Protocol (a) I8K-JE-JPDB

A Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3337641 in Japanese and Caucasian Healthy Subjects

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LY3337641

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
24 December 2016
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1. Protocol Synopsis

Title of Study:
A Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3337641 in Japanese and Caucasian Healthy Subjects

Rationale:
Study I8K-JE-JPDB (JPDB) is the first clinical evaluation of LY3337641 in Japanese subjects and is being conducted to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single-dose (SD) and multiple-dose (MD) administration of LY3337641 in healthy Japanese and Caucasian subjects. Findings from the study will be used to assess the safety and tolerability of LY3337641 in this study population including Japanese subjects, further characterize the PK properties of LY3337641, and explore the PD effects of Bruton's tyrosine kinase inhibition. Such findings in Japanese subjects are essential for further clinical development in Japan for various indications.

Objectives/Endpoints:

Objectives	Endpoints
Primary To explore the safety and tolerability of LY3337641 in healthy Japanese and Caucasian subjects	AEs and SAEs
Secondary To estimate the PK parameters of single and multiple doses of LY3337641 following oral administration in healthy Japanese and Caucasian subjects	C_{max} and AUC

Abbreviations: AEs = adverse events; AUC = area under the plasma concentration-time curve; C_{max} = maximum drug concentration; PK = pharmacokinetic; SAEs = serious adverse events.

Summary of Study Design:

Study JPDB is a single-site, subject- and investigator-blind, randomized, placebo-controlled, SD and MD study to assess the safety, tolerability, PK, and PD of LY3337641 in healthy Japanese and Caucasian subjects.

Treatment Arms and Duration:
Screening may occur up to 28 days prior to the first dose (Day 1). All cohorts will be randomized in a 3:1 ratio of LY3337641 to placebo. Study JPDB will numerically compare LY3337641 (30 mg once daily in MD cohorts and 5, 80, and 160 mg in SD cohorts) with placebo, when administered orally. An optional cohort may be included in the MD portion. The study drug is supplied as tablets containing 5 or 20 mg of LY3337641 with matching placebo tablets. For the MD cohorts, 6 Japanese subjects and 3 Caucasian subjects will receive LY3337641, while 2 Japanese subjects and 1 Caucasian subject will receive placebo. For the SD cohorts, 3 Japanese subjects and 3 Caucasian subjects will receive LY3337641, while 1 Japanese subject and 1 Caucasian subject will receive placebo.

In the MD cohorts, LY3337641 or placebo will be dosed on Days 1 through 15, and subjects will be followed for approximately 2 weeks. In the SD cohorts, LY3337641 or placebo will be dosed on Day 1, and subjects will be followed for approximately 2 weeks.

Number of Subjects:
Up to 60 subjects may be enrolled so that approximately 36 to 48 subjects complete the study.

Statistical Analysis:

PK analyses will be conducted for all subjects who receive at least 1 dose of LY3337641 and have evaluable PK data. PD analyses will be conducted on the full analysis set, which includes all data from all subjects receiving at least 1 dose of LY3337641 or placebo. Safety analyses will be conducted for all randomized subjects who receive at least 1 dose of LY3337641 or placebo and have at least 1 postdose safety assessment, regardless of whether they have completed all protocol requirements. For QT interval, all subjects with at least 1 postdose QT interval measurement will be included in the analysis. Summary statistics, data tabulations, and data graphs will be provided and may be separated by race (Japanese and Caucasian) as appropriate.

Safety: All adverse events will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. The incidence of symptoms for each treatment will be presented by severity and by association with the 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 serious adverse events will be reported. Laboratory parameters, vital signs, and electrocardiogram parameters will be summarized using standard descriptive statistics.

PK Analysis: PK parameter estimates for LY3337641 will be calculated using standard noncompartmental methods of analysis. In the SD cohorts, the primary parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$), and area under the concentration versus time curve from 0 to 24 hours (AUC_{0-24}) of LY3337641. In the MD cohorts, the primary parameters to be calculated will include C_{max} (or C_{max} during a dosing interval at steady state [$C_{max,ss}$]) and area under the concentration versus time curve during the dosing interval ($AUC_{0-\tau}$) of LY3337641 after the first and last dose of investigational product. Other noncompartmental parameters, such as half-life, apparent clearance, apparent volume of distribution, and accumulation ratio (MD period only), may be reported.

PD Analysis: Bruton's tyrosine kinase occupancy will be listed and summarized using standard descriptive statistics.

2. Schedule of Activities

Study Schedule Protocol I8K-JE-JPDB (Cohorts 1 and 5)

Visit	**Screening**	**Treatment Period[a]**								**Follow-Up[a]**					
Study Day	≤28 days	-2	-1	1[b]	2	4	8	11	15	16	17	19	22	25	29/ EoS
Inpatient stay at CRU		←									→				
Informed consent	X														
Review eligibility	X		X												
Randomization				X											
IP administration[c]				X	X	X	X	X	X						
Complete medical history	X														
Review preexisting conditions/AEs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review concomitant medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X										X				X
Symptom-directed physical examination[d]		X	X	X	X	X	X	X	X	X		X	X	X	
Body weight and height[e]	X		X						X						X
Vital signs (pulse rate, blood pressure, body temperature)[f]	X		0	0, 1, 2, 4, 12	24[i]	0	0	0	0, 1, 2, 4, 12	24	48				X
12-Lead ECG[g]	X			-1, -0.5, 0, 0.5, 1, 2, 3, 4, 6, 12	24[i]	0	0	0	0, 0.5, 1, 2, 3, 4, 6, 12	24	48				X
Chest x-ray (posterior, anterior, and lateral)	X														
Clinical laboratory measures (serum chemistry, hematology, urinalysis)	X			0	24[i]		0				48				X
HBcAb, HBsAg, HCV, and HIV tests	X														
Serum pregnancy test[h]	X														
Urine pregnancy test[h]			X				0		0						X

Visit	Screening	Treatment Period[a]								Follow-Up[a]					
Study Day	≤28 days	-2	-1	1[b]	2	4	8	11	15	16	17	19	22	25	29/ EoS
FSH[h]	X														
Drug and alcohol screen	X	X													
QuantiFERON®-TB Gold Plus	X														
PK sampling: blood				0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12	24[i]	0	0	0	0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12	24, 36	48	X	X	X	X
BTK occupancy				0, 1, 2, 4, 12	24[i]		0		0, 1, 2, 4, 12	24	48	X	X	X	X
Skin inspection[d]			X	0, 12	24[i]	0	0	0	0	X	X	X	X	X	X
Non-PGx stored sample				0			0			24					
PGx				0											

Abbreviations: AEs = adverse events; BTK = Bruton's tyrosine kinase; CRU = clinical research unit; ECG = electrocardiogram; EoS = end of study; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IP= investigational product; PGx = pharmacogenomics; PK = pharmacokinetic; TB = tuberculosis.

Note: numbers are in hours in relation to dosing; 0 = predose.

[a] All planned procedures will be done predose unless the time is indicated.

[b] For twice-daily regimen, the time is based on the first dose. The second dose should be administered after sample collection for the 12-hour time point.

[c] Subjects will be dosed every day from Day 1 through Day 15. For twice-daily regimen, only the morning dose will be administered on Day 15.

[d] Assessment should be performed every day during the subject's stay at the CRU.

[e] Height will be measured at screening only. Body weight will be measured in the morning.

[f] Refer to Section 9.4.2 for instructions on vital signs.

[g] Refer to Section 9.4.3 for instructions on ECGs. ECGs should be administered after subject has been resting in the supine position for approximately 5 minutes. On days without dosing, ECGs should be administered close to the Day 1 dosing time, when possible. ECGs will be collected in triplicate except at the screening visit.

[h] All female subjects of childbearing potential will undergo a serum pregnancy test at screening. For women who are considered postmenopausal, FSH should be drawn to confirm postmenopausal status as defined in inclusion criterion [1b] and exemption from further pregnancy tests (urine) during the study.

[i] This 24-hour sample is to be taken predose.

Study Schedule Protocol I8K-JE-JPDB (Cohorts 2, 3, and 4)

Visit	Screening	Treatment Period[a]			Follow-Up[a]					
Study Day	≤28 days	-2	-1	1	2	3	5	8	11	15/EoS
Inpatient stay at CRU		←	—	—	—	→				
Informed consent	X									
Review eligibility	X		X							
Randomization				X						
IP administration				X						
Complete medical history	X									
Review preexisting conditions/AEs	X	X	X	X	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X					X				X
Symptom-directed physical examination		X	X	X	X		X	X	X	
Body weight and height[b]	X		X			X				X
Vital signs (pulse rate, blood pressure, body temperature)[c]	X		0	0, 1, 2, 4, 12	24	48				X
12-Lead ECG[d]	X			-1, -0.5, 0, 0.5, 1, 2, 3, 4, 6, 12	24	48				X
Chest x-ray (posterior, anterior, and lateral)	X									
Clinical laboratory measures (serum chemistry, hematology, urinalysis)	X			0		48				X
HBcAb, HBsAg, HCV, and HIV tests	X									
Serum pregnancy test[e]	X									
Urine pregnancy test[e]			X							X
FSH[e]	X									

Visit	Screening	Treatment Period[a]			Follow-Up[a]					
Study Day	≤28 days	-2	-1	1	2	3	5	8	11	15/EoS
Drug and alcohol screen	X	X								
QuantiFERON®-TB Gold Plus	X									
PK sampling: blood				0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12	24, 36	48		X		X
BTK occupancy				0, 1, 2, 4, 12	24	48		X		X
Skin inspection			X	0, 12	X	X	X	X	X	X
Non-PGx stored sample				0				X		X
PGx				0						

Abbreviations: AEs = adverse events; BTK = Bruton's tyrosine kinase; CRU = clinical research unit; ECG = electrocardiogram; EoS = end of study; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IP= investigational product; PGx = pharmacogenomics; PK = pharmacokinetic; TB = tuberculosis.

Note: numbers are in hours in relation to dosing; 0 = predose.

[a] All planned procedures will be done predose unless the time is indicated.

[b] Height will be measured at screening only. Body weight will be measured in the morning.

[c] Refer to Section 9.4.2 for instructions on vital signs.

[d] Refer to Section 9.4.3 for instructions on ECGs. ECGs should be administered after subject has been resting in the supine position for approximately 5 minutes. On days without dosing, ECGs should be administered close to the Day 1 dosing time, when possible. ECGs will be collected in triplicate except at the screening visit.

[e] All female subjects of childbearing potential will undergo a serum pregnancy test at screening. For women who are considered postmenopausal, FSH should be drawn to confirm postmenopausal status as defined in inclusion criterion [1b] and exemption from further pregnancy tests (urine) during the study.

3. Introduction

3.1. Study Rationale

Study I8K-JE-JPDB (JPDB) is the first clinical evaluation of LY3337641 in Japanese subjects and is being conducted to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single-dose (SD) and multiple-dose (MD) administration of LY3337641 in healthy Japanese and Caucasian subjects. Findings from the study will be used to assess the safety and tolerability of LY3337641 in this study population including Japanese subjects, further characterize the PK properties of LY3337641, and explore the PD effects of Bruton's tyrosine kinase (BTK) inhibition. Such findings in Japanese subjects are essential for further clinical development in Japan for various indications.

3.2. Background

LY3337641 is an orally available, irreversible inhibitor of BTK, a member of the TEC family of cytoplasmic tyrosine kinases. BTK 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). BTK is primarily expressed in hematopoietic cells, including B cells, monocytes, and macrophages (Burger 2014). In humans, BTK loss-of-function mutations cause nonlethal X-linked agammaglobulinemia, resulting in reduced B-cell and immunoglobulin levels (Aalipour and Advani 2014). LY3337641 is currently being developed for rheumatoid arthritis (RA), and a Phase 2 study in patients with RA (I8K-MC-JPDA [JPDA]) is ongoing. Potential therapeutic benefits of BTK inhibition for RA include reduced pathogenic B-cell autoantibody production and myeloid-cell proinflammatory cytokine production and inhibition of mast cell and basophil degranulation (Horwood et al. 2012).

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

The in vivo activity of LY3337641 was investigated in mouse and rat models of collagen-induced arthritis and mouse models of systemic lupus erythematosus. LY3337641 was effective in the mouse arthritis model, where it halted progression of clinical arthritis and significantly diminished structural damage in the joints. The high level of efficacy for clinical disease activity was reproduced in the rat arthritis model. LY3337641 was also effective in a spontaneous mouse model of systemic lupus erythematosus, where it improved skin lesions, reduced proteinuria, and improved renal histopathology scores. Taken together, these results suggest that LY3337641 may be useful for treatment of autoimmune diseases, including RA.

CCI [redacted]

Results from nonclinical studies with LY3337641 and the Study JPDD safety profile support the design of this study.

3.3. Benefit/Risk Assessment

No clinically significant safety concerns have been identified at the doses proposed in this study for LY3337641. The dose levels included in this study are within the range of doses studied previously, and the tolerability has been confirmed.

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.

4. Objectives and Endpoints

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

Table JPDB.1. Objectives and Endpoints

Objectives	Endpoints
Primary To explore the safety and tolerability of LY3337641 in healthy Japanese and Caucasian subjects	AEs and SAEs
Secondary To estimate the PK parameters of single and multiple doses of LY3337641 following oral administration in healthy Japanese and Caucasian subjects	C_{max} and AUC
Exploratory Objectives 1. To explore the PD following single and multiple doses of LY3337641 in healthy Japanese and Caucasian subjects 2. To explore the safety, tolerability, PK, and PD of LY3337641 in Japanese subjects in relation to Caucasian subjects 3. To explore the effect of LY3337641 on ECG findings in healthy Japanese and Caucasian subjects	1. BTK occupancy 2. AEs, SAEs, C_{max}, AUC, and BTK occupancy 3. ECG parameters

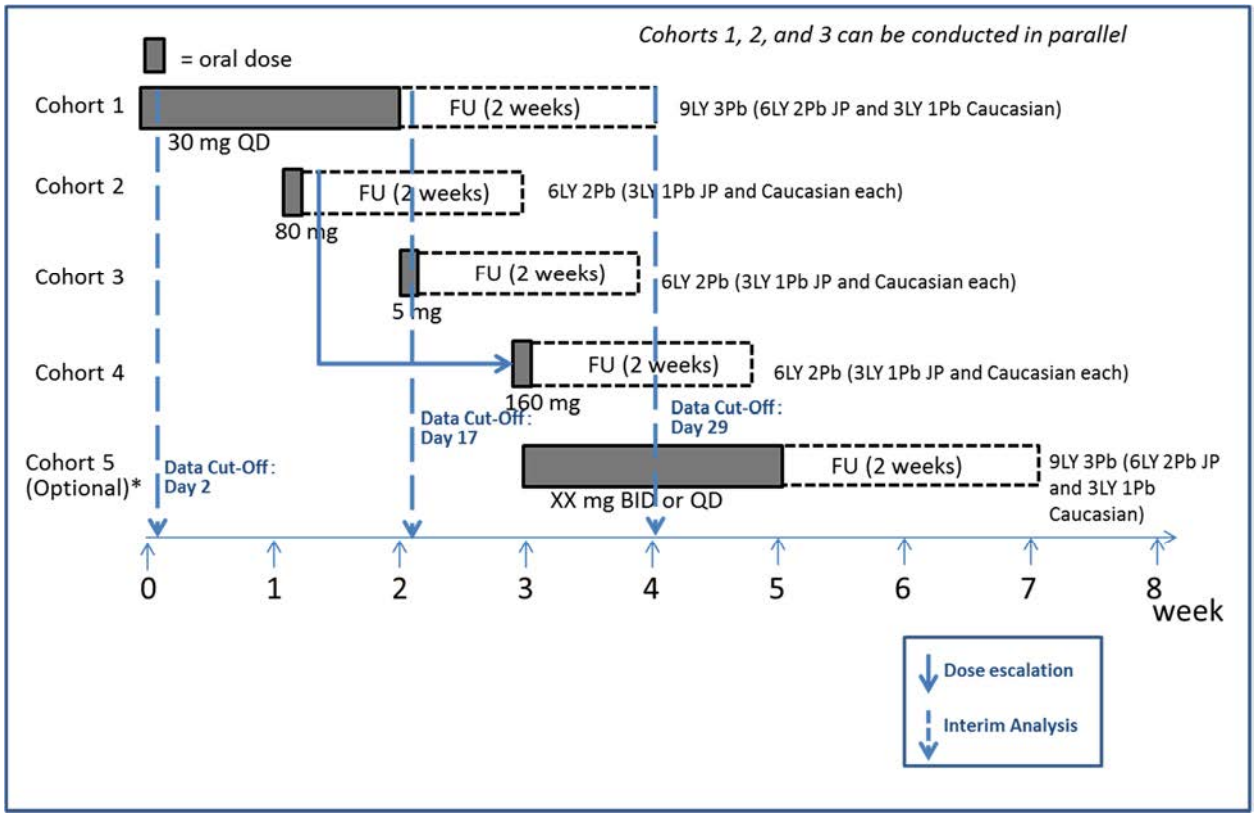
Abbreviations: AEs = adverse events; AUC = area under the plasma concentration-time curve; BTK = Bruton's tyrosine kinase; C_{max} = maximum drug concentration; ECG = electrocardiogram; PD = pharmacodynamics; PK = pharmacokinetic(s); SAEs = serious adverse events.

5. Study Design

5.1. Overall Design

This is a single-site, subject- and investigator-blind, randomized, placebo-controlled, SD and MD study to assess the safety, tolerability, PK, and PD of LY3337641 in healthy Japanese and Caucasian subjects. Subjects will be randomized to LY3337641 within each cohort as shown in Figure JPDB.1. All cohorts will be randomized in a 3:1 ratio of LY3337641 to placebo. MD Cohort 1 (30 mg QD for 2 weeks) and Cohort 5 (optional) will consist of 12 subjects (8 Japanese and 4 Caucasian). SD Cohorts 2, 3, and 4 (5, 80, and 160 mg SD) will consist of 8 subjects (4 Japanese and 4 Caucasian). For each MD cohort, 6 Japanese subjects and 3 Caucasian subjects will receive LY3337641, while 2 Japanese subjects and 1 Caucasian subject will receive placebo. For each SD cohort, 3 Japanese subjects and 3 Caucasian subjects will receive LY3337641, while 1 Japanese subject and 1 Caucasian subject will receive placebo. Investigational product (IP) will be administered orally. Cohorts 1, 2, and 3 may be conducted in parallel if the site is able to accommodate more than 1 cohort at a time; however, priority will be given to dose Cohort 1, since the timing of this cohort will determine the timing of the interim analysis. Cohort 4 will be started based on the safety assessment up to Day 3 (48 hours postdose) of Cohort 2. If the dose level/regimen for Cohort 1 is not tolerated or there is a need to dose more subjects to assess safety, a daily dose of 30 mg or less (QD or BID) may be given in Cohort 5 based on the findings from Cohort 1. This will be discussed and agreed upon by the investigator and the Lilly clinical pharmacologist. The randomization rules and procedures will be the same as Cohort 1.

Figure JPDB.1 illustrates the study design.



Abbreviations: BID = twice daily; FU = follow-up; JP = Japanese; LY = LY3337641; Pb = placebo; QD = once daily.
*Dose, regimen, and subject number may change for optional cohort.

Figure JPDB.1. Illustration of study design for Protocol I8K-JE-JPDB.

5.2. Number of Participants

Up to 60 subjects may be enrolled so that approximately 36 to 48 subjects complete the study.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This is a single-site, subject- and investigator-blind, randomized, placebo-controlled, SD and MD study in healthy Japanese and Caucasian subjects. This study is conducted to support the inclusion of Japanese subjects in future studies involving LY3337641. Healthy Caucasian subjects are also included in this study for assessment of both healthy Japanese and Caucasian subjects. The number of subjects in this study is deemed sufficient for the safety, tolerability, and PK data that will be assessed in both Japanese and Caucasian subjects. Intensive assessment of electrocardiograms (ECGs) will be done in this study, since thorough ECG data have not been obtained so far. The study will be subject and investigator blind, with the subjects, investigators, and site staff unaware of actual treatment (LY3337641 or placebo) but aware of dose level

assigned to the cohort. This design is being used to minimize bias in safety and tolerability assessments.

5.5. Justification for Dose

CCI

[redacted]

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 ECG.

A chest x-ray will be completed at screening unless one has been obtained within the past 12 months, and the x-ray and/or report are available for review.

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 Day 1. 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 and females, as determined by medical history and physical examination

[1a] male subjects:

agree to use an effective method of contraception (barrier contraceptives, such as latex condoms, or complete abstinence from sexual intercourse with women) for the duration of the study and 3 months following the last dose of IP

[1b] female subjects:

women of childbearing potential may participate and include those who test negative for pregnancy prior to initiation of treatment (as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure) and agree to remain abstinent or use either 1 highly effective method of contraception (such as combination oral contraceptive, implanted contraceptive, or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condom with spermicide, diaphragm with spermicide, or cervical sponge) during the study and for 4 weeks following the last dose of the IP

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

A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) performed at least 6 months prior to dosing or congenital anomaly such as müllerian agenesis or

B. postmenopausal, defined as either

i. A woman aged 50 years or older who has an intact uterus, is not on hormone therapy, and has had either

a) cessation of menses for at least 1 year or

b) 6 to 12 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL or

ii. A woman aged 55 years or older who is not on hormone therapy and has had at least 6 months of spontaneous amenorrhea or

iii. A woman aged 55 years or older with a diagnosis of menopause prior to starting hormone replacement therapy

[2] are aged 20 to 64 years, inclusive, at screening

[3] have a body mass index of 18.0 to 32.0 kg/m^2, inclusive, at 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 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

[37] are 1st generation Japanese or Caucasian.
To qualify as a subject of 1st generation Japanese origin, the subject, the subject's biological parents, and all of the subject's biological grandparents must be of exclusive Japanese descent and born in Japan.

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 or Covance employees

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

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

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

[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 or affects or confounds the QTc analysis (the ECG waveform morphology or rhythm are incompatible with reliable measurement of ECG intervals) or have Fridericia-corrected QT interval (QTcF) >450 msec for males and >470 msec for females

[15] have an abnormal blood pressure or pulse rate (supine) as determined by the investigator

[16] have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal (cholecystectomy not acceptable), endocrine, hematologic, dermatologic, or neurologic disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data

[17] have known or ongoing psychiatric disorders

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

[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 (HBsAg)

[22] are positive for hepatitis B core antibody (HBcAb+)

[23] are women who are lactating

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

[25] have donated blood of more than 500 mL within the month prior to screening

[26] have an average weekly alcohol intake that exceeds 21 units per week and are unwilling to follow instructions in Section 6.3.2 (1 unit = 12 ounces or 360 mL of beer, 5 ounces or 150 mL of wine, and 1.5 ounces or 45 mL of distilled spirits)

[27] are subjects whose tobacco consumption is more than 10 cigarettes per day or the equivalent or subjects who are not willing to refrain from smoking for 48 hours prior to clinical research unit (CRU) admission and during CRU stay

[28] have a history of, in the opinion of the investigator, excessive methylxanthine use within the previous 3 months or are unwilling to abide by restrictions as specified in Section 6.3.2. Excessive intake is defined as more than 6 units of caffeine per day; 1 caffeine unit is contained in the following items: 1 (177 mL) cup of coffee, 1 (355 mL) cup of tea, 2 (355 mL) cans of cola, or 3 ounces (85 g) of chocolate

[29] have had symptomatic herpes zoster within 3 months of screening, as determined by clinical history

[30] have active or latent tuberculosis (TB) based on a positive medical history, examination, and/or TB test results. QuantiFERON®-TB Gold Plus test (QFT-Plus or equivalent) will be used for TB testing, and subjects must test negative to participate

[31] have a screening chest x-ray with evidence of medically significant disease, such as malignancy, infection, pulmonary disease, or cardiac failure

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

[33] are immunocompromised

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

[35] have had exposure to significant diagnostic, therapeutic, or employment-related radiation within 12 months prior to dosing (eg, serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring)

[36] have a history of constipation or have had acute constipation within 3 weeks prior to admission

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

Before each morning dose in the SD and the MD cohorts, subjects will be fasted overnight for at least 10 hours following a light supper on the evening before. Following dosing, subjects will

fast for a period of 4 hours until lunch (for the MD cohorts, fasting after dosing will occur on Days 1 and 15 only; on all other dosing days in the MD cohorts, subjects should consume a non-standardized breakfast approximately 1 hour after dosing). For BID dosing, if studied, subjects will be fasted 1 hour before and after the evening dose. During fasting, no fluids are allowed except for water; however, water is not allowed from 2 hours predose until 1 hour postdose (apart from the water taken with the dose).

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine—Subjects should not be allowed caffeine consumption for 48 hours prior to all study visits and during CRU stays. At other times during the outpatient period, subjects will be allowed to maintain their regular caffeine consumption.

Alcohol—Alcohol consumption is not allowed from 48 hours prior to all study visits and during CRU stays. At all other times, alcohol consumption should be limited to no more than 2 units per day (1 unit = 12 ounces or 360 mL of beer, 5 ounces or 150 mL of wine, and 1.5 ounces or 45 mL of distilled spirits).

Tobacco—Subjects will be asked to refrain from smoking for approximately 48 hours prior to CRU admission and during CRU stays. During the follow-up period, subjects will be asked to refrain from smoking for 2 hours prior to study visits.

6.3.3. Activity

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened once with Lilly clinical pharmacologist's approval. The interval between re-screenings should be at least 2 weeks. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves a numerical comparison of LY3337641 (30 mg QD in MD cohorts and 5, 80, and 160 mg in SD cohorts) with placebo, when administered orally. The study drug is supplied as tablets containing 5 or 20 mg of LY3337641 with matching placebo tablets (Table JPDB.2).

LY3337641 and placebo will be administered orally with approximately 200 mL of room temperature water in the morning of each dosing day with the subject in a sitting position. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or as needed for study procedures.

Table JPDB.2. Treatment Administered

Cohort	Dose	Number of Tablets
Cohort 1	LY 30 mg QD	1 x 20-mg LY tablet 2 x 5-mg LY tablets
	Placebo 30 mg QD	1 x 20-mg placebo tablet 2 x 5-mg placebo tablets
Cohort 2	LY 80 mg	4 x 20-mg LY tablets
	Placebo 80 mg	4 x 20-mg placebo tablets
Cohort 3	LY 5 mg	1 x 5-mg LY tablet
	Placebo 5 mg	1 x 5-mg placebo tablet
Cohort 4	LY 160 mg	8 x 20-mg LY tablets
	Placebo 160 mg	8 x 20-mg placebo tablets

Abbreviations: LY = LY3337641; QD = once daily.

The investigator or designee is responsible for:

- explaining the correct use of the IP to the subject,
- verifying that instructions are followed properly,
- maintaining accurate records of IP 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

IP will be supplied by the sponsor in accordance with current good manufacturing practices. The material will be labeled with a unique identifier for drug accountability. Clinical trial materials will be labeled according to the country's regulatory requirements and will be labeled with the identity of the material contained in the package.

The study drug will be supplied as tablets containing 5 or 20 mg of LY3337641 with matching placebo tablets. The LY3337641 5-mg tablets and corresponding 5-mg matched placebo are identical in appearance, and the LY3337641 20-mg tablets and corresponding 20-mg matched placebo are identical in appearance. However, the 5 - and 20-mg tablets are not identical in appearance.

Packaging will be as follows:

5 mg LY3337641 blister card—9 tablets

Placebo to match 5 mg LY3337641 blister card—9 tablets

20 mg LY3337641 blister card—9 tablets

Placebo to match 20 mg LY3337641 blister card—9 tablets

7.2. Method of Treatment Assignment

Randomization tables for allocation of LY3337641 or placebo will be prepared by the statistician for the study and provided to the site pharmacists involved in dose preparation. The allocation and dispensing of the IP will be fully documented and verified by a second person. Detailed records of the amounts of the IP received, dispensed, and remaining at the end of the study will be maintained by the site pharmacist.

7.2.1. Selection and Timing of Doses

SDs will be administered in the morning. For the QD cohort(s), doses will be administered at approximately the same time in the morning on each day for each subject. If the BID regimen is tested in Cohort 5, the dose will be administered in the morning and the evening. The evening dose should be taken 12 hours apart from the morning dose. On Day 15, only the morning dose will be administered.

Meal conditions are discussed in Section 6.3.1. The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

Blinding will be maintained throughout the conduct of the trial until all data are cleaned to an acceptable level of quality and locked. The details are included in the Blinding/Unblinding Plan (Appendix 6).

The site pharmacist will be responsible for dispensing the IP to the subjects in a blinded manner. The investigator and subjects should remain blinded to study treatment within each cohort throughout the conduct of the study.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician or for the study participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. Subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical pharmacologist or clinical research physician prior to unblinding a study subject's treatment assignment, unless this could delay emergency treatment of the subject. If a study subject's treatment assignment is unblinded, Lilly must be notified immediately.

7.4. Dose Modification

7.4.1. Dose Escalation

All doses in this study have been previously tested and shown to be well tolerated in Study JPDD. However, Japanese subjects have not received LY3337641 previously. The dose escalation decision will be made based on the safety data from both Japanese and Caucasian subjects up to Day 3 (48 hours postdose) of 80-mg SD administration (Cohort 2) to proceed to the 160 mg SD cohort (Cohort 4).

Safety data for the 80-mg SD will be the primary criteria for dose escalation to the 160-mg SD. In addition, if available at the time of dose escalation decision, PK (C_{max}, AUC, and clearance) results may be used as supporting data for dose escalation, but such data are not required. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist or clinical research physician.

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

After review of these data, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for the 160-mg SD cohort. The magnitude of the dose escalation may be reduced following data review, but the highest SD will not exceed 160 mg.

If any of the following scenarios occur, dosing at the current level and further dose escalation will be stopped until the safety data can be reviewed:

1) 1 or more subjects experience an SAE
2) 2 or more subjects experience a clinically significant event that is related to LY3337641 administration
3) greater than 3 subjects at 1 dose level experience moderate treatment-related AEs that impair normal activities

After the safety review is completed, if Cohort 2 dosing has not been completed, dosing may resume if agreed upon by the investigator and sponsor. Once all data from Cohort 2 has been

obtained, an agreement on the appropriate dose escalation will be made by the investigator and sponsor for the 160-mg SD cohort or a lower dose.

7.5. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study may receive IP and only authorized site staff may supply or administer study treatment. All study treatments should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

7.6. Treatment Compliance

The IP will be administered at the CRU, and documentation of treatment administration will occur at the CRU.

7.7. Concomitant Therapy

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 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 for this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

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

In addition, subjects will be discontinued from the IP in the following circumstances:

- The investigator decides that the subject should be discontinued from the IP
- The subject requests to be discontinued from the IP
- Subject experiences an SAE or clinically significant event that is related to LY3337641 administration, or
- Subject experiences moderate treatment-related AEs that impair normal activities

When this situation arises, the investigator should inform a Lilly clinical pharmacologist or clinical research physician.

When subjects discontinue the IP early, procedures to be performed will be discussed between the investigator and the Lilly clinical pharmacologist or clinical research physician.

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 clinical pharmacologist or clinical research physician 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 clinical pharmacologist or clinical research physician to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with IP.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical trial involving an IP 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
- 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

Subjects who discontinue the study early will have end-of-study 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 laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

Investigators must document their review of each laboratory safety report.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the subject to discontinue the IP 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 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 IP, 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 IP 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.

Pregnancy (maternal or paternal exposure to IP) 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 Investigator's Brochure and that the investigator identifies as related to the 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 or drug delivery system 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 dose assigned through randomization.

Refer to the Investigator's Brochure.

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) and as clinically indicated.

9.4.2. Vital Signs

For each subject, vital sign measurements including body (oral) temperature, supine and standing blood pressure, and pulse rate should be conducted according to the Schedule of Activities (Section 2) and as clinically indicated.

Subjects will rest in the supine position for at least 5 minutes and have supine blood pressure and pulse rate measured. Subjects will then stand for 3 minutes and have standing blood pressure and pulse rate measured.

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

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

9.4.3. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2) as clinically indicated and the study-specific recommendations included in the Manual of Operations for the study.

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 12-lead digital ECG will be collected in triplicate according to the Schedule of Activities (Section 2). ECGs must be recorded before collecting any blood for safety or PK tests. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive triplicate ECGs will be obtained at approximately 1-minute intervals. ECGs may be administered at additional times, when deemed clinically necessary.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still

present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) to determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his or her review of the ECG printed at the time of evaluation from at least 1 of the triplicate ECGs from each time point.

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

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

9.4.4. Other Tests

9.4.4.1. Assessment and Management of Subjects Developing a Rash

Subjects who develop a rash should be evaluated as soon as possible. Investigators will be prompted to categorize and diagnose the rash (per clinical judgment), assess relatedness to IP, and grade its severity. This information will be recorded on the source document and entered into the eCRF. Additional information related to the rash evaluation will also be recorded on the source document and will include a history of infections and allergies and recent exposure to prescription or over-the-counter medications, skin products, detergents, or other potential skin irritants. A review of systems will be completed to assess for systemic symptoms and concurrent illnesses. A symptom-directed physical examination should be performed, including an evaluation of the rash distribution and type, vital signs and temperature, and other organ systems, as clinically indicated. In addition, photographs and laboratory measurements should be obtained as clinically indicated, according to investigator judgment. The subject should be evaluated to determine whether there are any signs or symptoms suggesting a severe, potentially life-threatening condition.

If a subject develops a rash that is assessed as not related to IP, is transient, or is not clinically significant in the opinion of the investigator, the IP may be continued without interruption. In some cases, the investigator may instead choose to interrupt the IP and restart it at a later date. The dates for stopping and restarting the IP should be captured. Immediate and permanent discontinuation of IP should be considered for all subjects with clinically significant rash. For rashes deemed clinically significant, punch biopsy of the rash may also be performed. In addition, a venous blood sample may be collected for PK analysis at the time of evaluation with documentation of the date and time of administration of the most recent dose of IP.

Subjects should be followed up until resolution of the rash, to the extent possible. The site should manage any rash that occurs during the study according to the judgment of the investigator. Interventions may include supportive care, pharmacotherapy, laboratory evaluation, additional skin biopsies, and consultation with a dermatologist, as clinically indicated. Data from these additional interventions should be provided to the sponsor as part of the AE reporting after being deidentified and summarized by the investigative site.

9.4.5. Safety Monitoring

The Lilly clinical pharmacologist 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 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, including monitoring of rash

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

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 LY3337641. 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 time (24-hour clock time) of each sampling will be recorded.

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

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-tandem mass spectrometry method. Analyses of samples collected from placebo-treated subjects are not planned.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as additional metabolism and/or protein binding work.

9.6. Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood of approximately 16 mL at each time point will be collected to determine free BTK and total BTK amount. Peripheral blood nuclear cells will be isolated. Lysates of the peripheral blood nuclear cells will be used to determine the concentrations of compound free BTK and total BTK using an enzyme-linked immunosorbent assay–based methodology.

The sample(s) will be stored for up to a maximum of 1 year after the last subject visit for the study at a facility selected by the sponsor.

9.7. Genetics

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure and response to LY3337641 and to investigate genetic variants thought to play a role in the perceived mechanism of action of LY3337641. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs (ethical review boards) 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 the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of

these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Serum, plasma, and/or whole blood RNA samples for nonpharmacogenetic biomarker research may be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3337641, pathways associated with diseases related to the immune system, mechanism of action of LY3337641, and/or research method, or for validating diagnostic tools or assay(s) related to diseases related to the immune system.

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly. 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.

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 60 subjects may be enrolled so that approximately 36 to 48 subjects complete the study.

The sample size is customary for Phase 1 studies evaluating safety, PK, and/or PD parameters and is not based on the power of statistical hypothesis tests.

Subjects who are randomized but discontinue the study may be replaced in the same cohort and race (Japanese or Caucasian) at the discretion of the sponsor.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.2.2. Study Participant Characteristics

Subjects' age, sex, weight, body mass index, height, race/subcategory, or other demographic characteristics will be recorded and summarized by treatment group as well as overall.

10.3. Statistical Analyses

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

PK analyses will be conducted for all subjects who receive at least 1 dose of LY3337641 and have evaluable PK data. PD analyses will be conducted on the full analysis set, which includes all data from all subjects receiving at least 1 dose of LY3337641 or placebo. Safety analyses will be conducted for all randomized subjects who receive at least 1 dose of LY3337641 or placebo and have at least 1 postdose safety assessment, regardless of whether they have completed all protocol requirements. For QT interval, all subjects with at least 1 postdose QT interval measurement will be included in the analysis.

Summary statistics, data tabulations, and data graphs will be provided and may be separated by race (Japanese and Caucasian) as appropriate.

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/PD analysis purposes.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All IP 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 the 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 IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Prior to any statistical analysis of QT interval, QT values will be corrected for heart rate based on QTcF. The relationship between concentrations of LY3337641 and changes from baseline QTcF (ΔQTcF) will be explored to assess the effect of LY3337641 concentration on the ΔQTcF. A detailed analysis for QT interval will be provided in the Statistical Analysis Plan. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for LY3337641 will be calculated by standard noncompartmental methods of analysis.

In the SD cohorts, the primary parameters for analysis will be C_{max}, area under the concentration versus time curve from zero to infinity ($AUC_{0-\infty}$), and area under the concentration versus time curve from 0 to 24 hours (AUC_{0-24}) of LY3337641. In the MD cohorts, the primary parameters to be calculated will include C_{max} (or C_{max} during a dosing interval at steady state [$C_{max,ss}$]) and area under the concentration versus time curve during the dosing interval ($AUC_{0-\tau}$) of LY3337641 after the first and last dose of IP. Other noncompartmental parameters, such as half-life, apparent clearance, apparent volume of distribution, and accumulation ratio (MD period only), may be reported.

Additional analysis may be conducted if appropriate.

10.3.2.2. Pharmacokinetic Statistical Inference

The dose proportionality of selected LY3337641 PK parameters, including log transformed C_{max} and relevant AUC values will be examined for all subjects and for each population across the entire dose range using a power model approach (Smith et al. 2000) to estimate the slope of the power model, which represents the ratio of dose-normalized geometric means. Exploratory power model analysis based on the model including race and race-by-dose interaction terms will also be performed to examine the effect of the race on dose proportionality.

10.3.3. Pharmacodynamic Analyses

BTK occupancy will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Exploratory graphical PK/PD analyses may be conducted to evaluate the relationship between LY3337641 concentrations (or exposure) and PD measures. Additional model-based analyses may be conducted if deemed appropriate.

10.3.5. Interim Analyses

The Lilly study team is unblinded. Data may be analyzed while the trial is ongoing, but no changes to the study design are planned. An assessment committee will not be formed.

Up to 3 interim analyses are planned to occur during the study according to the following timeframe: when at least safety and PK data of (1) Day 2 predose (24 hours after first dose) become available from at least 11 subjects in Cohort 1, including at least 4 Caucasian subjects; (2) Day 17 (48 hours after last dose) become available from Cohort 1; and (3) Day 29 become available from Cohort 1. All safety and PK data available from other cohorts by this time will be included in the interim analysis. The purpose of the interim analysis is to support the inclusion of Japanese subjects in future studies. The investigator and the Lilly clinical pharmacologist will review the safety and tolerability data, and the PK/PD scientist will review the PK data. The investigator will remain blinded, and the Lilly study team will be unblinded during this interim review.

Information that may unblind the study during the analyses will not be reported to study site or blinded personnel until the study has been unblinded.

Additional interim analysis may be conducted at any time throughout the study as required to ensure subject safety or to help guide dosing.

If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, clinical research physician/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the concentration versus time curve from zero to infinity
AUC_{0-24}	area under the concentration versus time curve from 0 to 24 hours
$AUC_{0-\tau}$	area under the concentration versus time curve during the dosing interval
BID	twice daily
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock.
BTK	Bruton's tyrosine kinase
C_{max}	maximum drug concentration
$C_{max,ss}$	maximum drug concentration during a dosing interval at steady state
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 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.
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit

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.
entered	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
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
ICF	informed consent form
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.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical 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.
IP	investigational product
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
MD	multiple dose
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
QD	once daily
QTcF	Fridericia-corrected QT interval

RA	rheumatoid arthritis
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.
SD	single dose
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TEAE	treatment-emergent adverse event
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
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Laboratory Tests[a]

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBCs)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBCs)	Magnesium
Absolute counts of:	Glucose fasting
Neutrophils	Blood urea nitrogen (BUN)
Lymphocytes	Uric acid
Monocytes	Total cholesterol
Eosinophils	Total protein
Basophils	Albumin
Platelets	Total bilirubin
	Alkaline phosphatase (ALP)
Urinalysis	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	Creatinine
Protein	Gamma-glutamyl transferase (GGT)
Glucose	CRP
Ketones	Amylase
Bilirubin	Lipase
Urobilinogen	Ethanol testing[b,c]
Blood	Urine drug screen[b,c]
Nitrite	Hepatitis B surface antigen[b]
	Hepatitis B core antibody[b]
	Hepatitis C antibody[b]
	HIV[b]
	Pregnancy test[d]
	FSH[b,d]
	QuantiFERON®-TB Gold test[b]

Abbreviations: CRP = C-reactive protein; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBCs = red blood cells; TB = tuberculosis; WBCs = white blood cells.

a To be performed at local laboratory.

b Performed at screening only.

c May be repeated prior to admission to the clinical research unit.

d To be performed for female subjects of childbearing potential. Serum pregnancy test at screening; urine pregnancy test at all other visits.

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 informed consent form (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 ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (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 good clinical practice (GCP).

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

- the current Investigator's Brochure 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 electronic case report forms, 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 electronic case report form 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, 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 judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBCs	Prothrombin time
WBCs	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti–smooth muscle antibody (or anti-actin**
CPK	**antibody)[a]**

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

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 I8K-JE-JPDB Sampling Summary for Cohorts 1 and 5

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12	5	60
Pharmacokinetics	2	33	66
Pharmacodynamics (BTK occupancy)	16	18	288
Pharmacogenetics	10	1	10
Non-PGx stored sample	9.5	3	28.5
Total			497.5
Total for clinical purposes [rounded up to nearest 10 mL]			500

Abbreviations: BTK = Bruton's tyrosine kinase; PGx = pharmacogenomics.

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

Protocol I8K-JE-JPDB Sampling Summary for Cohorts 2, 3, and 4

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12	3	36
Pharmacokinetics	2	16	32
Pharmacodynamics (BTK occupancy)	16	9	144
Pharmacogenetics	10	1	10
Non-PGx stored sample	9.5	3	28.5
Total			295.5
Total for clinical purposes [rounded up to nearest 10 mL]			300

Abbreviations: BTK = Bruton's tyrosine kinase; PGx = pharmacogenomics.

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

Appendix 6. Protocol I8K-JE-JPDB Blinding/Unblinding Plan

Levels of unblinding are indicated in the table below. This table provides general guidance as to who will be allowed access to randomization codes at various steps of the trial. The information in the protocol will always take precedence over this table. For interim analysis, appropriate interim analysis team members, including statistician, programmer, and data manager will be identified and agreed upon between Lilly and the third-party organization.

Randomization data are kept strictly confidential and are accessible only by authorized personnel until unblinding of the trial as described below. All measures possible must be taken to maintain the blind, which means that access to randomization codes must be restricted to authorized personnel as described in the protocol and summarized in the table below.

Protocol I8K-JE-JPDB Blinding and Unblinding Plan

	Study Timelines				
Study Team Member	**Screening**	**Randomization**	**Treatment Phase**	**Follow-Up**	**Database Lock**
General					
Drug Supply	NA	U	U	U	U
Randomization Statisticians	NA	U	U	U	U
ECG Reader	NA	B	B	B	B
Bioanalysis Lab/Sample Analysis	NA	U	U	U	U
Clinical Site					
Pharmacist	NA	U	U	U	U
Dosing Nurse	NA	U	U	U	U
Subject	NA	B	B	B	B
Investigator	NA	B	B	B	B
Study Monitor	NA	U	U	U	U
Covance/CDARO					
Project Integration	NA	U	U	U	U
Data Management	NA	U	U	U	U
Programming	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical Writing	NA	U	U	U	U
Pharmacokinetic Scientist/Associate	NA	U	U	U	U
Lilly					
Biopharm Coordinator	NA	U	U	U	U
CPA	NA	U	U	U	U
DSA	NA	U	U	U	U
SDTM Core Team	NA	U	U	U	U
Statistician	NA	U	U	U	U
Medical Writing	NA	U	U	U	U
CP	NA	U	U	U	U
Pharmacokinetic Scientist/Associate	NA	U	U	U	U
Medical Writing	NA	U	U	U	U

Abbreviations: B = blinded; CP = clinical pharmacologist; CPA = clinical pharmacology associate; DSA = data sciences associate; ECG = electrocardiogram; SDTM = study data tabulation model; U = unblinded.

Appendix 7. Protocol Amendment I8K-JE-JPDB(a) Summary
A Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3337641 in Japanese and Caucasian Healthy Subjects

Overview

Protocol I8K-JE-JPDB, A Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3337641 in Japanese and Caucasian Healthy Subjects, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Addition of "Review preexisting conditions/AEs" and "Review concomitant medications" to the Days 17, 22, 25, and 29/EoS for Cohorts 1 and 5 and to the Days 3, 8, 11, and 15/EoS for the Cohorts 2, 3, and 4 in the table of Schedule of Activities as these assessments are required for all visits.
- Clarified that on Day 15 in Cohort 5, only the morning dose will be administered for twice-daily regimen in the footnote of the Schedule of Activities.
- Addition of the exemption criteria for a chest x-ray at screening.
- Addition of subject's race criteria and the definition of 1st generation Japanese.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Table JPDB.3. Amendment Summary for Protocol I8K-JE-JPDB Amendment(a)

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities	Addition of "Review preexisting conditions/AEs" and "Review concomitant medications" to the Days 17, 22, 25, and 29/EoS for Cohorts 1 and 5 and to the Days 3, 8, 11, and 15/EoS for the Cohorts 2, 3, and 4 in the table of Schedule of Activities.	Both "Review preexisting conditions/AEs" and "Review concomitant medications" are required for all visits throughout the study, but were inadvertently missing for the visits.
2. Schedule of Activities	Clarified that on Day 15 in Cohort 5, only the morning dose will be administered for twice-daily regimen in the footnote of the Schedule of Activities.	The correct text is written in the section 7.2.1. Selection and Timing of Doses. However, to resolve the inconsistency between the 2 sections, the footnote was corrected.
6. Study Population	Addition of the exemption criteria for a chest x-ray at screening.	This sentence was added to avoid unnecessary x-rays.
6.1. Inclusion Criteria	Addition of subject's race criteria and the definition of 1st generation Japanese.	This criterion was inadvertently missing and has been added to ensure quality of study data by recruiting the intended race groups to the study.

Revised Protocol Sections

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

2. Schedule of Activities

Study Schedule Protocol I8K-JE-JPDB (Cohorts 1 and 5)

Visit	**Follow-Up**[a]					
Study Day	16	17	19	22	25	29/ EoS
Review preexisting conditions/AEs[d]	X	X	X	X	X	X
Review concomitant medications[d]	X	X	X	X	X	X

[c] Subjects will be dosed every day from Day 1 through Day 15. For twice-daily regimen, only the morning dose will be administered on Day 15~~dose will be administered in the morning only~~.

Study Schedule Protocol I8K-JE-JPDB (Cohorts 2, 3, and 4)

Visit	**Follow-Up**[a]					
Study Day	2	3	5	8	11	15/EoS
Review preexisting conditions/AEs	X	X	X	X	X	X
Review concomitant medications	X	X	X	X	X	X

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 ECG.

A chest x-ray will be completed at screening unless one has been obtained within the past 12 months, and the x-ray and/or report are available for review.

6.1. Inclusion Criteria

[37] are 1st generation Japanese or Caucasian.
To qualify as a subject of 1st generation Japanese origin, the subject, the subject's biological parents, and all of the subject's biological grandparents must be of exclusive Japanese descent and born in Japan.

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