs, the following guidance should be followed:

- the investigational product infusion should be slowed or stopped, depending on the symptoms/signs present
    - if slowed, the infusion should be completed at the slower rate, as tolerated
    - if stopped, no further attempts to administer the investigational product will be made

- supportive care should be employed in accordance with the symptoms/signs

7.4.1.3. Safety Protocol in the Event of a Retrospective Positive Sterility Finding from Extemporaneously Prepared Study Treatment

If a positive sterility finding arises in the terminally sterile filtered product, the subjects who were dosed from the impacted batch should be immediately contacted and asked to return to the CRU for a full medical examination. This should include a physical examination/medical assessment, including blood pressure, pulse rate, and body temperature. Blood samples should be collected for culture and assayed for inflammatory markers such as C-reactive protein and elevations in white blood cell counts. If the signs and symptoms indicate a subject is suffering from possible infection(s), they will be clinically managed, treated, and followed up until resolution. Any AEs will be recorded as appropriate.

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).

The [$^{13}C_4{}^{15}N_3$]-LY3314814 solution for IV infusion will be prepared at the study site. Details of the preparation and storage of the IV solution will be provided in separate instructions to the site.

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 or substances that are known strong inducers or inhibitors of CYP3A, strong inhibitors or inducers of Pgp, or inhibitors of BCRP are specifically excluded within 14 days prior to the administration of study drug and during the study. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

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 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

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

8.1.1. *Discontinuation of Inadvertently Enrolled Subjects*

If the investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled prior to any dosing, the subject will be discontinued from the study with no further data collection or study procedures performed. If the investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled and dosed, the subject will be discontinued from the study and early discontinuation procedures performed.

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 4 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, 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.

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 the 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 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.

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 is considered any dose higher than planned. There is no specific antidote for LY3314814. In case of known or suspected overdose, monitoring of cardiac and hepatic effects and appropriate standard supportive therapy should be initiated as clinically indicated.

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 sign 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. .

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 study if clinically indicated or at the investigator's discretion.

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. 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 or corrected QT 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.

9.4.4. *Physical Examination*

Physical examinations and medical review with targeted examinations 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. *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

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.

9.4.6.1. Hepatic Safety

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

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

- elevation of serum ALT to ≥ [5X] ULN on two or more consecutive blood tests
- elevated serum TBL to ≥ [2X] ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥ [2X] ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a 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 concentrations of LY3314814, and [$^{13}C_4{}^{15}N_3$]-LY3314814. 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.

Concentrations of LY3314814, and [$^{13}C_4{}^{15}N_3$]-LY3314814 will be assayed using a validated LC/MS/MS method.

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

This section is 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 and to investigate genetic variants thought to play a role in AD. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

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

This section is not applicable for this study.

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 8 subjects may be enrolled and dosed to ensure that at least 6 subjects complete and have evaluable PK data.

This sample size is considered adequate for Phase 1 studies evaluating absolute bioavailability and is not intended to meet any a priori statistical requirement.

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 the investigational product and who have evaluable data. If a subject has an AE of vomiting that occurs at or before 2 times median t_{max} after dosing 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.

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 clinical lab parameters, vital signs, and ECGs. The clinical lab parameters will be listed. Vital signs will be listed and summarized using standard descriptive statistics. Electrocardiograms and physical examinations 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 LY3314814, and [$^{13}C_4{}^{15}N_3$]-LY3314814 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be AUC(0-∞) and AUC(0-t_{last}). Secondary parameters will be C_{max}, t_{max}, and $t_{1/2}$. Other noncompartmental parameters, such as total body clearance of drug calculated after IV administration (CL), apparent clearance (CL/F), apparent volume of distribution during the terminal phase (V_Z and V_Z/F), and apparent volume of distribution at steady state (V_{SS} and V_{SS}/F), may be reported.

The absolute bioavailability of LY3314814 will be calculated using the LY3314814 AUC estimates calculated after oral dosing with LY3314814 and IV administration of [$^{13}C_4{}^{15}N_3$]-LY3314814, with adjustment for dose.

10.3.2.2. Pharmacokinetic Statistical Inference

To quantify the absolute bioavailability of LY3314814, a mixed-effect analysis of variance model will be applied to the log-transformed dose-adjusted AUC of LY3314814 obtained after oral dosing and that of the IV administered [$^{13}C_4{}^{15}N_3$]-LY3314814. The model will contain formulation (oral or IV) as a fixed effect and subject as a random effect. The absolute bioavailability will be expressed as the ratio of the least-squares geometric means of the formulations (oral : IV) along with its corresponding 90% confidence interval.

The PK parameter estimates for LY3314814, and [$^{13}C_4{}^{15}N_3$]-LY3314814 will be summarized using appropriate descriptive statistics.

Additional analysis may be conducted if deemed appropriate.

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.

11. References

Not applicable.

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.
AUC	area under the drug concentration-time curve
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 t_{last}, where t_{last} is the last time point with a measurable concentration
AV	Atrioventricular
BCRP	breast cancer resistance protein
BMI	body mass index
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
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
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.
IV	Intravenous
LC/MS/MS	liquid chromatography-tandem mass spectrometry
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)
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.

SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal elimination phase
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 protein
Absolute counts of:	Albumin
Neutrophils	Total bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	Aspartate aminotransferase
Eosinophils	Alanine aminotransferase
Basophils	Creatinine
Platelets	
Urinalysis[a]	
Specific gravity	
pH	
Protein	
Glucose	Ethanol testing[c]
Ketones	Urine drug screen[c]
Bilirubin	Hepatitis B surface antigen[d]
Urobilinogen	Hepatitis C antibody[d]
Blood	HIV[d]
Nitrite	Pregnancy test (females)[e]
Microscopic examination of sediment[b]	FSH (females, if applicable)[d]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; 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 for all females (if applicable) at screening and at follow-up or early discontinuation. A urine pregnancy test may be performed on admission to the clinical research unit and may be repeated during the study at the investigator's discretion. Serum and urine tests will be performed by local 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 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 patients in consultation with Lilly 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	
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	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth muscle antibody (or anti-actin**
CPK	**antibody)[a]**

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I8D-MC-AZEP Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	11	1	11
Clinical laboratory tests[a]	7.5	3	22.5
Pharmacokinetics[b]	4	19	76
Pharmacogenetics	10	1	10
Total			119.5
Total for clinical purposes rounded up to nearest 10 mL			120

[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-AZEP(d) Summary
An Absolute Bioavailability Study of LY3314814 in Healthy Subjects Using an Intravenous Tracer Method

Protocol I8D-MC-AZEP, An Absolute Bioavailability Study of LY3314814 in Healthy Subjects Using an Intravenous Tracer Method, has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The protocol now states that

If the investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled prior to any dosing, the subject will be discontinued from the study with no further data collection or study procedures performed. If the investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled and dosed, the subject will be discontinued from the study and early discontinuation procedures performed (Section 8.1.1.).

Revised Protocol Sections

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

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.~~

If the investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled prior to any dosing, the subject will be discontinued from the study with no further data collection or study procedures performed. If the investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled and dosed, the subject will be discontinued from the study and early discontinuation procedures performed.