Protocol I8K-MC-JPDF

Relative Bioavailability and the Effect of Food on the Bioavailability of LY3337641 in Healthy Subjects

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Confidential Information

LY3337641

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

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1. Protocol Synopsis

Title of Study:
Relative Bioavailability and the Effect of Food on the Bioavailability of LY3337641 in Healthy Subjects

Rationale:
The effect of formulation may have implications for dosage and administration recommendations. This study will evaluate the relative bioavailability of the LY3337641 test formulation, commercial image tablet (esylate salt) [$T1_{fasted}$] compared to the reference formulation, Phase 1/2 tablet (diHCl salt) [R_{fasted}]. In addition, this study will evaluate the relative bioavailability of the large active pharmaceutical ingredient (API) particle size distribution (PSD) commercial image tablet (esylate salt) [$T2_{fasted}$] compared to the test formulation, commercial image tablet (esylate salt) [$T1_{fasted}$]. This study will also evaluate the effect of a high-fat meal on the relative bioavailability of the LY3337641 commercial image tablet (esylate salt) [$T1_{fed}$].

Objectives/Endpoints:

Objectives	**Endpoints**
Primary	
To evaluate the relative bioavailability of a single 20-mg dose of LY3337641 as the commercial image tablet (esylate salt) [$T1_{fasted}$] compared to the Phase 1/2 tablet (diHCl salt) [R_{fasted}].	Ratio of least square means between $T1_{fasted}$ and R_{fasted} for C_{max} and AUC(0-∞).
Secondary	
• To evaluate the effect of a high-fat meal on the bioavailability of a single 20-mg dose of LY3337641 when administered as the commercial image tablet (esylate salt) [$T1_{fed}$].	Ratio of least square means between $T1_{fed}$ and $T1_{fasted}$ for C_{max} and AUC(0-∞).
• To evaluate the relative bioavailability of a single 20-mg dose of LY3337641 when administered as the large API PSD commercial image tablet (esylate salt) [$T2_{fasted}$] compared to the commercial image tablet (esylate salt) [$T1_{fasted}$].	Ratio of least square means between $T2_{fasted}$ and $T1_{fasted}$ for C_{max} and AUC(0-∞).
• To assess the tolerability of LY3337641 when administered as a single 20-mg dose to healthy subjects.	Incidence of treatment-emergent adverse events (TEAEs).

Summary of Study Design:

This is an open-label, 4-period, 4-sequence, randomized, crossover study in healthy subjects.

Subjects will be admitted to the clinical research unit (CRU) on Day -1 of Period 1. In each treatment period, subjects will be fasted overnight for at least 10 hours and a single dose of their assigned treatment will be administered on the morning of Day 1, following a high-fat meal if applicable. At a minimum, subjects will reside at the CRU until the collection of the 72-hour pharmacokinetic blood sample; all subsequent assessments may be conducted on an outpatient visit at the discretion of the investigator.

Blood samples will be collected up to 72 hours (3 days) after each dosing occasion for the measurement of plasma concentrations of LY3337641.

Safety assessments performed during the study will include recording of adverse events (AEs), clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

Treatment Arms and Duration:
Subjects will receive single oral doses of 20 mg LY3337641 on 4 separate occasions, as the Phase 1/2 tablet (diHCl salt) in the fasted state (R_{fasted}), as the commercial image tablet (esylate salt) in the fasted state ($T1_{fasted}$) and following a high-fat meal ($T1_{fed}$), and as the large API PSD commercial image tablet (esylate salt) in the fasted state ($T2_{fasted}$). There will be a washout period of at least 5 days between dose administrations in consecutive periods.

Number of Subjects:
Up to 32 subjects may be enrolled in order to ensure that at least 24 subjects complete the study.

Statistical Analysis:

Pharmacokinetic parameter estimates for LY3337641 will be compared between formulations and between the fed and fasted states. Log-transformed C_{max} and area under the concentration versus time curve estimates will be evaluated in a linear mixed-effects model with fixed effects for treatment, period, and sequence, and random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).

The t_{max} will be analyzed non-parametrically. Median of differences and approximate 90% CI for the median of differences will be calculated for the fed versus fasted states and for the comparisons between the different formulations.

2. Schedule of Activities

Study Schedule Protocol I8K-MC-JPDF

	Screening	Periods 1, 2, 3, and 4			Follow-up/ Early discontinuation	Comments
Procedure	Up to 28 days prior to enrollment	Day -1	Days 1 to 3	Day 4	≥7 days after last dose	
Informed Consent	X					
Subject Admission to CRU		X				
Subject Discharge from CRU				X		
Outpatient Visit					X	
Study Drug Administration			Day 1, 0 h			
Medical History	X					
Height	X					
Weight	X				X	
Vital Signs (Supine)	X		Predose, 1, 2, 4, 8, 24, 48 h	72 h	X	Supine blood pressure and/or pulse rate may be measured as clinically indicated. Additional vital signs may be measured during each study period, if warranted and agreed by the investigator.
Clinical Lab Tests	X		Predose, 24 h	X	X	See Appendix 2, Clinical Laboratory Tests, for details.
Pregnancy Test	X	X			X	Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at other times.
Physical Exam/Medical Assessment	X		Predose	X	X	After screening, medical assessment only performed to include medical review and targeted examination, as appropriate.
Single 12-lead ECG	X		Predose, 1, 2, 24 h	72 h	X	

PK Samples			Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 24, 36, 48 h	72 h		Sampling times are relative to the time of study treatment administration (0 min). These are scheduled sampling times; the actual date and time of each PK sample will be recorded. Minor time deviations (e.g. ±5 min for samples prior to 24 hours) will not be considered a protocol violation.
Genetic Sample			Predose (Period 1 only)			Single sample for pharmacogenetic analysis taken on Day 1 of Period 1.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; h = hour(s); PK = pharmacokinetics.
Note: Predose assessments/sampling will be performed within 4 hours of dosing.

3. Introduction

3.1. Study Rationale

The effect of formulation may have implications for dosage and administration recommendations. The aim of this study is to evaluate the relative bioavailability of the LY3337641 test formulation, commercial image tablet (esylate salt) [$T1_{fasted}$] compared to the reference formulation, Phase 1/2 tablet (diHCl salt) [R_{fasted}]. In addition, this study will evaluate the relative bioavailability of the large active pharmaceutical ingredient (API) particle size distribution (PSD) commercial image tablet (esylate salt) [$T2_{fasted}$] compared to the test formulation, commercial image tablet (esylate salt) [$T1_{fasted}$]. This study will also evaluate the effect of a high-fat meal on the relative bioavailability of the LY3337641 commercial image tablet (esylate salt) [$T1_{fed}$].

A tablet formulation using the diHCl salt has been utilized in Phase 1 and Phase 2a studies. Two tablet strengths, 5 and 20 mg, were developed. Since the the diHCl salt has a tendency to disproportionate (physical instability liability), an alternative salt (esylate) has been pursued for commercial development. The esylate salt is more physically stable and has comparable solubility to the diHCl. Neither the diHCl nor the esylate salt is considered highly soluble per Biopharmaceutics Classification System (BCS) guidance. Hence, understanding the impact of drug substance particle size on in vivo performance is needed to determine what particle size range can be used to supply clinical trials and to justify specifications upon common technical document submission. A 20 mg tablet strength of the esylate salt is the highest tablet strength developed so far and is the strength to be used in this relative bioavailability study.

A pilot food effect evaluation using the Phase 1/2 tablet (diHCl salt) showed that administration of LY3337641 after a high-fat meal did not affect the extent of oral absorption (area under the concentration versus time curve [AUC]) but decreased the rate of absorption, resulting in a 13% lower maximum observed drug concentration (C_{max}) and delayed time to the maximum observed drug concentration (t_{max}) by 1.5 hours. Based on these findings, a high-fat meal is not expected to have a significant effect on the bioavailability of LY3337641 when administered as the commercial image tablet (esylate salt) formulation.

3.2. Background

LY3337641 is an orally available, irreversible inhibitor of Bruton's tyrosine kinase (BTK), a member of the TEC family of cytoplasmic tyrosine kinases. Bruton's tyrosine kinase is a key signaling molecule in the B-cell–receptor and Fc-receptor pathways and an essential mediator of B-cell– and myeloid-cell–dependent inflammatory arthritis (Di Paolo et al. 2011; Chakravarty et al. 2013). Bruton's tyrosine kinase is primarily expressed in hematopoietic cells, including B-cells, mast cells, and macrophages. In humans, BTK loss-of-function mutations cause nonlethal X-linked agammaglobulinemia, resulting in reduced B-cell and immunoglobulin (Ig) levels (Smith et al. 1994).

LY3337641 demonstrates potent, irreversible BTK inhibition in BTK enzyme assays, cell-based BTK phosphorylation assays, and BTK occupancy assays.

Preclinical data suggests that LY3337641 may be useful for treatment of a variety of autoimmune diseases.

In healthy adult subjects, LY3337641 was rapidly absorbed after oral administration in the fasted state, with geometric mean t_{max} ranging from 1 to 3 hours after a single dose and 1 to 2 hours after multiple doses, and elimination of LY3337641 from systemic circulation was rapid; the geometric mean half-life associated with the terminal rate ($t_{1/2}$) was 4.6 to 6.6 hours.

The metabolism of LY3337641 has not been fully elucidated. However, two metabolites, N-demethylation (M1) and N-oxidation (M2), have been detected in human plasma and urine. M1 and M2 plasma concentrations are low relative to parent concentrations in humans. Mean renal excretion of unchanged LY3337641 was <0.5% of the administered dose in humans. In excretion studies in rats and monkeys in which radiolabelled [^{14}C] LY3337641 was orally administered, the urine recovery of total radioactivity (metabolites and/or parent compound) was ≤3% of the administered dose, so renal elimination is expected to be a minor clearance route in humans.

3.3. Benefit/Risk Assessment

A single Phase 1 study (Study I8K-MC-JPDD [JPDD]) was conducted in healthy adult males to determine the safety, tolerability, pharmacokinetics (PK), and food effect of single and multiple doses of orally administered LY3337641. In the single dose portion of the study, the drug was well tolerated following single doses ranging from 10 to 200 mg. In the 20 mg dosing arm, 4 of the 6 subjects administered LY3337641 reported 6 treatment-emergent AEs (TEAEs), only one of which (nausea, mild intensity) was attributed to study drug. In the multiple-dosing portion of the study (14 days duration, once daily and twice-daily dosing), the drug was generally well tolerated at dosages up to 40 mg once daily. At dosages totaling 80 mg per day and higher, significant TEAEs (ie, TEAEs leading to discontinuation or deemed clinically significant by the investigator) were reported. The majority of these events involved skin-related manifestations, the most common being rash, with an onset occurring on or after 10 days of LY3337641administration. Some cases were associated with systemic signs and symptoms, such as fever, arthritis, and laboratory abnormalities. Skin related TEAEs were all accompanied with a rise in C-reactive protein and in one subject with a mild increase in tryptase as well. In Study JPDD, over a dose range of 10 to 200 mg single oral doses, C_{max} and AUC of LY3337641 were proportional to dose.

On the basis of projected BTK occupancy using the Phase 1 data, 20 mg is expected to be in the clinically efficacious dose range. The Phase 1 safety profile supports further clinical development of LY3337641 for treatment of autoimmune diseases; LY3337641 is currently progressing into Phase 2 at dose levels of 5, 10, and 30 mg once daily.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of LY3337641 are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table JPDF.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the relative bioavailability of a single 20-mg dose of LY3337641 as the commercial image tablet (esylate salt) [$T1_{fasted}$] compared to the Phase 1/2 tablet (diHCl salt) [R_{fasted}].	Ratio of least square means between $T1_{fasted}$ and R_{fasted} for C_{max} and AUC(0-∞).
Secondary	
• To evaluate the effect of a high-fat meal on the bioavailability of a single 20-mg dose of LY3337641 when administered as the commercial image tablet (esylate salt) [$T1_{fed}$].	Ratio of least square means between $T1_{fed}$ and $T1_{fasted}$ for C_{max} and AUC(0-∞).
• To evaluate the relative bioavailability of a single 20-mg dose of LY3337641 when administered as the large API PSD commercial image tablet (esylate salt) [$T2_{fasted}$] compared to the commercial image tablet (esylate salt) [$T1_{fasted}$].	Ratio of least square means between $T2_{fasted}$ and $T1_{fasted}$ for C_{max} and AUC(0-∞).
• To assess the tolerability of LY3337641 when administered as a single 20-mg dose to healthy subjects.	Incidence of treatment-emergent adverse events (TEAEs).

5. Study Design

5.1. Overall Design

This is an open-label, 4-period, 4-sequence, randomized, crossover study in healthy subjects. Up to 32 subjects may be enrolled in order to ensure that at least 24 subjects complete the study (ie, complete all 4 treatment periods).

Subjects will receive single oral doses of 20 mg LY3337641 on 4 separate occasions. Each subject will receive the following:

- Reference formulation (R_{fasted}): 20 mg LY3337641 Phase 1/2 tablet (diHCl salt) administered in the fasted state;
- Test formulation 1 ($T1_{fasted}$): 20 mg LY3337641 commercial image tablet (esylate salt) administered in the fasted state;
- Test formulation 1 ($T1_{fed}$): 20 mg LY3337641 commercial image tablet (esylate salt) administered in the fed state;
- Test formulation 2 ($T2_{fasted}$): 20 mg LY3337641 large API PSD commercial image tablet (esylate salt) administered in the fasted state.

Subjects will be randomly allocated to one of the treatment sequences below (Table JPDF.2).

Table JPDF.2. Treatment Sequences in Study I8K-MC-JPDF

Sequence	Period 1	Period 2	Period 3	Period 4
1	Reference formulation (R_{fasted})	Test formulation 2 ($T2_{fasted}$)	Test formulation 1 ($T1_{fasted}$)	Test formulation 1 ($T1_{fed}$)
2	Test formulation 1 ($T1_{fasted}$)	Reference formulation (R_{fasted})	Test formulation 1 ($T1_{fed}$)	Test formulation 2 ($T2_{fasted}$)
3	Test formulation 1 ($T1_{fed}$)	Test formulation 1 ($T1_{fasted}$)	Test formulation 2 ($T2_{fasted}$)	Reference formulation (R_{fasted})
4	Test formulation 2 ($T2_{fasted}$)	Test formulation 1 ($T1_{fed}$)	Reference formulation (R_{fasted})	Test formulation 1 ($T1_{fasted}$)

In each period, subjects will be admitted to the clinical research unit (CRU) on Day -1. In each treatment period, subjects will be fasted overnight and a single dose of 20 mg LY3337641 will be administered in the morning of Day 1. Subjects will receive a high-fat meal prior to dosing with LY3337641 if applicable (see Section 6.3.1). Subjects will reside at the CRU until the collection of the 72-hour pharmacokinetic blood sample.

There will be a washout period of at least 5 days between dose administrations in consecutive periods.

If the investigator decides not to administer the first dose to a subject or not to enroll a subject on a particular day, the subject may be rescheduled to participate in the study; and any procedures performed up to that point may be repeated.

Blood samples will be collected up to 72 hours after each dosing occasion for the measurement of plasma concentrations of LY3337641.

Safety assessments will be performed during the study included recording of AEs, clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

5.2. Number of Participants

Up to 32 subjects may be enrolled in order to ensure that at least 24 subjects complete all 4 periods of 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 will be an open-label study. Blinding is not necessary because the primary endpoint is PK, and thus not vulnerable to subject or investigator bias.

A crossover design is chosen to enable each subject to act as their own control in the assessment of formulation and food effects. Treatment order randomization will prevent any selection bias that might otherwise result from treatment order, and will mitigate period effects.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications in patients.

5.5. Justification for Dose

The dose level of 20 mg is in the expected therapeutic dose range and is high enough to fully characterize the single-dose PK of the compound. This is also the highest unit dose strength. In addition, as single doses up to 200 mg LY3337641 have been well tolerated, the 20-mg dose is considered appropriate for this study.

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 electrocardiogram (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 criteria at screening and/or enrollment:

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

[1a] male subjects:

agree to use an effective method of contraception and not donate sperm for the duration of the study and for 90 days following the last dose of study drug (see Section 6.3.4)

[1b] female subjects:

(i) women not of child-bearing 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 – postmenopausal is defined as women with an intact uterus who have not taken hormones or oral contraceptives within 1 year, who have had either cessation of menses for at least 1 year, or 6 to 12 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) consistent with menopause (FSH >40 IU/L).

(ii) women of child-bearing potential may participate, and include those who test negative for pregnancy prior to initiation of treatment based on a urine pregnancy test and agree to use one highly effective method of contraception or a combination of 2 effective methods of contraception during the study and for 28 days following the last dose of study drug (see Section 6.3.4).

[2] aged 21 to 65 years (inclusive) at the time of screening

[3] have a body mass index of 18.5 to 32.0 kg/m^2, inclusive

[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 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

[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 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

[12] have previously completed or withdrawn from this study or any other study investigating LY3337641, and have previously received the investigational product

[13] have known allergies to LY3337641, related compounds or any components of the formulation, or history of significant atopy

[14] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[15] have an abnormal blood pressure as determined by the investigator

[16] have significant history of or current cardiovascular, dermatological (such as eczema, psoriasis, and acne), respiratory, hepatic, renal, gastrointestinal (cholecystectomy is not acceptable), 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

[17] have known or ongoing psychiatric disorders

[18] regularly use known drugs of abuse

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

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

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

[22] are women who are lactating

[23] have used or intend to use over-the-counter or prescription medication, including herbal medications, within 14 days prior to planned dosing

[24] have donated blood or had blood loss of more than 450 mL within 3 months of screening

[25] 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 for 48 hours prior to admission in each study period, 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)

[26] have had symptomatic herpes zoster infection within 3 months of screening

[27] medical history, examination finding(s) and/or chest radiograph suggestive of active or latent tuberculosis

[28] have received live vaccine(s) within 1 month of screening, or intend to during the study

[29] are immunocompromised

[30] are currently smoking more than 10 cigarettes per day (or equivalent in tobacco or nicotine products) or are unwilling to abide by smoking restrictions as specified in Section 6.3.2

[31] 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 (except when test meals are administered prior to dosing).

Administration of LY3337641 in the fasted state

Following an overnight fast of at least 10 hours, subjects will be administered 20 mg LY3337641 with approximately 240 mL water. Water can be allowed as desired except from 1 hour before until 1 hour after drug administration. No food will be allowed for at least 4 hours postdose,

after which time a standardized meal will be provided. Meals will be provided as appropriate at all other times.

Administration of LY3337641 in the fed state

Following an overnight fast of at least 10 hours, subjects will start a Food and Drug Administration (FDA)-defined high-fat meal 30 minutes prior to administration of LY3337641. It is intended that the meals will be ingested in their entirety over an approximate 25-minute period, such that they are completed at least 5 minutes before dosing. A 20-mg dose of LY3337641 will be given with approximately 240 mL of water. Water can be given as desired, except for 1 hour before and 1 hour after drug administration. No further food will be permitted until at least 4 hours postdose, after which time a standardized meal will be provided. Meals will be provided as appropriate at all other times.

High-fat meal

The high-fat meal (fat comprises approximately 50% of total calorific content) should consist of approximately 800 to 1000 calories in total. No additional food or substitute is allowed. An example of a typical test meal is 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. The test meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine – Subjects will refrain from consuming xanthine- or caffeine-containing food and drinks from 48 hours prior to admission in each study period, and while resident in the CRU. Examples of these food and drinks include coffee, tea, cola drinks and chocolate.

Alcohol – Subjects will not consume alcohol for 48 hours prior to admission in each study period, and while resident in the CRU.

Smoking – Subjects should not smoke or use any nicotine products from 2 hours prior to each admission until after collection of the 72-hour PK sample.

6.3.3. Activity

No strenuous activity will be allowed for 48 hours prior to admission and during the study.

6.3.4. Contraception

Male subjects

Male subjects or their partners will be required to use an effective method of contraception during the study and for 90 days after the last dose of study drug. Acceptable methods of contraception may include:

- Condom (male condom or female condom) in conjunction with spermicidal gel, foam, cream, film, or suppository.

- Diaphragm or cervical vault cap used in conjunction with spermicidal gel, foam, cream, film, or suppository.
- Male sterilization, with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.
- True abstinence (this must be due to subject's lifestyle choice; ie, the subject should not become abstinent just for the purpose of study participation). Withdrawal or calendar methods are not considered acceptable.
- Female partner with placement of an effective hormonal intrauterine device.
- Female partner with established use of oral, injected, or implanted hormonal methods of contraception.

Sexual intercourse with pregnant partners should also be avoided during the course of the study unless condoms are used from the time of the first dose until 28 days after dosing.

Male subjects must agree not to donate sperm for the duration of the study and for 90 days following the last dose of study drug

Female subjects of child-bearing potential

Female subjects of child-bearing potential must agree to use one highly effective method of contraception or a combination of 2 effective methods of contraception during the study and for 28 days following the last dose of study drug.

Highly effective methods of contraception are contraceptive measures with a failure rate of <1% per year, and include:

- Intrauterine device (IUD; eg, Mirena). Steel or copper IUDs are not acceptable.
- Established use of oral, implanted, transdermal, or hormonal method of contraception associated with inhibition of ovulation.
- Male sterilization, with verbal confirmation of surgical success
- Bilateral tubal ligation.

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 comparisons of different formulations of LY3337641. LY3337641 will be administered at a dose of 20 mg in each treatment period.

The treatment arms are as follows:

- Reference formulation (R_{fasted}): 20 mg LY3337641 Phase 1/2 tablet (diHCl salt) administered in the fasted state;
- Test formulation 1 ($T1_{fasted}$): 20 mg LY3337641 commercial image tablet (esylate salt) administered in the fasted state;
- Test formulation 1 ($T1_{fed}$): 20 mg LY3337641 commercial image tablet (esylate salt) administered in the fed state;
- Test formulation 2 ($T2_{fasted}$): 20 mg LY3337641 large API PSD commercial image tablet (esylate salt) administered in the fasted state.

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;
- 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

Tablets containing 20 mg LY3337641 will be provided to the site.

Multiple subjects may be dosed from a single package.

Clinical trial materials will be labeled according to the country's regulatory requirements. Packages will be labeled to distinguish each tablet in the dosing schedule:

- Phase 1/2 diHCl salt (reference formulation)
- Commercial image tablet (esylate salt) (test formulation 1)
- Large API PSD commercial image tablet (esylate salt) (test formulation 2)

There is no requirement to store retention samples.

7.2. Method of Treatment Assignment

Subjects will be randomized to 1 of 4 treatment sequences using a computer-generated allocation schedule.

7.2.1. Selection and Timing of Doses

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

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Dose reductions or adjustments will not be allowed during 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 or designee 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

The use of topical medication, provided there is no evidence of chronic dosing with the risk of systemic exposure, and occasional acetaminophen/ibuprofen is acceptable at the discretion of the investigator. Additional drugs are prohibited during the study unless required to treat an AE.

If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator with consultation with a Lilly clinical pharmacologist or clinical research physician. Any additional medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

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

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- enrollment in any other clinical 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;
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent;
- Subject Decision:
    - the subject, or designee, for example, parents or legal guardian requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

Appendix 2 lists the 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.

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

A "reasonable possibility" means that there is a 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 (IP), AND is considered reasonably possibly related to a study procedure then it MUST be reported.

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

Pregnancy (maternal or paternal exposure to IP) does not meet the definition of an adverse event. 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 IP or procedure. United States 21 CFR 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 collects product complaints on IPs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3337641 is considered any dose higher than the planned study dose. There is no specific antidote for LY3337641. In the event of overdose, the subject should receive appropriate supportive care and any AEs should be documented.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

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

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

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 by the investigator.

9.4.3. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2).

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

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities. Electrocardiograms must be recorded before collecting any blood for safety or pharmacokinetic tests. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon as possible after the time of ECG collection, 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, clinically significant changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in subject management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an adverse event.

9.4.4. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or research physician will consult with the functionally independent Global Patient Safety medical physician or clinical research scientist when appropriate, and periodically review:

- trends in safety data;
- laboratory analytes;
- AEs.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of LY3337641. A maximum of 2 samples per treatment period may be collected at additional time points 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 time (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 LY3337641 will be assayed using a validated liquid chromatography with tandem MS detection methods.

Bioanalytical samples collected to measure LY3337641 concentrations will be retained for a maximum of 1 year following last subject visit for the study.

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, 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 LY3337641 and to investigate genetic variants thought to play a role in rheumatoid arthritis. Assessment of variable response may include evaluation of AEs or differences in exposure.

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 the ethical review board (ERB)/institutional review board (IRBs) 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 LY3337641 or after LY3337641 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 32 subjects may be enrolled in order to ensure that 24 subjects complete all 4 study periods.

The sample size chosen will provide a precision of 8% for the estimate of the geometric mean ratio in AUC between the test formulations versus the reference formulation, and between the test formulations administered in the fed versus the fasted state. It means that there is a 90% probability that the half-width of the resulting 90% confidence interval (CI) of the geometric mean ratio in AUC is no larger than 8%. No direct estimate of intra-subject variability is available.

The sample size chosen will provide a precision of 13% for the estimate of the geometric mean ratio in C_{max} between the test formulations versus the reference formulation, and between the test formulations administered in the fed versus the fasted state. It means that there is a 90% probability that the half-width of the resulting 90% CI of the geometric mean ratio in AUC is no larger than 13%. No direct estimate of intra-subject variability is available.

Based on Study JPDD, the coefficient of variation (CV%) for AUC and C_{max} were approximately 30% and 50%, respectively, for a 20-mg dose of LY3337641 administered. Assuming that half of the total CV% is contributed by intra-subject variability, an approximation of the intra-subject variability of 15% for AUC and 25% for C_{max}.

Subjects who are randomized but not complete all 4 treatment periods may be replaced to ensure that enough subjects complete the study. The replacement subject will assume the withdrawn subject's treatment sequence (receiving each treatment allocated).

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.

10.2.2. Study Participant Characteristics

The subjects' age, sex, weight, height, and other demographic characteristics will be recorded and summarized using descriptive statistics.

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 randomized subjects receiving at least one dose of the IP according to the treatment the subjects actually received. Safety analyses will be conducted on the safety population, defined as all randomized subjects receiving at least one dose of the IP, whether or not they completed all protocol requirements.

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

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All drug-related and procedural 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 IP 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 drug-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for LY3337641 will be calculated by standard noncompartmental methods of analysis and reported by treatment period.

The primary parameters for analysis will be C_{max} and AUC from time zero to infinity (AUC[0-∞]), and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]). The t_{max} will be observed from the data. Other noncompartmental parameters, such as half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$), apparent total body clearance of drug calculated after extra-vascular administration (CL/F), and apparent volume of distribution during the terminal phase after extra-vascular administration (V_z/F) may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameter estimates for LY3337641 will be compared between formulations and between the fed and fasted states. Log-transformed C_{max} and the AUC estimates will be analyzed using a linear mixed-effects model with PK estimate as response variable, treatment, period, and sequence as fixed effects; and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The t_{max} will be analyzed non-parametrically. Median of differences and approximate 90% CI for the median of differences will be calculated for the fed versus fasted states and for the comparisons between the different formulations.

10.3.3. Interim Analyses

An interim analysis is scheduled to occur after approximately 24 subjects complete the first 3 periods to support an internal formulation decision for clinical planning activities associated with LY3337641. The primary purpose of this interim analysis is to compare the AUC(0-∞) and C_{max} of $T1_{fasted}$ and R_{fasted}, however all available PK data will be evaluated during the interim. After Period 3, crossover data from approximately 12 subjects for these 2 treatments should be available. A sample size of 12 subjects will provide a precision of 13% and 20% for the estimate of the geometric mean ratio in AUC and C_{max}, respectively, between the two formulations. Assumptions are the same as detailed in Section 10.1. An additional interim analysis after Period 4 and before the final database lock may be conducted if needed.

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
API	active pharmaceutical ingredient
AUC	area under the concentration versus time curve
AUC(0-∞)	AUC from time zero to infinity
AUC(0-t_{last})	AUC from time zero to time t, where t is the last time point with a measurable concentration
BTK	Bruton's tyrosine kinase
CI	confidence interval
CL/F	apparent total body clearance of drug calculated after extra vascular administration
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
CRF	case report form
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
ECG	electrocardiogram
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
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug: An application to the FDA to allow testing of a new drug in humans.
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 (IP)	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.
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical trial, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
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.
PK	pharmacokinetic(s)
PSD	particle size distribution
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 rate constant in noncompartmental analysis
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
t_{max}	time to the maximum observed drug concentration
V_z/F	apparent volume of distribution during the terminal phase after extra vascular administration

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Hematology[a]	Clinical Chemistry[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Chloride
Mean cell volume	Calcium
Mean cell hemoglobin	Phosphorus
Mean cell hemoglobin concentration	Fasting glucose
Leukocytes (WBC)	Urea
Absolute counts of:	Uric acid
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase (ALP)
Basophils	Aspartate aminotransferase (AST)
Platelets	Alanine aminotransferase (ALT)
	Creatinine
Urinalysis[a]	Gamma-glutamyl transferase (GGT)
Specific gravity	Lactate dehydrogenase (LDH)
pH	
Protein	
Glucose	
Ketones	Hepatitis B surface antigen[b,c]
Bilirubin	Hepatitis C antibody[b,c]
Urobilinogen	HIV[b,c]
Blood	Pregnancy test
Nitrite	FSH[b]
Leukocytes	
Microscopic examination of sediment (test only if dipstick result is abnormal and per investigator's discretion)	

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

a Results will be reported and validated by the local lab at the time of testing.

b Performed at screening only if clinically indicated and per investigator's discretion.

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

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 IP.
- 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 or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to 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 (CIOMS) International Ethical Guidelines;
2) applicable ICH GCP Guidelines;
3) applicable laws and regulations.

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

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

In addition, 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. 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 I8K-MC-JPDF Sampling Summary

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	17	1	17
Clinical laboratory tests[a]	11	13	143
Pharmacokinetics[b]	2	76	152
Pharmacogenetics	10	1	10
Total			322
Total for clinical purposes [rounded up to nearest 10 mL]			330

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

b Includes up to 2 additional samples per treatment period.

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