Protocol I4V-MC-JAGU A Bioequivalence and Food Effect Study in Healthy Subjects Comparing Baricitinib Suspension and Commercial Tablet Formulations

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Baricitinib (LY3009104)

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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:
A Bioequivalence and Food Effect Study in Healthy Subjects Comparing Baricitinib Suspension and Commercial Tablet Formulations

Rationale:
This study is designed to support development of the baricitinib suspension formulation which is being developed for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) in pediatric patients from the age of 2 years, who have had inadequate responses to previous disease-modifying antirheumatic drugs. In Part A, single oral 4-mg doses of baricitinib suspension formulation administered with and without water will each be compared with a single oral dose of 4 mg commercial tablet formulation to determine whether the bioavailability of baricitinib administered as suspension, under either condition, is equivalent to baricitinib administered as the commercial tablet formulation. Interim analysis of data from Part A will be used to determine the administration of the suspension formulation in Part B of the study.

Additionally, in Part B, a single oral dose of the suspension formulation administered under fed conditions will be compared to administration under fasted conditions to assess the effects of food on the rate and extent of absorption.

Objectives/Endpoints:

Objectives	**Endpoints**
Primary To determine if 4 mg of baricitinib administered in a single dose of the suspension formulation (2 mL of 2 mg/mL suspension), with or without water, is bioequivalent (with 0.80, 1.25 as the bioequivalence boundaries) to 4 mg of baricitinib administered as a single 4-mg tablet.	The ratio of geometric least square means between each test formulation and the reference formulation for maximum observed drug concentration (C_{max}), area under the concentration versus time curve (AUC) from time zero to the last time point with a measurable concentration (AUC[0-t_{last}]), and AUC from time zero to infinity (AUC[0-∞]).
Secondary The secondary objectives are: • To evaluate the tolerability of baricitinib given as a single dose when administered to healthy adult subjects. • To compare the relative bioavailability of the suspension formulation administered with and without water. • To determine the effect of a high-fat, high-calorie meal on the pharmacokinetics (PK) of baricitinib when administered as a single 4-mg dose of the suspension formulation.	• Incidence of treatment-emergent adverse events (TEAEs). • The ratio of geometric least square means between administration of suspension formulation with and without water for C_{max}, AUC(0-t_{last}), AUC(0-∞), and median of differences for time of maximum observed drug concentration (t_{max}). • The ratio of geometric least square means between the fasted and fed state for C_{max}, AUC(0-t_{last}), AUC(0-∞), and median of differences for t_{max}.

Summary of Study Design:

Study I4V-MC-JAGU is a 2-part, single-center, Phase 1, open-label, randomized, crossover study in healthy subjects.

Part A will be a 3-period, randomized, crossover study to evaluate the bioequivalence of 4 mg baricitinib administered as a single dose of the suspension formulation, with and without water, and 4 mg of baricitinib administered as a single 4-mg tablet with water.

Part B will be a 2-period, randomized, crossover study to determine the effect of a high-fat, high-calorie meal on the PK of baricitinib administered as a single dose of the suspension formulation. Subjects who participate in Part A of the study will not participate in Part B.

Subjects in each part of the study will be admitted to the clinical research unit (CRU) on Day -1 of each period. Following an overnight fast of at least 10 hours, subjects will be administered 4 mg baricitinib according to the randomization schedule. At a minimum, subjects will be resident at the CRU until collection of the 12-hour PK sample; all subsequent assessments may be conducted on an outpatient basis at the discretion of the investigator. Blood sampling for assessment of baricitinib PK will be performed up to 48 hours postdose (Day 3).

Safety will be assessed through adverse event (AE) recording, medical review and targeted examination, clinical laboratory evaluations, and vital signs.

Treatment Arms and Duration:
Part A: Subjects will receive single doses of 4 mg baricitinib as suspension formulation administered without water, suspension formulation administered with 240 mL water, and commercial tablet formulation administered with 240 mL water, with sequence determined by randomization.

Part B: Subjects will receive a single dose of 4 mg baricitinib suspension in a fasted state and a single dose of 4 mg baricitinib suspension after a high-fat, high-calorie meal, with sequence determined by randomization.

Screening will occur up to 28 days prior to dosing in Period 1 and each treatment period will last approximately 48 hours. There will be at least 72 hours between dosing in each consecutive period and a follow-up visit will occur 7 to 14 days after the last dose of baricitinib.

Number of Subjects:
Part A: Twenty-six subjects may be enrolled to ensure that 20 subjects complete Part A of the study.

Part B: It is planned that up to a maximum of 18 subjects may be enrolled so that approximately 14 subjects complete Part B of the study but this number may be revised upon interim analysis of data from Part A.

Statistical Analysis:

Safety parameters that will be assessed include TEAEs, clinical laboratory parameters, and vital signs. The parameters will be listed and summarized using standard descriptive statistics, as appropriate.

Pharmacokinetic parameter estimates for baricitinib will be calculated by standard noncompartmental methods of analysis. Pharmacokinetic parameter estimates will be evaluated to delineate effects of baricitinib formulation. For the primary analysis, log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) estimates will be evaluated in a linear mixed-effects model with fixed effects for formulation, period, sequence, and a random effect for subject

(sequence). The treatment differences between each test compared to the reference formulation will be back-transformed to present the ratios of geometric least squares means and the corresponding confidence interval (CI). The Holm step-down procedure for an overall 0.1 alpha level will be used.

Bioequivalence between the suspension formulation administered either with or without water and the commercial tablet will be concluded if the 95% CI for C_{max}, AUC(0-t_{last}), and AUC(0-∞) are all completely contained within the interval (0.80, 1.25). Bioequivalence between the suspension formulation using the other administration and the commercial tablet will be concluded if the 90% CIs for C_{max}, AUC(0-t_{last}), and AUC(0-∞) are all completely contained within the interval (0.80, 1.25).

For secondary analyses, the same model specified above will be used for C_{max}, AUC(0-t_{last}), and AUC(0-∞). Ratios of geometric least squares means and the corresponding 90% CIs will be presented. The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

2. Schedule of Activities

Study Schedule Protocol I4V-MC-JAGU

	Screening	Part A Periods 1,2, and 3 Part B Periods 1 and 2				Follow-Up/Early Discontinuation	Comments
Procedure	≤28 days prior to Period 1 dose	-1	1	2	3	7 to 14 days after last dose	
Informed Consent	X						
Subject Admission to CRU		X					
Subject Discharge from CRU			X				Subjects may be discharged after the 12 hour PK sample is collected in each period and return for all other assessments on an outpatient basis, at the discretion of the investigator.
Outpatient Visit				X	X		At the investigator's discretion, subjects may be discharged anytime between 12-hours postdose and Day 3 and thus may attend as outpatients for collection of the 24-, 36-, and 48-hour PK samples.
Overnight Fast		X					Subjects will be fasted from ≥10 hours prior to dosing.
Study Treatment Administration			X				
Medical History	X						
Height	X						
Weight	X	X					BMI will be calculated at screening.
Vital Signs (supine)	X		Predose			X	Supine blood pressure and/or pulse rate may be measured as clinically indicated as well as at the scheduled times. Additional scheduled vital signs may be measured during each study period, if warranted and agreed upon between Lilly and the investigator.

	Screening	Part A Periods 1,2, and 3 Part B Periods 1 and 2				Follow-Up/Early Discontinuation	Comments
Procedure	≤28 days prior to Period 1 dose	-1	1	2	3	7 to 14 days after last dose	
Clinical Laboratory Tests	X		Predose			X	See Appendix 2, Clinical Laboratory Tests, for details.
Pregnancy Test	X					X	Serum pregnancy test will be performed at screening. A serum or urine pregnancy test will be performed at follow-up/early discontinuation and may be performed at other times at the investigator's discretion.
Physical Exam/Medical Assessment	X		Predose	X		X	A complete physical examination to be conducted at screening. All other medical assessment to include medical review and targeted examination, as appropriate. Day 2 medical assessment may be performed any time prior to discharge if subject remains resident in the CRU beyond Day 2.
12-lead ECG (single)	X					X	
Genetic Sample			Predose (Period 1 only)				Single sample for pharmacogenetic analysis.
PK Samples (hours)			Predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12	24, 36	48		Sampling times are relative to the time of study treatment administration.

Abbreviations: BMI = body mass index; CRU = clinical research unit; ECG = electrocardiogram; PK = pharmacokinetics.

3. Introduction

3.1. Study Rationale

This study is designed to support development of the baricitinib suspension formulation which is being developed for the treatment of polyarticular juvenile idiopathic arthritis (pJIA) in pediatric patients from the age of 2 years, who have had inadequate responses to previous disease-modifying antirheumatic drugs. In Part A, single oral 4-mg doses of baricitinib suspension formulation administered with and without water will each be compared with a single oral dose of 4 mg commercial tablet formulation to determine whether the bioavailability of baricitinib administered as suspension, under either condition, is equivalent to baricitinib administered as the commercial tablet formulation. Interim analysis of data from Part A will be used to determine the administration of the suspension formulation in Part B of the study.

Additionally, in Part B, a single oral dose of the suspension formulation administered under fed conditions will be compared to administration under fasted conditions to assess the effects of food on the rate and extent of absorption.

3.2. Background

Baricitinib is presently being studied for the treatment of adult patients with rheumatoid arthritis (RA) and has completed Phase 2 and 3 trials for the treatment of RA at doses up to 4 mg once daily (QD). Baricitinib represents a selective inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases with excellent potency and selectivity for JAK2 and JAK1, and a lower potency for JAK3, or tyrosine kinase 2 (Fridman et al. 2010). Signal transducers and activators of transcription (STATs), once phosphorylated by JAKs, become active transcription factors and drive the expression of multiple genes important for cell activation, localization, survival, and proliferation (Valentino and Pierre 2006).

Chronic inflammatory conditions are associated with aberrant production of cytokines and growth factors. Inhibition of JAK-STAT signaling to target multiple RA-associated cytokine pathways has the potential to simultaneously reduce inflammation, cellular activation, and proliferation of key immune cells. Inhibitors of JAK have been demonstrated to have a clinically meaningful efficacy in patients with RA (Boy et al. 2009; Kremer et al. 2009). Nonbiological agents, such as baricitinib, that are orally administered and have a shorter half-life may provide an alternative to the longer-acting injectable biologic therapies currently available.

For the Phase 3 studies conducted in adults with RA, a tablet formulation of baricitinib was developed and is the proposed commercial formulation for RA.

Following oral administration in healthy subjects, the time of maximum observed drug concentration (t_{max}) was approximately 1.5 hours, indicating that baricitinib is rapidly absorbed. Dose-proportional increases in exposure across the dose range 1 to 30 mg have been observed. There is no indication suggesting the pharmacokinetics (PK) is time-dependent. The half-life associated with the terminal rate constant in noncompartmental analysis ($t_{1/2}$) of baricitinib is approximately 6 to 8 hours in healthy subjects, leading to observation of minimal accumulation with QD dosing. Following a single oral dose of 10 mg baricitinib containing 100 μCi of

[^{14}C]-baricitinib in healthy subjects, a mean (± standard deviation) of 75.2% (± 6.7%) of the dose was excreted in urine and 19.9% (± 4.9%) was excreted in feces through the last collection interval (see Section 6.1.3.4 of the Investigator's Brochure [IB] for further information on disposition).

In addition to the commercial tablet formulation, an age appropriate suspension formulation is being developed in order to allow potential treatment of pediatric patients with pJIA. This study will be conducted to determine whether the suspension formulation is bioequivalent to the commercial tablet formulation when the suspension is administered alone and with water, which may increase the amount of drug substance in solution, thus achieving bioequivalence should bioavailability of the suspension formulation be decreased.

No clinically meaningful food effect was observed with the tablet formulation of baricitinib; a high-fat meal decreased the mean area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}) of baricitinib by approximately 11% and 18%, respectively, and delayed the median t_{max} by 0.5 hours. Part B of this study aims to assess the effect of a high-fat meal on the bioavailability of the baricitinib suspension formulation.

3.3. Benefit/Risk Assessment

Cumulatively, approximately 4332 subjects have received baricitinib during the clinical development program (481 healthy subjects, 36 subjects with varying degrees of renal impairment, 8 subjects with hepatic dysfunction, and 3807 subjects with RA or other inflammatory diseases). In clinical pharmacology studies, baricitinib was generally safe and well tolerated in single doses ranging from 1 to 40 mg and in repeat oral doses ranging from 2 to 20 mg for up to 10 days, in healthy subjects. One male subject with end stage renal disease died of renal failure approximately 22 days after receiving the second of 2 single 5-mg doses of baricitinib. The subject was on dialysis and had a history of type 2 diabetes and hypertension. The event was considered by the investigator to be unrelated to study drug. A serious adverse event (SAE) of migraine was reported in 1 healthy adult, after a single 20-mg dose of baricitinib, and there was 1 event of maternal exposure during pregnancy following QD dosing of 10 mg baricitinib. Adverse events (AEs) leading to discontinuation of healthy subjects from studies of baricitinib include conjunctivitis (5 mg twice-daily dosing and single 10-mg dose), blood bilirubin increased (10 mg QD), influenza-like illness (10 mg QD), complicated migraine (single 20-mg dose), oral herpes (single 10-mg dose), ear infection (10 mg QD), and diarrhea (single 10-mg dose).

In healthy subjects, the most notable post-treatment drug effect reported was a reduction in absolute neutrophil count (ANC). Mean ANC decreased after dosing in a generally dose-dependent manner. The lowest levels were reached approximately 8 hours postdose, and then returned to predose levels by 24 hours after each dose. The maximum ANC decrease from baseline following a single 10-mg dose was 36.5%. These decreases may be attributed to neutrophil margination.

As this study is enrolling healthy subjects, no clinical benefit is anticipated from study participation.

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

4. Objectives and Endpoints

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

Table JAGU.1. Objectives and Endpoints

Objectives	Endpoints
Primary To determine if 4 mg of baricitinib administered in a single dose of the suspension formulation (2 mL of 2 mg/mL suspension), with or without water, is bioequivalent (with 0.80, 1.25 as the bioequivalence boundaries) to 4 mg of baricitinib administered as a single 4-mg tablet.	The ratio of geometric least square means between each test formulation and the reference formulation for C_{max}, area under the concentration versus time curve (AUC) from time zero to the last time point with a measurable concentration (AUC[0-tlast]), and AUC from time zero to infinity (AUC[0-∞]).
Secondary The secondary objectives are: • To evaluate the tolerability of baricitinib given as a single dose when administered to healthy adult subjects. • To compare the relative bioavailability of the suspension formulation administered with and without water. • To determine the effect of a high-fat, high-calorie meal on the PK of baricitinib when administered as a single 4-mg dose of the suspension formulation.	• Incidence of treatment-emergent adverse events (TEAEs). • The ratio of geometric least square means between administration of suspension formulation with and without water for C_{max}, AUC(0-t_{last}), AUC(0-∞), and median of differences for t_{max}. • The ratio of geometric least square means between the fasted and fed state for C_{max}, AUC(0-t_{last}), AUC(0-∞), and median of differences for t_{max}.

5. Study Design

5.1. Overall Design

This is a 2-part, single-center, Phase 1, open-label, randomized, crossover study in healthy subjects.

Part A will be a 3-period, randomized, crossover study to evaluate the bioequivalence of 4 mg baricitinib administered as a single dose of the suspension formulation, with and without water, and 4 mg of baricitinib administered as a single 4-mg tablet with water.

Subjects will be randomly allocated to 1 of 3 treatment sequences (Table JAGU.2). Approximately 8 subjects may be allocated to each treatment sequence. Subjects will receive single oral doses of baricitinib on 3 separate occasions, separated by washout periods of at least 72 hours. Each subject will receive the following:

- a single 4-mg (2 mL × 2 mg/mL) dose of baricitinib suspension formulation administered without water (T1), in the fasted state
- a single 4-mg (2 mL × 2 mg/mL) dose of baricitinib suspension formulation administered with 240 mL water (T2), in the fasted state
- a single 4-mg (1 × 4 mg) dose of baricitinib commercial tablet formulation administered with 240 mL water (R), in the fasted state

Table JAGU.2. Treatment Sequences in Part A of Study I4V-MC-JAGU

Sequence	Period 1	Period 2	Period 3
1	T1	T2	R
2	T2	R	T1
3	R	T1	T2

Abbreviations: R = 4-mg dose of baricitinib commercial tablet formulation administered with 240 mL water; T1 = 4-mg dose of baricitinib suspension formulation administered without water; T2 = 4-mg dose of baricitinib suspension formulation administered with 240 mL water.

Part B will be a 2-period, randomized, crossover study to determine the effect of a high-fat, high-calorie meal on the PK of baricitinib administered as a single dose of the suspension formulation. Subjects who participate in Part A of the study will not participate in Part B.

Subjects will be randomly allocated to 1 of 2 treatment sequences (Table JAGU.3). Subjects will receive single oral doses of baricitinib on 2 separate occasions, separated by a washout period of at least 72 hours. Whether or not these doses are administered with water (ie what the Part B suspension test formulation [TF] will be) will be decided after an interim analysis of the data from Part A of the study (see Section 10.3.3). Each subject will receive the following:

- a single 4-mg (2 mL × 2 mg/mL) dose of baricitinib TF administered after a high-fat, high-calorie meal
- a single 4-mg (2 mL × 2 mg/mL) dose of baricitinib TF administered in the fasted state

Table JAGU.3. Treatment Sequences in Part B of Study I4V-MC-JAGU

Sequence	Period 1	Period 2
1	TF_{fasted}	TF_{fed}
2	TF_{fed}	TF_{fasted}

Abbreviations: TF_{fasted} = 4-mg dose of baricitinib suspension test formulation administered in the fasted state; TF_{fed} = 4-mg dose of baricitinib suspension test formulation administered after a high-fat, high-calorie meal.

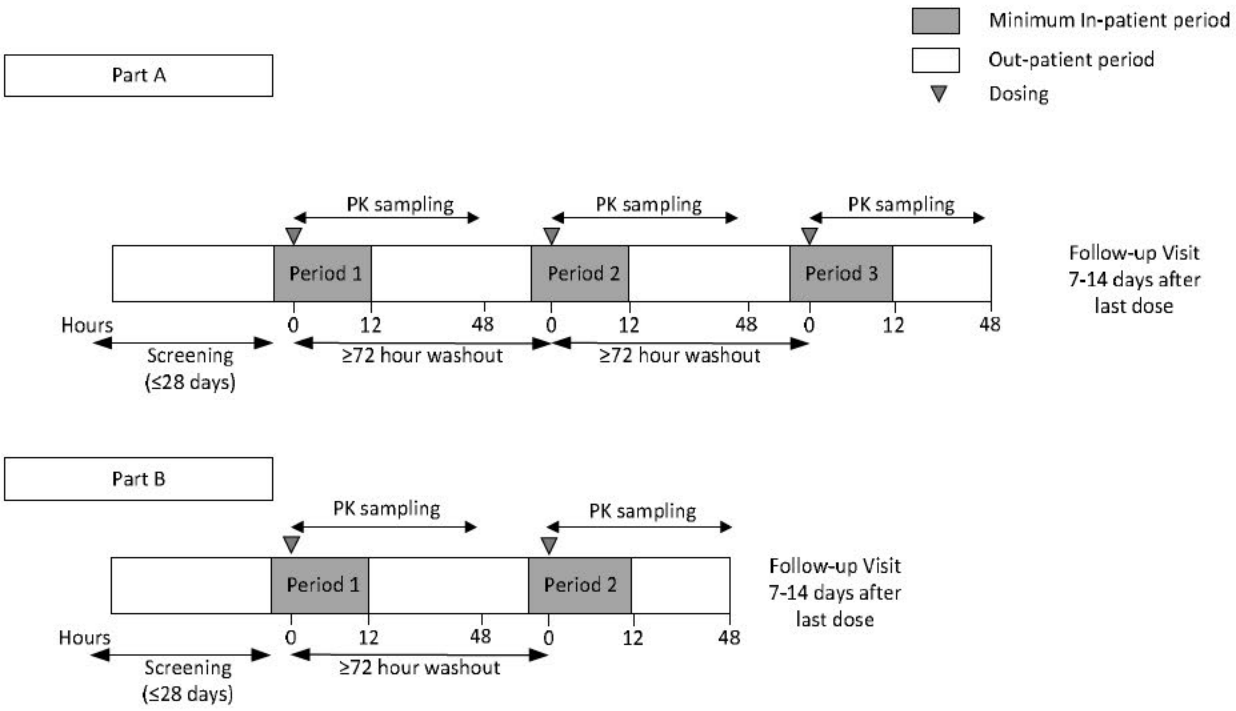
Each subject will provide informed consent for study participation and will undergo a screening examination within 28 days prior to the first dose.

In each study period (of Part A or Part B), subjects will be admitted to the clinical research unit (CRU) on Day -1 and will be dosed with baricitinib, following an overnight fast of at least 10 hours, according to their assigned treatment sequence, on the morning of Day 1. At a minimum, subjects will be resident at the CRU until collection of the 12-hour PK sample; all subsequent assessments may be conducted on an outpatient basis at the discretion of the investigator. There will be at least a 72-hour washout period between dosing in 2 consecutive study periods. A follow-up visit will occur 7 to 14 days after the last dose of baricitinib.

In each period, serial blood samples will be collected predose and at prespecified times up to 48 hours postdose (Day 3) for the determination of plasma concentrations of baricitinib for PK assessments.

Safety will be assessed throughout each part of the study by AE recording, medical review and targeted examination, clinical laboratory evaluations, and vital signs.

Figure JAGU.1 illustrates the study design.



Abbreviations: PK = pharmacokinetic

Figure JAGU.1. Illustration of study design for Protocol I4V-MC-JAGU.

5.2. Number of Participants

Part A: Twenty-six subjects may be enrolled to ensure that 20 subjects complete Part A of the study.

Part B: It is planned that up to a maximum of 18 subjects may be enrolled so that approximately 14 subjects complete Part B of the study, but this number may be revised upon interim analysis of data from Part A.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This study will be open-label as the study endpoints are objective rather than subjective. The crossover design in both Part A and Part B is a uniform design and allows each subject to act as his/her own control, thus reducing variability.

Part A of the study will assess bioequivalence of the new, age appropriate, suspension formulation to the existing commercial tablet formulation. This will provide a formal statistical comparison of exposure between these formulations. The suspension formulation will be administered both with and without water as, should the suspension formulation fail to

demonstrate bioequivalence to the commercial tablet formulation, it is anticipated that administration with water may increase the amount of drug substance in solution, thus aiding absorption and the achievement of bioequivalence.

The administration method for the suspension that demonstrates bioequivalence to the commercial tablet formulation in Part A of the study will be used in Part B (see Section 10.3.3). Interim analysis of intra-subject variability data in Part A will also inform on required subject numbers for Part B of the study.

This study has been designed to show definitive equivalence between the commercial tablet and suspension formulation, potentially facilitating the interchangeability of suspension and tablet formulations in future clinical studies with pediatric pJIA patients.

Part B of the study will assess the effect of a high-fat, high-calorie meal on the bioavailability of the suspension formulation, in accordance with regulatory guidance for new formulations (US Food and Drug Administration [FDA] 2002).

The washout period of at least 72 hours adequately minimizes the potential PK carryover effects of baricitinib, given its median $t_{1/2}$ of approximately 6 to 8 hours in healthy subjects.

5.5. Justification for Dose

The 4 mg commercial tablet formulation to be used as a reference in this study is the highest unit dose strength used in Phase 3 trials for RA. A 4-mg dose of baricitinib has been extensively studied in previous Phase 1 studies assessing baricitinib PK and has been well tolerated in healthy subjects. The 2 mg/mL suspension concentration is planned to be used in future clinical studies with this formulation.

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).

Screening may occur up to 28 days prior to dosing in Period 1. Subjects who are not dosed 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 28 days following the last dose of baricitinib

[1b] female subjects:

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 consistent with menopause

[2] are aged 21 to 65 years, inclusive, at the time of screening

[3] have a body mass index (BMI) of 18.5 to 29.9 kg/m^2, inclusive, at screening

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

[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] have given 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 baricitinib, and have previously received the investigational product

[13] have known allergies to baricitinib, 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 a history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data

[17] have known or ongoing psychiatric disorders that would interfere with study participation as determined by the investigator

[18] regularly use known drugs of abuse

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

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

[24] have donated blood of more than 450 mL within 3 months of study enrollment

[25] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to abide by alcohol restrictions as specified in Section 6.3.2 (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] are subjects who currently smoke 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

[27] have a current or recent history (<30 days prior to screening and/or <45 days prior to Day -1 in Period 1) of a clinically significant bacterial, fungal, parasitic, viral (not including rhinopharyngitis), or mycobacterial infection

[28] have an ANC <2000 cells/μL (2×10^9/L) at screening. For abnormal values, a single repeat will be allowed.

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

[30] have received live vaccine(s) within 3 months of screening, or intend to during the study

[31] are unwilling to comply with the dietary requirements/restrictions during the study: (i) consume only the meals provided during inpatient visits (see Section 6.3), and (ii) refrain from consuming grapefruit, star fruit, pomelos, or products containing these fruits, for at least 14 days prior to the first dose and during the study

[32] have used or intend to use drugs or substances that are known to be strong or moderate inhibitors or inducers of cytochrome P450 (CYP) 3A or strong inhibitors of organic anion transporter 3 (OAT3; such as probenecid) within 30 days prior to the first dose and throughout the study

[33] Have a history of, in the opinion of the investigator, excessive methylxanthine use within the previous 6 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; one 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 oz (85 g) of chocolate.

[34] 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

Grapefruit, star fruit, pomelos, or products containing these fruits will not be allowed from 14 days prior to the first dose and during the study.

Administration of baricitinib in the fasted state

Following an overnight fast (water only permitted) of at least 10 hours, subjects will be administered 4 mg baricitinib with or without approximately 240 mL room temperature water (as determined by the randomization schedule [Part A] or based on the results from the interim analysis planned for Part A [Part B]). Water can be allowed as desired except from 1 hour before until 2 hours after drug administration. No food or fluid (except water) will be allowed for at least 4 hours postdose. Lunch will be provided after the 4-hour PK sample is collected.

Administration of baricitinib in the fed state (Part B only)

Following an overnight fast (water only permitted) of at least 10 hours, subjects will start a US FDA-defined high-fat, high-calorie meal 30 minutes prior to administration of baricitinib. It is intended that the meal will be ingested in its entirety over an approximate 25-minute period, such that it is completed at least 5 minutes before dosing. A 4-mg dose of baricitinib will be given with or without approximately 240 mL room temperature water (as determined by interim analysis of data from Part A). Water can be given as desired except for 1 hour before and 2 hours after drug administration. No further food or fluids (except water) will be permitted until at least 4 hours postdose and lunch will be provided after collection of the 4-hour PK sample.

High-fat meal: The high-fat, high-calorie meal (fat comprises approximately 50% of total calorific content) should consist of approximately 800 to 1000 kilocalories in total. No additional food or substitute is allowed. 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 kilocalories from protein, carbohydrate, and fat, respectively.

6.3.2. Caffeine, Alcohol, and Tobacco

Alcohol – Alcohol will not be permitted from 48 hours prior to each admission until after collection of the 48-hour PK sample in each period and within 48 hours prior to the follow-up visit. During the washout period, alcohol will be restricted to a maximum of 2 units per day.

Caffeine/methylxanthine – Subjects will be advised not to exceed their usual intake of caffeine- or methylxanthine-containing food and drinks, such as coffee, tea, cola, and chocolate during the study.

Smoking – Subjects should not smoke or use any nicotine products from 2 hours prior to each admission until after collection of the 48-hour PK sample.

6.3.3. Activity

Subjects should not engage in strenuous physical exercise from 1 week prior to the first dose until completion of the follow-up assessments.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened only once, at the discretion of the investigator. The interval between rescreenings should be at least 1 week. If rescreening 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

Part A of this study involves a comparison of baricitinib administered as a 4-mg dose of the suspension formulation administered with and without 240 mL water with baricitinib administered as a 4-mg dose of the commercial tablet formulation administered with 240 mL water.

Table JAGU.4 shows the treatment regimens for Part A.

Baricitinib will be administered orally as 1 × 4-mg tablet with approximately 240 mL room temperature water, as 2 mL × 2 mg/mL suspension administered without water, or as 2 mL × 2 mg/mL suspension followed immediately by 240 mL of room temperature water, in the morning of Day 1 of the appropriate treatment period (as defined by the randomization). Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table JAGU.4. Treatments Administered in Part A

Treatment name	Baricitinib	Baricitinib	Baricitinib
Dosage formulation	Suspension	Suspension	Commercial Tablet
Dosage level(s)/ Unit dose strengths	2 mL × 2 mg/mL	2 mL × 2 mg/mL	1 × 4-mg
Route of administration	Oral	Oral	Oral
Dosing instructions[a]	Dose administered following ≥10-hour fast without water	Dose administered following ≥10-hour fast and immediately prior to 240 mL water	Dose administered following ≥10-hour fast with 240 mL water

[a] Further instructions for the storage and dispensing of the suspension formulation will be provided to the site in a separate document.

Part B of this study involves a comparison of baricitinib administered as a 4-mg dose of the suspension formulation in the fasted state compared to following a high-fat, high-calorie meal.

A 4-mg dose of baricitinib will be administered orally as 2 mL × 2 mg/mL suspension in the morning of Day 1 of each treatment period. Whether the doses are administered alone or followed by 240 mL room temperature water will be subject to a decision based on interim analysis of data from Part A of the study (see Section 10.3.3). Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling

Each tablet of baricitinib contains 4 mg of active ingredient, and is provided as bulk supply in high-density polyethylene bottles.

Baricitinib suspension formulation contains 2 mg/mL baricitinib and is provided as bulk supply in polyethylene terephthalate bottles.

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

7.2. Method of Treatment Assignment

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

7.2.1. Selection and Timing of Doses

This study will use a fixed dose of 4 mg baricitinib. A dose of 4 mg is selected as it is the primary dose studied in Phase 3 clinical studies and is the recommended commercial dose in patients with RA.

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

7.3. Blinding

This will be 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.

Baricitinib tablets and suspension will be stored at room temperature.

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

Over-the–counter or prescription medications, including herbal medications, are to be avoided within 14 days prior to dosing and during the study. Drugs that are known to be strong or moderate inhibitors or inducers of CYP3A or strong inhibitors of OAT3 (such as probenecid) are not allowed within 30 days prior to the first dose and throughout the study. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist (CP) or clinical research physician (CRP). 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

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

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, the subject will be discontinued from the study and early discontinuation assessments will be performed as shown in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the subject should be discontinued from the study
- subject decision
    - the subject requests to be withdrawn from the study

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

8.3. Subjects Lost to Follow-up

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

9. Study Assessments and Procedures

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

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

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

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

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

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

9.2.1. Serious Adverse Events

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

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

Study site personnel must alert Lilly, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting begins after the subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

For the purposes of this study, an overdose of baricitinib is considered any dose higher than the dose assigned.

The IB contains information on the highest single doses administered to healthy subjects. There is no specific antidote for baricitinib. In the event of an 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.

Additional vital signs may be assessed as clinically indicated as well as at the scheduled times. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 3 minutes. If the subject feels unable to stand, supine vital signs only will be recorded.

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).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational product should be reported to 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 (Section 2). Electrocardiograms 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. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/QT corrected for heart rate interval from baseline) after enrollment, the investigator will determine if the subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in subject management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Safety Monitoring

The Lilly CP or 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 CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist when appropriate, and periodically review:

- trends in safety data
- laboratory analytes
- AEs

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of baricitinib. A maximum of 5 samples may be collected at additional time points during each part of 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.

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 baricitinib will be assayed using a validated liquid chromatography with tandem mass spectrometric detection method.

Bioanalytical samples collected to measure investigational product 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 (Section 2), where local regulations allow.

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

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

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

In Part A, 26 subjects may be enrolled to ensure that 20 complete the study.

For C_{max}, assuming an intra-subject coefficient of variation of 16%, 20 subjects provide 90% power to show bioequivalence for a 95% confidence interval (CI) using 0.8 and 1.25 as the lower and upper bioequivalence limits, respectively. A 95% CI was used to calculate the power for this study to assure both comparisons of the suspension formulation (with and without water) versus the commercial tablet had adequate power using the Holm's step-down procedure. This procedure adjusts for multiplicity maintaining the family-wise type 1 error rate.

For AUC(0-∞) and AUC(0-t_{last}), assuming an intra-subject coefficient of variation of 7.8% and 7.6%, respectively, 20 subjects provide greater than 99% power to show bioequivalence for a 95% CI using 0.8 and 1.25 as the lower and upper bioequivalence limits, respectively.

In Part B, it is planned that up to a maximum of 18 subjects will be enrolled in order that 14 complete the study; however, this number may be revised based on interim analysis of the intra-subject variation in PK parameters of baricitinib suspension formulation i n Part A of the study.

Subjects who are randomized and discontinue the study prior to completion of all study periods in their assigned study part may be replaced to ensure that a minimum of 20 subjects complete Part A of the study and 14 complete Part B. Replacement subjects will complete all 3 periods (Part A) or 2 periods (Part B), following the sequence of the withdrawn subject.

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 subject's age, sex, weight, height, BMI, race, 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 and completer analysis sets. For each study part (Part A or Part B), the full analysis set includes all data from all subjects receiving at least 1 dose of baricitinib in that study part, with evaluable PK data, according to the treatment the subjects actually received. The completer analysis set for each study part includes data from subjects who receive all doses of baricitinib for that study part and have evaluable PK data, according to the treatment the subjects actually received. Safety analyses will be conducted for

all enrolled subjects, whether or not they completed all protocol requirements. Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

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

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include TEAEs, clinical laboratory parameters, and vital signs. 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 baricitinib will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max}, AUC(0-t_{last}), and AUC(0-∞). The t_{max} will be observed from the data. Other noncompartmental parameters may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameter estimates will be evaluated to delineate effects of baricitinib formulation. For the primary analysis, log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) estimates will be evaluated in a linear mixed-effects model with fixed effects for formulation, period, sequence, and a random effect for subject (sequence). The treatment differences between each test compared to the reference formulation will be back-transformed to present the ratios of geometric least squares means and the corresponding CIs. The Holm step-down procedure for an overall 0.1 alpha level will be used.

Bioequivalence between the suspension formulation administered either with or without water and the commercial tablet will be concluded if the 95% CI for C_{max}, AUC(0-t_{last}), and AUC(0-∞) are all completely contained within the interval (0.80, 1.25). Bioequivalence between the suspension formulation using the other administration and the commercial tablet will be

concluded if the 90% CIs for C_{max}, AUC(0-t_{last}), and AUC(0-∞) are all completely contained within the interval (0.80, 1.25).

For secondary analyses, the same model specified above will be used for C_{max}, AUC(0-t_{last}), and AUC(0-∞). Ratios of geometric least squares means and the corresponding 90% CIs will be presented. The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

10.3.3. Interim Analyses

A formal interim analysis will be performed after completion of Part A of the study. This is an open-label study. Pharmacokinetic data will be analyzed after all PK data are available for Part A of the study. Statistical analysis will be conducted to test the baricitinib suspension formulation, administered with and without water, for bioequivalence with the commercial tablet formulation. The administration method for the suspension formulation that is bioequivalent to the commercial tablet formulation will be used in Part B of the study. If both administration methods are bioequivalent to the commercial tablet formulation, suspension will be administered without water in Part B of the study, for ease of administration. If the suspension formulation is not bioequivalent to the commercial tablet formulation using either administration method, all available data will be used to assess the most appropriate way to administer the drug in Part B.

Intra-subject variability estimates of PK parameters will be used to determine the number of subjects required to complete Part B of the study.

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.
ANC	absolute neutrophil count
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to the last time point with a measurable concentration
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.

enter	Subjects entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
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.
JAK	Janus kinase
OAT3	organic anion transporter 3
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.
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
QD	once daily
R	4-mg dose of baricitinib commercial tablet formulation administered with 240 mL water
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.
STAT	signal transducer and activator of transcription
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life associated with the terminal rate constant in noncompartmental analysis
T1	4-mg dose of baricitinib suspension formulation administered without water
T2	4-mg dose of baricitinib suspension formulation administered with 240 mL water
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
TF	test formulation
TF_{fasted}	4-mg dose of baricitinib suspension test formulation administered in the fasted state
TF_{fed}	4-mg dose of baricitinib suspension test formulation administered after a high-fat, high-calorie meal
t_{max}	time of maximum observed drug concentration

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	Glucose (fasting)
Mean cell hemoglobin concentration	Urea
Leukocytes (WBC)	Total cholesterol
Absolute counts of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
Platelets	Creatinine
Urinalysis[a]	Gamma-glutamyl transferase (GGT)
Specific gravity	Creatine kinase
pH	
Protein	Hepatitis B surface antigen[b]
Glucose	Hepatitis C antibody[b]
Ketones	HIV[b]
Bilirubin	Pregnancy test (females)[c]
Urobilinogen	FSH (females, if applicable)[b,d]
Blood	
Nitrite	
Leukocytes	
Microscopic examination of sediment[e]	

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

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

b Performed at screening only. Hepatitis B surface antigen, Hepatitis C antibody, and HIV tests will only be performed if results have not been obtained for the subject in the last 6 months.

c Serum pregnancy test to be performed at screening. A serum or urine pregnancy test will be performed at follow-up/early discontinuation and may be performed at other times at the investigator's discretion.

d Postmenopausal women only; analyzed in serum.

e Test only if dipstick result is abnormal and per investigator's discretion.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the potential risks and benefits of participating in the study
- Ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial

Ethical Review

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

The study site's ERB 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 eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and/or use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

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

Data Collection Tools/Source Data

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. 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 each part of the study. Fewer venipunctures and blood draws may actually occur, but this will not require a protocol amendment.

Protocol I4V-MC-JAGU Part A 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	4	44
Pharmacokinetics	3	50[b]	150
Blood discard for cannula patency	0.3	50[b]	15
Pharmacogenetics	10	1	10
Total			236
Total for clinical purposes [rounded up to nearest 10 mL]			240

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

[b] Including 5 additional samples, if needed.

Protocol I4V-MC-JAGU Part B 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	3	33
Pharmacokinetics	3	35[b]	105
Blood discard for cannula patency	0.3	35[b]	10.5
Pharmacogenetics	10	1	10
Total			175.5
Total for clinical purposes [rounded up to nearest 10 mL]			180

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

[b] Including 5 additional samples, if needed.

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