I4V-MC-JAIV Protocol b

A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study Evaluating the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Primary Biliary Cholangitis Who Have an Inadequate Response or Are Intolerant to UDCA

NCT03742973

Approval Date: 24-Apr-2019

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Baricitinib (LY3009104)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Initial Protocol Electronically Signed and Approved by Lilly on 20 July 2018.
Protocol Amendment (a) was approved on 28-Sep-2018
Protocol Amendment (b) was Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 24-Apr-2019 GMT

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1. Synopsis

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study Evaluating the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Primary Biliary Cholangitis Who Have an Inadequate Response or Are Intolerant to UDCA.

Rationale:

Baricitinib (LY3009104) is an oral Janus kinase 1 (JAK1)/Janus kinase 2 (JAK2) selective inhibitor, representing a potentially effective therapy for the treatment of patients with primary biliary cholangitis (PBC). The current study will evaluate the safety and tolerability of baricitinib 2-mg and, if acceptable, will continue to evaluate the efficacy and safety profile of baricitinib 4-mg when administered once daily to patients with primary biliary cholangitis (PBC) who have had an inadequate response or who are intolerant to ursodeoxycholic acid (UDCA). The efficacy, safety, and tolerability data from this study are intended to inform the benefit-risk relationship of baricitinib in patients with PBC.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of baricitinib 4-mg QD compared to placebo on PBC disease	• Change from baseline in ALP at Week 12
Secondary	
• To evaluate the effect of baricitinib 4-mg QD compared to placebo on PBC disease	• Proportion of patients with ALP <1.67 x ULN (and at least 15% decrease from baseline) and total bilirubin<ULN at Week 12
• To evaluate the effect of baricitinib 2-mg QD compared to placebo on PBC disease	• Change from baseline in ALP at Week 12 • Proportion of patients with ALP<1.67 x ULN (and at least 15% decrease from baseline) and total bilirubin < ULN at Week 12
• To evaluate the effect of baricitinib 4-mg and 2-mg QD compared to placebo on PBC symptoms	• Change from baseline in itch as measured by Itch NRS at Week 12 • Change from baseline in fatigue as measured by Fatigue NRS at Week 12

Abbreviations: ALP = alkaline phosphatase; NRS = Numeric Rating Scale; PBC = primary biliary cholangitis; QD = once daily; ULN = upper limit of normal.

Summary of Study Design:

Study I4V-MC-JAIV is a multicenter, randomized, double-blind, parallel, placebo-controlled study with 3 study periods in patients with PBC who have an inadequate response or who are intolerant to UDCA that will be conducted in 2 cohorts

Cohort A is a randomized, double-blind, parallel, placebo-controlled cohort comprised of the first group of patients. This Cohort will randomize at least twelve patients to baricitinib 2-mg and at least eight patients to placebo.

Cohort B is a randomized, double-blind, parallel, placebo-controlled cohort comprised of the second group of patients. This Cohort will randomize at least twenty patients to baricitinib 4 mg and twelve patients to placebo.

Enrollment in Cohort B will begin only after the DMC review of Cohort A is complete and Lilly has received and accepted a recommendation to proceed.

Patients in Cohort A and Cohort B will follow the same study schedule.

Number of Patients:

The study will include approximately 52 patients with PBC.

Statistical Analysis:

Unless otherwise specified, the efficacy, health outcomes, and safety analyses will be conducted on the modified intent-to-treat (mITT) population. The mITT population is defined as all randomized patients who take at least one dose of study treatment.

Comparisons between baricitinib and placebo will be performed for all analyses in the treatment period. Baseline will be defined as the last available value before the first dose of investigational product for both efficacy and safety analyses, unless otherwise specified.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed-effects models for repeated measures (MMRM) with treatment, [redacted] An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. Type III sums of squares for the least-squares (LS) means will be used for the statistical comparison and the 90% confidence interval (CI) will also be reported. Treatment group comparisons with placebo at Week 12 and other visits will be tested.

Treatment comparisons of categorical efficacy variables will be made using a logistic regression analysis with treatment, cohort, baseline ALP (≤2.5X ULN, >2.5X ULN) and baseline UDCA use (yes/no) in the model. The proportions and 90% CI will be reported.

2. Schedule of Activities

Table JAIV.1. Schedule of Activities for Cohorts A and B

Procedure	Screening		Treatment Period						Follow-up
Visit Number	V1	V2	V3[a]	V4	V5	V6	V7	ET	V801
	(up to 49 days prior to V3)	(at least 4 weeks after V1)	Week 0	Week 1 (±2 days)	Week 4 (±4 days)	Week 8 (±4 days)	Week 12 (±4 days)		28 days post last dose (±4 days)
Informed consent	X								
Inclusion and exclusion criteria review	X		X						
Patient demography	X								
Physical examination[b]	X								
Pre-existing conditions and medical history (includes substance usage)[c]	X								
Randomization			X						
Investigational product dispensed			X		X	X			
Investigational product returned and compliance assessed				X	X	X	X	X	
Study Procedures									
TB test[d]	X								
Read PPD if applicable (48-72 hours post PPD)	X[e]								
Chest x-ray[f]	X								
ECG[g]	X								
AE/SAE review	X		X	X	X	X	X	X	X
Concomitant medication review	X		X	X	X	X	X	X	X
Symptom-directed physical examination			X	X	X	X	X	X	X
Targeted event history[h]			X	X	X	X	X	X	X
Vital signs (blood pressure, pulse, and temperature)	X		X	X	X	X	X	X	X
Waist circumference			X				X	X	

Procedure	Screening		Treatment Period						Follow-up
Visit Number	V1	V2	V3[a]	V4	V5	V6	V7	ET	V801
	(up to 49 days prior to V3)	(at least 4 weeks after V1)	Week 0	Week 1 (±2 days)	Week 4 (±4 days)	Week 8 (±4 days)	Week 12 (±4 days)		28 days post last dose (±4 days)
Height			X						
Weight			X	X	X	X	X	X	X
Itch NRS	X		X	X	X	X	X	X	X
PBC-40	X		X	X	X	X	X	X	X
FACIT-F	X		X	X	X	X	X	X	X
Fatigue NRS	X		X	X	X	X	X	X	X
Physician Global Assessment	X		X	X	X	X	X	X	X
QIDS-SR[16]			X	X	X	X	X	X	
Laboratory Tests									
FSH[i]	X								
TSH	X								
Serum pregnancy test[j]	X								
Urine pregnancy test[j]			X	X	X	X	X	X	
HIV	X								
Hepatitis B testing (HBsAg, HBcAb, HBsAb)	X								
Hepatitis C virus (HCV) antibody testing	X								
ANA	X								
ASMA	X								
CK-18 M30 and M65			X				X	X	X
ELF: hyaluronic acid (HA), procollagen type III amino N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinase 1 (TIMP-1)			X				X	X	X
Immunoglobulins (IgG, IgA, IgM)	X		X	X	X	X	X	X	X
hsCRP	X		X	X	X	X	X	X	X
ESR[k]	X		X	X	X	X	X	X	X
FGF 19			X		X		X	X	X
Cytokine panel[l]			X		X		X	X	X

Procedure	Screening		Treatment Period						Follow-up
Visit Number	V1	V2	V3[a]	V4	V5	V6	V7	ET	V801
	(up to 49 days prior to V3)	(at least 4 weeks after V1)	Week 0	Week 1 (±2 days)	Week 4 (±4 days)	Week 8 (±4 days)	Week 12 (±4 days)		28 days post last dose (±4 days)
INR	X								
Clinical chemistry[m]	X	X	X	X	X	X	X	X	X
ALP isoenzyme			X	X	X	X	X	X	X
Hematology[m]	X		X	X	X	X	X	X	X
Fasting lipid panel[n]			X				X	X	X
Baricitinib plasma concentrations (PK sample)[o]			X	X	X	X	X	X	
Urinalysis			X		X		X	X	X
Exploratory storage samples (serum and plasma)			X		X		X	X	X
Exploratory storage samples (urine)			X		X		X	X	X
Exploratory samples for storage (RNA)			X		X		X	X	X

Abbreviations: AE = adverse event; ANA = antinuclear antibody ; ASMA = anti-smooth-muscle antibody; CK-18 = cytokeratin 18; ECG = electrocardiogram; ELF = enhanced liver fibrosis; ESR = erythrocyte sedimentation rate; ET = early termination; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; FGF = fibroblast growth factor; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody test; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; INR = International Normalized Ratio; NRS = Numeric Rating Scale; PBC-40 = Quality of Life for Primary Biliary Cirrhosis; PK = pharmacokinetics; PPD = purified protein derivative; QIDS-SR = Quick Inventory of Depressive Symptomatology-Self-Report–16; RNA = ribonucleic acid; SAE = serious adverse event; TB = tuberculosis; TSH = Thyroid-stimulating hormone.

Footnotes on next page.

[a] At Visit 3, all baseline assessments must be performed and baseline laboratory samples (except postdose PK sample [Section 9.5]) must be drawn prior to administration of the first dose of investigational product for randomized patients.

[b] One complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1. All subsequent physical examinations may be symptom-directed. A complete physical examination may be repeated at the investigator's discretion any time.

[c] Substances include drugs, alcohol, tobacco, and caffeine.

[d] TB test(s) including PPD, QuantiFERON®-TB Gold, and T-SPOT®. See Exclusion Criterion [23] for description of TB testing. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally. (Note: Exception: Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing but must have a chest x-ray at screening.)

[e] If PPD testing was chosen to test for TB, then the patient must return and PPD test read 48 to 72 hours after Visit 1 (post-PPD).

[f] A chest x-ray (posterior-anterior view) will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available for review by the investigator.

[g] 12-lead ECGs (single) will be performed locally and will be locally (machine) read.

[h] The targeted event history will assess for signs and symptoms of thromboembolic events, serious infections, and malignancies.

[i] For female patients aged 50 to ≤55 years with an intact uterus, not on hormone therapy, with 6 to ≤12 months of spontaneous amenorrhea, an FSH test will be performed to confirm nonchildbearing potential (FSH >40 mIU/mL).

[j] For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and at all subsequent study visits during the treatment period. Visit 2 results must be known prior to first dose of investigational product.

[k] ESR to be performed locally.

[l] The cytokine panel will include IL-12 (Appendix 2).

[m] See Appendix 2 for details.

[n] Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, the sample should still be collected.

[o] See Section 9.5 for details

.

3. Introduction

3.1. Study Rationale

Baricitinib belongs to the pharmacological class of Janus kinase (JAK) inhibitors. Janus kinases are a family of 4 protein tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) that play an important role in cytokine signal transduction. Baricitinib is a JAK1/JAK2 inhibitor that demonstrates selectivity for and inhibition of JAK1 and JAK2 with lower potency towards inhibition of JAK3 or TYK2 (Fridman et al. 2010).

In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2, and JAK3 with half-maximal inhibitory concentration values of 5.9, 5.7, 53, and >400 nM, respectively (Fridman et al. 2010). Janus kinases are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation, and immune function (e.g., interleukin [IL]-2, IL-6, IL-12, IL-15, IL-23, interferons, and granulocyte-macrophage colony-stimulating factor signal through the JAK family) (O'Shea et al. 2015). Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signaling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, then reducing the phosphorylation and activation of STATs and thereby reducing inflammation, cellular activation, and proliferation of key immune cells (O'Shea et al. 2013).

The current study will evaluate the safety and tolerability of baricitinib 2-mg and, if acceptable, will continue to evaluate the efficacy and safety profile of baricitinib 4-mg when administered once daily to patients with primary biliary cholangitis (PBC) who have had an inadequate response or who are intolerant to ursodeoxycholic acid (UDCA). The efficacy, safety, and tolerability data from this study are intended to inform the benefit-risk relationship of baricitinib in patients with PBC.

Associations between PBC and common genetic variants at the human leukocyte antigen class II, IL-12A, and IL-12RB2 loci have been established and suggest that the IL-12 immunoregulatory signaling axis is relevant to the pathophysiology of PBC (Hirschfield et al. 2009). More recent data have identified a relationship between the interferon (IFN), IL-12, and IL-23 pathways and the pathogenesis of PBC (Kawata et al. 2013). The mechanism of action of baricitinib suggests that it will inhibit the activity of cytokines implicated in PBC, most notably type I IFN (JAK1/TYK2), IL-12, and IL-23 (JAK1/TYK2).

Baricitinib 2- and 4-mg have been studied in patients with autoimmune diseases (rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]), atopic dermatitis (AD), and autoinflammatory diseases (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperatures [CANDLE] syndrome and stimulator of interferon genes-associated vasculopathy with onset in infancy [SAVI]). Clinical efficacy and safety have been shown in 4 completed Phase 3 studies in patients with RA (Genovese et al. 2016; Dougados et al. 2017; Fleischmann et al. 2017; Taylor et al. 2017). Completed Phase 2 studies of baricitinib also

demonstrated efficacy in patients with moderate-to-severe plaque psoriasis (Papp et al. 2016) and diabetic kidney disease (Tuttle et al. 2018).

[redacted]

Baricitinib undergoes little liver metabolism (<10% of the administered oral dose); the main elimination pathway is renal (75%) through glomerular filtration and active secretion. [redacted]

Given the efficacy of baricitinib demonstrated in clinical trials for treating autoimmune/autoinflammatory diseases, the acceptable safety profile of baricitinib observed through the current stage of development, and a continuing unmet medical need in patients with PBC, there is a compelling rationale for the initiation of a proof of concept study to evaluate baricitinib in the treatment of PBC. Baricitinib has not been studied in patients with PBC, so the study will be conducted in 2 cohorts. In cohort A patients will be randomized to placebo or baricitinib 2-mg once daily. If the safety and tolerability profile is acceptable, the study will continue to Cohort B, which will randomize patients to placebo and baricitinib 4-mg once daily.

3.2. Background

Primary biliary cholangitis is a chronic and progressive cholestatic liver disease thought to be autoimmune in nature and is characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts (Webb et al. 2015; Hirschfield et al. 2018). It is an orphan disease with a diagnosed prevalence in North America and Europe of about 40 per 100,000 persons (Boonstra et al. 2011). Primary biliary cholangitis is diagnosed frequently from routine liver biochemical tests obtained for other reasons (i.e., increased ALP) while the patient is still asymptomatic or in early-stage disease when a patient seeks treatment for pruritus or fatigue (Hirschfield et al. 2018). Untreated PBC typically progresses over several years to liver cirrhosis resulting in liver transplant or death. Currently, proposed treatments are directed toward 2 approaches (Hirschfield et al. 2018). The first is to manage the production and disposal of bile acids that accumulate in the liver because of progressive destruction and impaired function of the bile ducts caused by chronic inflammation. The second approach is to modify the autoimmune process that drives the disease.

Ursodeoxycholic acid was approved for treating PBC in 1997 and is now the standard of care for treating this disease (UDCA USPI; Hirschfield et al. 2018). Ursodeoxycholic acid works by facilitating bile flow through the liver and protecting liver cells. It is thought that UDCA is concentrated in bile and decreases biliary cholesterol by suppressing hepatic synthesis and secretion of cholesterol and by inhibiting its intestinal absorption (UDCA Drugbank [WWW]). Ursodeoxycholic acid is credited with significantly reducing disease progression, liver transplant, and death (Kowdley 2000). Treatment with UDCA is recommended at diagnosis, regardless of disease stage. About 40% to 50% of patients have an inadequate response to UDCA, as assessed by lack of improvement in liver biochemistry (Corpechot et al. 2008; Carbone et al. 2013). A second medication, obeticholic acid, was approved as a treatment for PBC in 2016 (USPI; Nevens et al. 2016). The mechanism of treating PBC is by decreasing the intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol, as well as by increasing transport of bile acids out of the hepatocytes. Obeticholic acid treatment is approved as an add-on to UDCA in patients with an inadequate response or as monotherapy in patients who are intolerant to UDCA. Among these patients and according to efficacy data, approximately 55% will have an ALP less than 1.67 times ULN after 12 months of treatment. However, neither of these treatments effectively address other major symptoms of PBC such as itch or fatigue. In fact, obeticholic acid is associated with increased pruritus, and achieving and maintaining an effective dose is limited by this adverse effect (Nevens et al. 2016).

Several groups have shown that survival in patients who respond to UDCA is comparable to that of the general population, whereas liver transplant-free survival in UDCA nonresponders is substantially reduced (Zhu et al. 2015). In a recent study of 2300 patients enrolled in the UK-PBC Research Cohort, it was confirmed that UDCA response strongly predicted prognosis. UDCA nonresponders by the Paris-I definition had a hazard ratio (HR) of 2.2 for liver transplant or death from liver failure, compared with responders (PBC Genetics Study [WWW]). New treatment options that reduce symptoms and treat the underlying disease are needed for patients with PBC.

3.3. Benefit/Risk Assessment

Potential benefits are discussed in the study rationale section (Section 3.1) and known risks from the baricitinib clinical program are discussed here.

Serious infections, venous thromboembolism, hepatotoxicity, and fetal malformations were identified as important potential risks with baricitinib. Inclusion/Exclusion criteria in the protocol limit enrolment of patients who are at risk for these important potential risks. Although infections were seen in about half of the RA study population, the incidence rate of serious infection in patients exposed to baricitinib in the RA program was 3.0 per 100 patient-years. During the controlled period (through 16 weeks), rates were similar in both baricitinib- and placebo-treated patients. The nonserious infections (upper respiratory tract infections, herpes zoster, and herpes simplex) associated with baricitinib in the RA program are readily diagnosed, manageable, and typically resolve without long-term sequelae. It is recommended that where indicated, herpes zoster vaccination be offered to patients prior to receiving baricitinib.

Increases in levels of ALT, AST, and total bilirubin have been observed in patients with RA. Most of these increases improved with continued use or temporary discontinuation of baricitinib with no long-term effects. No cases of severe drug-induced liver injury were observed with baricitinib treatment.

Fetal malformations were reported in animal toxicology studies at higher doses than those used in human patients. Only a small number of patients have become pregnant in baricitinib clinical trials and there have been no reports of fetal malformations in these pregnancies.

Venous thromboembolic events (VTEs) have been determined to be an important potential risk for baricitinib. There was a numerical imbalance in reports of VTEs in the 24-week placebo-controlled period of the Phase 3 trials of patients with RA. Available evidence does not establish a causal association. With long-term exposures, the exposure-adjusted incidence rate of VTE for baricitinib-treated patients with RA was similar to the background rates published in the literature for the target population. There was no pattern of increased or decreased risk during long-term exposures. An analysis of risk factors showed that prior VTE, age, body mass index, and use of a cyclooxygenase-2 inhibitor were associated with the risk for a VTE observed during treatment with baricitinib. To mitigate risk of venous thromboembolism, exclusion and discontinuation criteria have been added to the protocol to limit participation of patients who are at an increased risk of VTE.

Safety reports from postmarketing surveillance of the use of baricitinib in RA have been consistent with the safety profile reported from clinical trials.

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

4. Objectives and Endpoints

Table JAIV.2 shows the objectives and endpoints of the study.

Table JAIV.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of baricitinib 4-mg QD compared to placebo on PBC disease	• Change from baseline in ALP at Week 12
Secondary	
• To evaluate the effect of baricitinib 4-mg QD compared to placebo on PBC disease	• Proportion of patients with ALP <1.67 x ULN (and at least 15% decrease from baseline) and total bilirubin<ULN at Week 12
• To evaluate the effect of baricitinib 2-mg QD compared to placebo on PBC disease	• Change from baseline in ALP at Week 12 • Proportion of patients with ALP<1.67 x ULN (and at least 15% decrease from baseline) and total bilirubin < ULN at Week 12
• To evaluate the effect of baricitinib 4-mg and 2-mg QD compared to placebo on PBC symptoms	• Change from baseline in itch as measured by Itch NRS at Week 12 • Change from baseline in fatigue as measured by Fatigue NRS at Week 12

Abbreviations: ALP = alkaline phosphatase; NRS = Numeric Rating Scale; PBC = primary biliary cholangitis; QD = once daily; ULN = upper limit of normal.

5. Study Design

5.1. Overall Design

Study I4V-MC-JAIV (JAIV) is a multicenter, randomized, double-blind, parallel, placebo-controlled, proof-of-concept Phase II study in patients with primary biliary cholangitis (PBC) who have an inadequate response or are intolerant to UDCA that will be conducted in 2 cohorts. Both cohorts will follow the same study schedule.

Cohort A

Cohort A is a randomized, double-blind, parallel, placebo-controlled cohort comprised of the first group of patients. At least twelve patients will be randomized to baricitinib 2-mg and at least eight patients will be randomized to placebo. Once Cohort A has fully enrolled, enrollment will be suspended.

Once all Cohort A patients have completed the 12 week treatment period their data will be reviewed by an external DMC.

The primary goal of Cohort A will be to assess the tolerability and safety of baricitinib 2-mg compared to placebo through Week 12. Efficacy measures, such as change in ALP will also be assessed to provide context for the benefit:risk ratio.

A DMC will oversee this study (Section 9.4.8.2).

Cohort B

Cohort B is a randomized, double-blind, parallel, placebo-controlled phase comprised of the second group of patients. At least twenty patients will be randomized to baricitinib 4-mg and at least twelve patients will be randomized to placebo.

Enrollment in Cohort B will begin only after the DMC review of Cohort A is complete and Lilly has received and accepted a recommendation to proceed.

Figure JAIV.1 illustrates the study design.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Section 2). Section 7.6 describes permitted concomitant therapy. Study governance considerations are described in detail in Appendix 3.

Each cohort of the study consists of 3 periods:

Screening Period: The screening period is up to 49 days and begins when the patient signs the informed consent form (ICF). In exceptional circumstances, the screening window can be extended after consultation with the sponsor where local authorities permit. During the screening period, the investigator must confirm the patient meets all inclusion and no exclusion criteria for the study (Section 6). Two assessments of AST, ALT, ALP, and total bilirubin values are required prior to randomization (by at least two measurements obtained at least 4 weeks apart). If the AST, ALT, ALP, or bilirubin values from the second sample are increased more

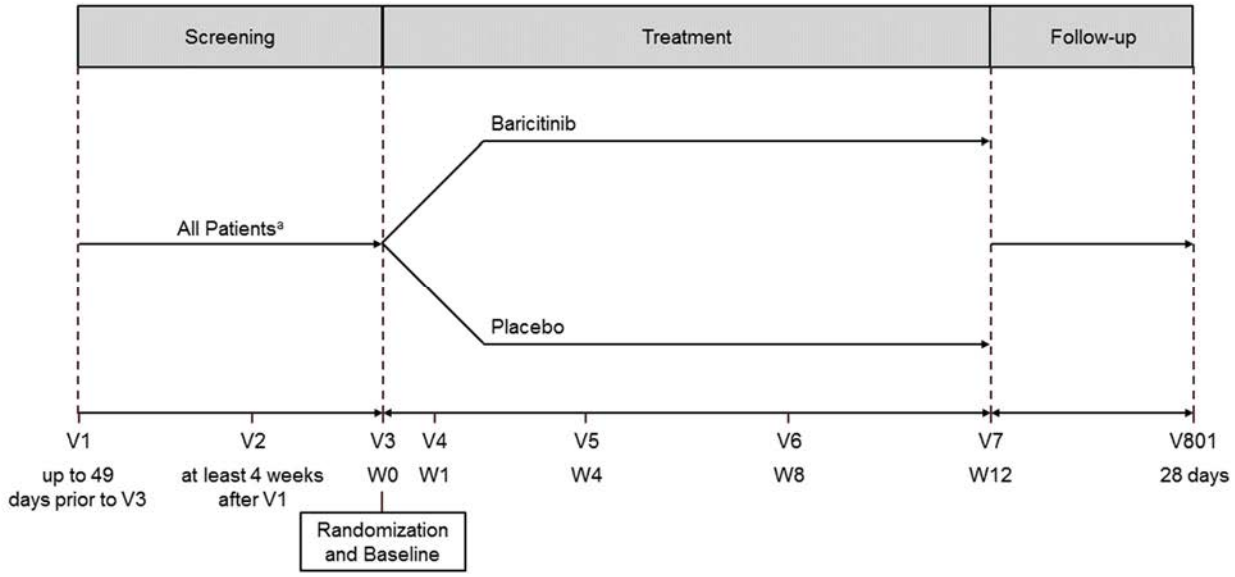
than 20% compared to the first sample (second test result/first test result >1.2) **and** the second sample exceeds the ULN, then the patient will be excluded (exclusion criterion 44). Screening procedures will be performed according to the Schedule of Activities (Section 2). Eligible patients will be randomized at Week 0 (Visit 3).

Treatment Period: At Visit 3 (Week 0, baseline) all assessments are completed and baseline laboratory samples obtained according to the Schedule of Activities prior to the first dose of investigational product for both cohorts. Randomized patients will take the first dose of investigational product at the clinic and pharmacokinetic (PK) samples will be drawn 15 minutes and 1 hour post dose.

Investigational product will be taken daily for 12 weeks. Clinical assessments and laboratory samples, including additional PK sampling, will be obtained at scheduled visits according to the Schedule of Activities (Section 2). Special timing considerations of administration of investigational product relative to PK sample collection at study visits are described in Section 9.5.

During the treatment period, in addition to randomized treatment, patients will also maintain their usual medication regimen for PBC (Section 7.6 for details on concomitant therapy).

Follow-up Period: Patients who complete the treatment period, as well as those who discontinue Study JAIV treatment early, will have a post-treatment follow-up visit (Visit 801) approximately 4 weeks after the last dose of investigational product.



Abbreviations: V = Visit; W = Week.

[a] Patients able to tolerate ursodeoxycholic acid (UDCA) will take UDCA orally as background therapy during the study.

Figure JAIV.1. **Illustration of study design for Clinical Protocol I4V-MC-JAIV.** Patients in Cohort A and Cohort B will follow the same study schedule as outlined in this figure. Cohort A will randomize 12 patients to baricitinib 2-mg and 8 patients to placebo. After a DMC review of Cohort A data, Cohort B will then randomize 20 patients to baricitinib 4-mg and 12 patients to placebo.

5.2. Number of Participants

Approximately 52 subjects are planned to be randomized in this study. Approximately 12 patients will receive baricitinib 2-mg, approximately 20 patients will receive baricitinib 4-mg, and approximately 20 patients will receive placebo.

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 patient.

5.4. Scientific Rationale for Study Design

[redacted]

[redacted]

5.5. Justification for Dose

[redacted]

6. Study Population

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

Note: The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion which is maintained in the case of a protocol amendment. Specifically, if a criterion removed as a result of an amendment, the number and the criterion will be removed and will not be reused. If an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of where it is located in the list.

6.1. Inclusion Criteria

Subjects will be eligible for randomization only if they meet all of the following criteria within the screening period, which is ≤49 days prior to randomization, unless specifically defined:

Type of Patient and Disease Characteristics

[1] Male or female patients who are at least 18 years of age.

[2] Have a diagnosis of PBC (consistent with American Association for the Study of Liver Disease [AASLD] and European Association for Study of the Liver [EASL] Practice Guidelines; [Lindor 2009; EASL 2017]), as demonstrated by the presence of at least 2 of the following 3 diagnostic factors:

- History of elevated ALP levels for at least 6 months
- Positive antimitochondrial antibodies titer
- Liver biopsy consistent with PBC

[3] Have ALP ≥1.67 x ULN but ≤6 x ULN

[4] Taking UDCA for at least 52 weeks (stable dose for at least 12 weeks) prior to Visit 3 (Week 0), or have previously taken, but are intolerant (in the opinion of the investigator) to UDCA and have not received UDCA for at least 12 weeks prior to Visit 3 (Week 0).

Patient Characteristics

[5] Nonpregnant, nonbreastfeeding female patients of childbearing potential:

a. Patients who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with the opposite sex during the entirety of the study and for at least 1 week following the last dose of investigational product.

Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 1 week following the last dose of investigational product. Periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception.

b. Otherwise, patients must agree to use for the entirety of the study and for at least 1 week following the last dose of investigational product, 2 effective methods of contraception, where at least 1 form is highly effective (such as combination oral contraceptives, implanted contraceptives or intrauterine devices). Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method.

Female patients of nonchildbearing potential may participate without requirements for contraception. This includes female patients who are:

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

b. Postmenopausal – defined as either

   i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

      1. Cessation of menses for at least 1 year, or

      2. At least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone (FSH) >40 mIU/mL; or

   ii. A woman 55 years of age or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

   iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Informed Consent

[6] Must read and understand the informed consent approved by Eli Lilly and Company (Lilly), or its designee, and the institutional review board (IRB)/ethics review board (ERB) governing the site, and provide written informed consent.

6.2. Exclusion Criteria

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

Medical Conditions

[7] History or presence of other concomitant liver diseases including:

a. Hepatitis C virus (HCV) infection (hepatitis C antibody-positive and HCV ribonucleic acid [RNA] positive).

- Note: Patients who have documented anti-HCV treatment for a past HCV infection AND are HCV RNA-negative with a sustained viral response may be enrolled in the study.

b. Hepatitis B virus (HBV) infection defined as:

- positive for hepatitis B surface antigen (HBsAg), or
- positive for hepatitis B core antibody (HBcAb)

c. Primary sclerosing cholangitis

d. Alcoholic liver disease

e. Autoimmune liver disease other than PBC, such as overlap hepatitis

f. Nonalcoholic steatohepatitis

g. Gilbert's syndrome

[8] Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

a. Liver transplantation, current placement on a liver transplant list or current Model for End Stage Liver Disease (MELD) score ≥ 15

b. Portal hypertension with complications, including known gastric or esophageal varices, ascites, history of variceal bleeds or related therapeutic or prophylactic interventions (e.g., beta blockers, insertion of variceal bands or transjugular intrahepatic portosystemic shunt), or hepatic encephalopathy

c. Cirrhosis with complication, i.e., decompensated cirrhosis, including history or presence of one or more of the following:

- spontaneous bacterial peritonitis
- hepatocellular carcinoma
- hepatorenal or hepatopulmonary syndrome

[9] Have an estimated glomerular filtration rate (eGFR) based on the most recent available serum creatinine of <90 mL/min/1.73 m^2.

[10] Have screening electrocardiogram (ECG) abnormalities that in the opinion of the investigator or the sponsor are clinically significant and indicate an unacceptable risk for the patient's participation in the study.

[11] Have experienced any of the following within 12 weeks of screening: myocardial infarction, unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure.

[12] Have active fibromyalgia that in the investigator's opinion, would make it difficult to appropriately assess fatigue for the purposes of this study.

[13] Have had any major surgery within 8 weeks prior to study entry or will require major surgery during the study that in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient.

[14] Have a diagnosis of any systemic inflammatory condition other than PBC such as, but not limited to, RA, spondyloarthropathy, Crohn's disease, ulcerative colitis, psoriatic arthritis, active vasculitis, or gout.

[15] Have a history of VTE (deep vein thrombosis/pulmonary embolism [DVT/PE]).

[16] Have a history or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that, in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data.

[17] Have a history of lymphoproliferative disease; have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years prior to randomization.

a. Patients with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study.

b. Patients with basal cell or squamous epithelial skin cancers that have been completely resected with no evidence of recurrence for at least 3 years may participate in the study.

[18] Have a current or recent (<4 weeks prior to randomization) clinically serious infection or any other active or recent infection that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

Note: a recent viral upper respiratory tract infection or uncomplicated urinary tract infection need not be considered clinically serious.

[19] Have symptomatic herpes simplex at the time of randomization.

[20] Have had symptomatic herpes zoster infection within 12 weeks prior to randomization.

[21] Have a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or postherpetic neuralgia).

[22] Have had household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB.

[23] Have active TB disease determined on the basis of a positive medical history, physical examination, or chest radiography (per local standard of care) or latent TB infection (LTBI) determined on the basis of:

a. A positive tuberculin skin test (TST, also called a purified protein derivative [PPD] or Mantoux test) result (skin induration ≥5 mm at 48 to 72 hours after the test date, or

b. A positive QuantiFERON®-TB Gold or T-Spot®.TB test

If the QuantiFERON-TB Gold is indeterminate or the T-Spot.TB is invalid or borderline, one retest is allowed. Patients with 2 indeterminate QuantiFERON-TB Gold or 2 invalid or borderline T-Spot.TB assays are excluded from the study.

The choice to perform either a TST or an interferon-gamma release assay (IGRA) test must be made by the investigator according to local licensing and standard of care. Interferon-gamma release assay test is a preferred method in patients with a history of Bacillus Calmette-Guerin (BCG) vaccination, given the rate of false positive TST results in this population.

Patients who have a documented history of completing an appropriate TB treatment regimen for active TB or LTBI and with no risk of re-exposure since their treatments were completed are eligible to participate in the study. These patients should not undergo TST or IGRA testing.

Patients with documentation of a "negative" IGRA or TST testing within 3 months before initial screening may not need to repeat TB testing at screening, based on judgment of the investigator. Source documentation must include the original laboratory report for IGRA or a record of size in millimeters of the induration response (for TST). A TST recorded as "negative" without documenting the size of induration in millimeters will not be acceptable and will require a retest.

[24] Have been exposed to a live vaccine within 12 weeks of randomization or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination).

Note: All patients who have not previously received the herpes zoster vaccine by screening will be encouraged (per local guidelines) to do so prior to randomization; vaccination with live herpes zoster vaccine must occur >4 weeks prior to randomization and start of investigational product. Patients will not be randomized if they were exposed to a live herpes zoster vaccination within 4 weeks of planned randomization. If a virus subunit, that is, Shingrix®, is used to vaccinate against herpes zoster, there is no requirement of a waiting period prior to randomization.

Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination.

[25] Are currently enrolled in or have discontinued within 4 weeks of screening from any other clinical trial involving an investigational product or nonapproved use of a drug or device or any other type of medical research judged not to be scientifically or medically compatible with this study.

[26] Have previously completed or been randomized and withdrawn from any other study investigating baricitinib.

Diagnostics Assessments

[27] Have evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies.

[28] Have a thyroid-stimulating hormone (TSH) outside the reference range for the population that in the opinion of the investigator poses an unacceptable risk for the patient's participation in the study or is suggestive of an additional or another hepatic disorder.

Patients who are receiving thyroxine as replacement therapy may participate in the study, provided stable therapy has been administered for ≥12 weeks and TSH is within the laboratory's reference range. Patients who have TSH marginally outside the laboratory's normal reference range and are receiving stable thyroxine replacement therapy may participate if the treating physician has documented that the thyroxine replacement therapy is adequate for the patient.

[29] Have any of the following specific abnormalities based on screening central lab test results:

- Hemoglobin <10 g/dL (100.0 g/L)
- ALT >3 x ULN
- AST >3 x ULN
- ALP >6 x ULN
- Total bilirubin level (TBL) >ULN
- Creatine phosphokinase (CPK) > ULN
- Serum albumin < LLN
- International Normalized Ratio of Prothrombin Time (INR) > ULN
- Total white blood cell (WBC) count <LLN
- Absolute neutrophil count [ANC] <LLN
- Lymphocyte count <LLN
- Platelet (thrombocyte) count < LLN

In the case of any of the aforementioned laboratory abnormalities, the tests may be repeated once during screening, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

[44] The second set of screening values for ALT, AST, or total bilirubin are above the upper limit of normal **and** > 20% higher than the first values obtained during screening

[45] The second screening value for ALP is > 20% higher than the first value obtained during screening

Prior/Concomitant Therapy

[30] Are receiving unstable treatment for pruritus within 6 weeks prior to Visit 3 (Week 0).

[31] Have been treated with systemic (oral or parenteral) corticosteroids within 6 weeks prior to Visit 3 (Week 0).

Note: the use of topical, ophthalmic, intranasal, and inhaled corticosteroids will be permitted.

[32] Have received biologic treatments for an immunologic disease within 4 weeks of screening such as etanercept, infliximab, certolizumab, adalimumab, golimumab, tocilizumab, abatacept, ustekinumab, ixekizumab, secukinumab, or anakinra.

[33] Have received a JAK inhibitor.

[34] Have received obeticholic acid.

[35] Have received fenofibrate or other fibrates for the treatment of PBC.

[36] Are currently treated with probenecid that cannot be discontinued for the duration of the study.

Other Exclusions

[37] Are largely or wholly incapacitated permitting little or no self-care, such as being bedridden.

[38] In the opinion of the investigator, are at an unacceptable risk for participating in the study.

[39] Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.

[40] Have a history of IV drug abuse, other illicit drug abuse, or chronic alcohol abuse within the 2 years prior to screening or are concurrently using, or expected to use during the study, illicit drugs (including marijuana). Alcohol abuse is defined as consumption of more than 210 mL of alcohol per week (i.e., the equivalent of 14 four-ounce (125 mL) glasses of wine or 14 twelve-ounce (330 mL) cans/bottles of beer), or other substance abuse within 1 year prior to Visit 3 (Week 0).

[41] Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.

[42] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[43] Are Lilly or Incyte employees.

6.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study, and for 30 days following the last dose of investigational product.

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 1 time. The interval to rescreening should be at least 2 weeks. The individual must sign a new ICF and will be assigned a new identification number at the time of the second screening.

7. Treatments

7.1. Treatments Administered

This study involves a comparison between baricitinib administered once daily and placebo. Patients able to tolerate UDCA will continue to take a stable dose of UDCA orally as background therapy during the study. Table JAIV.3 shows the treatment regimens.

Table JAIV.3. Treatment Regimens

Cohort A

Regimen	Dose Week 1 through 12
Baricitinib	2 mg Baricitinib (2 x 1-mg tablets)
Placebo	PTM 2 mg (2 x PTM 1-mg tablets)

Cohort B

Regimen	Dose Week 1 through 12
Baricitinib	4-mg Baricitinib (1 x 4-mg tablet)
Placebo	PTM 4 mg (1 x PTM 4-mg tablet)

Abbreviation: PTM = placebo to match.

The investigator or his or her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the patient
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labelling

The sponsor (or its designee) will provide the following investigational product:

- tablets containing 1-mg of baricitinib
- tablets containing 4-mg of baricitinib
- tablets containing placebo to match 1-mg of baricitinib
- tablets containing placebo to match 4-mg of baricitinib.

Clinical trial materials will be labeled according to the country's regulatory requirements. Patients will be instructed to take the tablet(s) each day as assigned.

7.2. Method of Treatment Assignment

[redacted]

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign double-blind investigational product to each patient. Site personnel will confirm that they have located the correct package by entering a confirmation number found on the package into the IWRS.

7.2.1. Selection and Timing of Doses

Investigational product will be provided to patients following randomization at Visit 3 (Week 0).

The tablet(s) should be taken orally each day, without regard to food and if possible, at approximately the same time every day. Special timing considerations of administration of investigational product relative to PK sample collection at study visits are described in Section 9.5.

For patients taking concomitant cholestyramine it is recommended that patients take baricitinib at least 1 hour before or 4 to 6 hours after cholestyramine.

7.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. All study assessments will be performed by study personnel who are blinded to the patient's treatment group. Except in clinical circumstances where unblinding is required, the patients, investigators, Lilly study team, and any personnel interacting directly with patients or investigative sites will remain blinded to baricitinib and placebo assignment. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the patient.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. Patient's safety must always be the first consideration in making such a determination. Where feasible and when the timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a subject's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the IWRS. If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly designated medical monitor for the patient to continue in the study.

7.4. Preparation/Handling/Storage/Accountability

All investigational product (used and partially used) will be returned to the sponsor or destroyed at the site level with the sponsor's written approval. 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.

Follow storage and handling instructions on the investigational product packaging.

7.5. Treatment Compliance

Patient compliance with study medication will be assessed at Visit 4 through Visit 7 and at Early Termination during the treatment period by counting returned tablets and direct questioning. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

The patient will be considered significantly noncompliant if he or she misses more than 20% of study medication during the study, unless the patient's investigational product was withheld by the investigator for safety reasons. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

7.6. Concomitant Therapy

Patients will maintain their usual medication regimen for PBC and for any other concomitant diseases throughout the study unless specifically excluded in the protocol (Section 6.2, Exclusion Criteria). Patients taking these medications should be on chronic stable doses at the time of randomization, as specified by the Inclusion Criteria (Section 6.1, Inclusion Criteria).

All concomitant medication, whether prescription or over the counter, used at baseline and/or during the course of the study must be recorded on the relevant eCRF. Any changes to the patient's medication must be discussed with the investigator. Patients should be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study.

7.6.1. Permitted Medications and Procedures

[redacted]

7.6.2. Prohibited Medications and Procedures

[redacted]

7.7. Treatment after the End of the Study

7.7.1. Treatment after Study Completion

Baricitinib will not be made available to patients after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Interruption of Investigational Product

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. It is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting therapy for reasons other than those defined in Table JAIV.4. Unless otherwise specified, retest timing and frequency is at the investigator's discretion.

Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value not specifically covered in Table JAIV.4 may be restarted at the discretion of the investigator. Investigational product must be held in the following situations and may only be resumed as noted in the table.

Table JAIV.4. Criteria for Interruption of Investigational Product

Hold Investigational Product if the Following Abnormalities Occur:	Investigational Product May be Resumed When:
WBC count <2000 cells/µL (<2.00 x 10^3/µL or <2.00 GI/L)	WBC count ≥2500 cells/µL (≥2.50 x 10^3/µL or ≥2.50 GI/L)
ANC <1000 cells/µL (<1.00 x 10^3/µL or <1.00 GI/L)	ANC ≥1200 cells/µL (≥1.2 x 10^3/µL or ≥1.2 GI/L)
Lymphocyte count <500 cells/µL (<0.50 x 10^3/µL or <0.50 GI/L)	Lymphocyte count ≥750 cells/µL (≥0.75 x 10^3/µL or ≥0.75 GI/L)
Platelet count <75,000/µL (<75 x 10^3/µL or <75 GI/L)	Platelet count ≥100,000/µL (≥100 x 10^3/µL or ≥100 GI/L)
ALT or AST>3X ULN for patients with normal ALT or AST at baseline	ALT and AST return to ≤3X ULN and investigational product is not considered the cause of enzyme elevation.
ALT or AST > 3X baseline value for patients with ALT or AST >ULN at baseline	ALT and AST return to ≤3X baseline value for patients with increased baseline and investigational product is not considered the cause of enzyme elevation.
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥9 g/dL (≥90.0 g/L)
eGFR <50 mL/min/1.73 m^2	eGFR ≥60 mL/min/1.73 m^2
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being withheld[a]	Resolution of infection that, in the opinion of the investigator, merits the IP being restarted
Clinical features of VTE (deep vein thrombosis or pulmonary embolism) are present	After diagnosis of VTE has been excluded. If diagnosis of VTE is confirmed, study treatment must be permanently discontinued

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; IP = investigational product; ULN = upper limit of normal; VTE = venous thromboembolism; WBC = white blood cell.

[a] Permanent discontinuation of IP should be considered for patients who develop a serious infection that, in the opinion of the investigator, would pose an unacceptable risk if IP were resumed.

8.1.2. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Subject Decision**
  - the patient requests to discontinue investigational product.
- **Investigator Decision**
  - the investigator decides that the patient should be discontinued from investigational product
- **Discontinuation due to a hepatic event or liver test abnormality:** Patients who are discontinued from investigational product because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF. Details on continued hepatic monitoring are provided in Section 9.4.7.

  If multiple values are obtained during screening, the highest value prior to receipt of investigational product will be used as baseline. Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:

  a. For patients with **baseline normal ALT and/or AST**, the following will result in discontinuation:

single laboratory test	ALT or AST >8 x ULN
single laboratory test	ALT or AST >3 x ULN and TBL >2 x ULN or International Normalized Ratio (INR) >1.5
single laboratory test	ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
confirmed laboratory test (2 tests)	ALT or AST >2 x ULN and no other known cause.
during temporary interruption of IP	ALT or AST >5 x ULN for more than 2 weeks after temporary interruption of investigational product

  b. For patients with **baseline elevated ALT and/or AST**, the following will result in discontinuation:

confirmed laboratory test (2 tests)	ALT >5 x baseline, or >400 U/L (whichever occurs first)
confirmed laboratory test (2 tests)	ALT >3 x baseline and TBL >2 x ULN or INR >1.5
confirmed laboratory test (2 tests)	ALT >3 x baseline with appearance of severe fatigue, nausea, vomiting, right upper-quadrant abdominal pain, fever, rash, and/or eosinophilia (>5%)
confirmed laboratory test (2 tests)	ALT or AST >2 x ULN and no other known cause
confirmed laboratory test (2 tests)	TBL >1.5 x baseline upon retesting and no other known cause
during temporary interruption of IP	ALT >4 x baseline or >300 U/L (whichever occurs first) for more than 2 weeks after temporary interruption of investigational product

c. For **all patients**, the following will result in discontinuation:

confirmed laboratory test (2 tests)	ALP >3 x baseline and >6 x ULN
confirmed laboratory test (2 tests)	ALP >2.5 x baseline and TBL >2 x ULN or INR >1.5
confirmed laboratory test (2 tests)	ALP >2.5 x baseline with appearance of severe fatigue, vomiting, right upper-quadrant pain, fever, rash, and/or eosinophilia (>5%)

- **Discontinuation due to other laboratory abnormalities:**
  - White blood cell count <1000 cells/µL (1.00 x 10^3/µL or 1.00 GI/L)
  - Absolute neutrophil count <500 cells/µL (0.50 x 10^3/µL or 0.50 GI/L)
  - Lymphocyte count <200 cells/µL (0.20 x 10^3/µL or 0.20 GI/L)
  - Hemoglobin <6.5 g/dL (<65.0 g/L)
  - Creatine phosphokinase >5x ULN
  - eGFR ≤40mL/min/1.73m^2.

Temporary interruption rules (Section 8.1.1) must be followed where applicable. For laboratory values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the investigator, the laboratory abnormality is due to intercurrent illness or another identified factor, laboratory tests may be repeated. The investigator may be able to restart investigational product after consultation with the Lilly designated medical monitor, only when the laboratory value meets resumption thresholds (Table JAIV.4) following the resolution of the intercurrent illness or other identified factor.

- **Discontinuation due to other circumstances:**
  - pregnancy
  - malignancy (except for successfully treated basal cell or squamous epithelial skin cancers)
  - occurrence of a VTE (DVT/PE)
  - serious infection that, in the opinion of the investigator, merits the investigational product being discontinued
  - if the patient, for any reason, requires treatment with another therapeutic agent that may be effective for treatment of PBC that is listed in the exclusion criteria (Section 6.2) or is noncompliant to the concomitant therapy requirements (Section 7.6) during the study. Discontinuation from the investigational product must occur prior to introduction of the new agent.

Throughout the study, investigators should continue to assess benefit/risk for patients to remain in the trial and should consider discontinuing patients if sufficient clinical benefit is not observed with protocol allowed concomitant treatments.

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor designated medical monitor agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor designated medical monitor to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study 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 patient should be discontinued from the study
    - if the patient, 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 patient requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-up

A patient 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 patients 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, with the study procedures and their timing (including tolerance limits for timing).

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

Unless otherwise stated in the 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.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy assessment in Study JAIV will be change in ALP at Week 12.

9.1.2. Secondary and Exploratory Efficacy Assessments

Secondary efficacy assessments will include the proportion of patients with ALP <1.67 x ULN (and at least 15% decrease from baseline), Itch NRS, fatigue NRS. Exploratory efficacy assessments will include Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), PBC-40, and total bilirubin.

The Itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching is indicated by selecting the number that describes the worst level of itching in the past 7 days.

The Fatigue NRS is a single-item, patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine." Overall severity of a patient's fatigue is indicated by selecting the number that describes the worst level of fatigue during the past 7 days.

The FACIT-F measures an individual's self-reported level of fatigue during their usual daily activities over the past 7 days. The scale is composed of 13 items measured on a 4-point Likert scale (4 = very much to 0 = not at all). The total score ranges from 0 to 52, and higher scores representing less fatigue. A score of less than 30 indicates severe fatigue (Webster et al. 2003).

The PBC-40 is a disease-specific, 40-item, patient-reported survey containing 6 domains: overall symptoms, itch, fatigue, cognition, social, and emotional. Response options for overall symptoms, itch, fatigue, and cognition are on a 5-point scale: "Never," "Rarely," "Sometimes," "Most of the time," and "Always." Response options are also on a 5-point scale for social and emotional: "Not at all," "A little," "Somewhat," "Quite a bit," and "Very much." Items are scored from 1 to 5 and the individual item scores are summed to give a total domain score where high scores represent high impact of PBC on quality of life (Jacoby et al. 2005).

The Physician's Global Assessment of Disease Activity is the physician's assessment of the patient's overall disease activity due to PBC, as compared with all possible patients with PBC. The Physician's Global Assessment of Disease Activity is scored using a 100-mm visual analog scale (VAS), where 0 mm (measured from the left starting point of the line) indicates no disease activity and 100 mm (measured from the left starting point of the line) indicates the most severe disease activity possible for all patients with PBC. The Physician's Global Assessment of Disease Activity score is indicated by making a vertical tick mark on the line between 0 and 100 mm. There are benchmarks of 0 (0 mm), 1 (33 mm), 2 (67 mm), and 3 (100 mm) on the line corresponding to no, mild, moderate, and severe PBC disease activity, respectively.

9.1.3. Appropriateness of Assessments

Itch and fatigue are 2 prevalent and bothersome symptoms to PBC patients. The PBC-40 is a disease-specific quality of life measure developed for PBC.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients 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 patient.

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

Investigators must document their review of each laboratory safety report.

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 patient to discontinue the investigational product before completing the study. The patient 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.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record the following via the eCRF for each AE: time of onset, time of termination, severity and their assessment of the potential relatedness of each AE to protocol procedure or investigational product.

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

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

The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- 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
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
- All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE-reporting requirements and timelines (Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a paper SAE form. If alerts are issued via telephone, they are to be immediately followed with official notification on study specific SAE forms. The SAE form should be completed by the investigator, and submitted via fax to the Sponsor's global patient safety department. This form includes a fax cover page that is prepopulated with the appropriate fax number. The 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the eCRF.

Pregnancy (during 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.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition 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 or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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 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 identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

Adverse events of special interest will include the following:

- Infections (including TB, herpes zoster, or opportunistic infections)
- Malignancies
- Hepatic events (Section 9.4.7)
- Major adverse cardiovascular events (MACE) (Section 9.4.8)
- Arterial thrombotic events
- Thrombotic events (DVT and PE) (Section 9.4.8.1).

Sites will provide details on these AEs as instructed on the eCRF and may be asked for additional description by Lilly.

9.2.3. Complaint Handling

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

Patients will 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

Refer to the IB.

9.4. Safety

9.4.1. Electrocardiograms

A single 12-lead standard ECG will be obtained locally at Visit 1 and read by a qualified physician (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2). Subjects should be seated and relaxed with both feet on the floor for at least 5 minutes prior to taking measurements.

Three replicate blood pressure readings should be made at each time point at approximately 30- to 60-second intervals. A single-pulse measurement should be taken simultaneously with at least one of the blood pressure readings. Blood pressure and pulse measurements should be made using either automated or manual equipment. If measurements are machine averaged, the average blood pressure reading should be recorded on the CRF. If measurements are manual or the machine does not provide an average reading, then each individual reading should be recorded on the CRF. Measurements should be made before any scheduled blood draws.

Additional measurements of vital signs may be performed at the discretion of the investigator.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.3. Physical Examination

For each patient, physical examinations will be conducted according to the Schedule of Activities (Section 2). One complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1 (Screening). All remaining physical examinations throughout the study should include a symptom-directed physical examination. A complete physical examination may be repeated at the investigator's discretion at any time a patient presents with physical complaints.

9.4.4. Laboratory Tests

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

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.5. Chest x-Ray and Tuberculosis Testing

A posterior anterior view chest x ray will be obtained locally at screening (Visit 1), unless results from a chest x-ray obtained within 6 months prior to the study are available. The chest x-ray will be reviewed by the investigator or his or her designee to exclude patients with active TB infection. In addition, patients will be tested at screening (Visit 1) for evidence of active or latent TB as described in the exclusion criteria, Section 6.2.

9.4.6. Quick Inventory of Depressive Symptomatology Self-Rated–16

The Quick Inventory of Depressive Symptomatology Self-Rated–16 ($QIDS\text{-}SR_{16}$) is a 16-item, self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (APA 1994). Patients are asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27, with higher scores denoting greater symptom severity. The domains assessed by the instrument include sad mood, concentration, self-criticism, suicidal ideation, interest, energy/fatigue, sleep disturbance (initial, middle, and late insomnia or hypersomnia), decrease/increase in appetite/weight, and psychomotor agitation/retardation. Additional information and the $QIDS\text{-}SR_{16}$ questions may be found on the University of Pittsburgh Epidemiology Data Center web site (Inventory of Depressive Symptomatology/Quick Inventory of Depressive Symptomatology [WWW]) (Rush et al. 2003; Trivedi et al. 2004).

9.4.7. Hepatic Safety Monitoring

If a study patient with ALT and AST within the normal range at baseline experiences elevated transaminases greater than 2x ULN, then a repeat measurement should be performed within 48 - 72 hours. If elevations greater than 2x ULN persist, then subjects should be evaluated for other causes of transaminase elevation and with additional tests of hepatic status. Close observation for suspected DILI will be conducted. If no other cause is found, then investigational product should be discontinued (see guidelines in Section 8.1).

If a study patient with ALT and AST above the normal range at baseline develops further elevations of ALT or AST >2x the baseline value or a bilirubin >2x ULN during the study, then repeat testing should be performed within 48 - 72 hours. If there are persistent elevations (ALT or AST >2x baseline or bilirubin >2x ULN), then close observation for suspected DILI will be conducted. If no other cause is found, then discontinuation of investigational product should be considered (see guidelines in Section 8.1).

The decision to discontinue or temporarily interrupt investigational product should be considered based on factors that include how much higher than baseline ALT and AST were relative to the upper limit of normal (ULN) and how much the on-study ALT and AST levels have increased relative to baseline, in addition to whether there is concomitant elevation of bilirubin or INR (see guidelines in Section 8.1).

If the patient lives in a remote area, repeat laboratory testing and close monitoring can be performed locally and the results should be promptly communicated to the investigator.

Close Observation for Suspected DILI

- Repeat liver enzyme and serum bilirubin tests two or three times weekly. Frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtain a more detailed history of symptoms and prior or concurrent diseases.

- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).

Follow up testing may include ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine phosphokinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection
Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

- Elevation of serum ALT to ≥5 x ULN for patients with normal/near-normal baseline ALT or to ≥5 x baseline value for patients with baseline ALT >1.5 x ULN on 2 or more consecutive blood tests
- Elevated serum TBL to ≥2 x ULN
- Elevation of serum ALP to ≥2 x baseline value on 2 or more consecutive blood tests
- Patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE.

9.4.8. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

The Lilly designated medical monitor will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures. The Lilly designated medical monitor will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist and periodically review trends in safety data and laboratory analytes. Any concerning trends in frequency or severity noted by an investigator and/or Lilly (or designee) may require further evaluation.

All deaths and SAE reports will be reviewed in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to ensure completeness and accuracy, but will not be unblinded to Lilly during the clinical study. If a death or a clinical AE is deemed serious, unexpected, and possibly related to investigational product, only Lilly Global Patient Safety will be unblinded for regulatory reporting and safety monitoring purposes. These measures will

preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

Investigators will monitor vital signs and carefully review findings that may be associated with cardiovascular events. Adverse event reports and vital signs will be collected at each study visit.

The cardiovascular monitoring plan includes the following:

- Regular monitoring of lipid levels
- Potential MACE (cardiovascular death, myocardial infarction, and stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, and coronary interventions), and noncardiovascular deaths will be identified by the investigative site or through medical review and will be sent to a blinded Clinical Event Committee for adjudication at regular intervals.

9.4.8.1. Venous Thromboembolic Event Assessment

If a patient develops the signs and symptoms of a DVT or PE, appropriate local laboratory tests and imaging should be performed, as necessary, for diagnosis of the event. For confirmed cases, additional laboratory testing is recommended as outlined in Appendix 5. All suspected DVT or PE will be independently adjudicated by a blinded Clinical Event Committee.

9.4.8.2. Data Monitoring Committee

A DMC will oversee the conduct of this study. The DMC will consist of members external to Lilly. This DMC will be guided by the DMC charter. At a minimum the DMC will include the following who have previous DMC experience:

- a specialist with expertise in hepatology and
- a statistician.

The DMC will review and evaluate data from the 12 week treatment period from patients in Cohort A.

In addition, the DMC may be convened if 2 or more patients permanently discontinue due to safety. The DMC chair will determine if the full DMC needs to convene.

The DMC chair will have access to all SAEs as reported to regulatory authorities and may convene a meeting at any time.

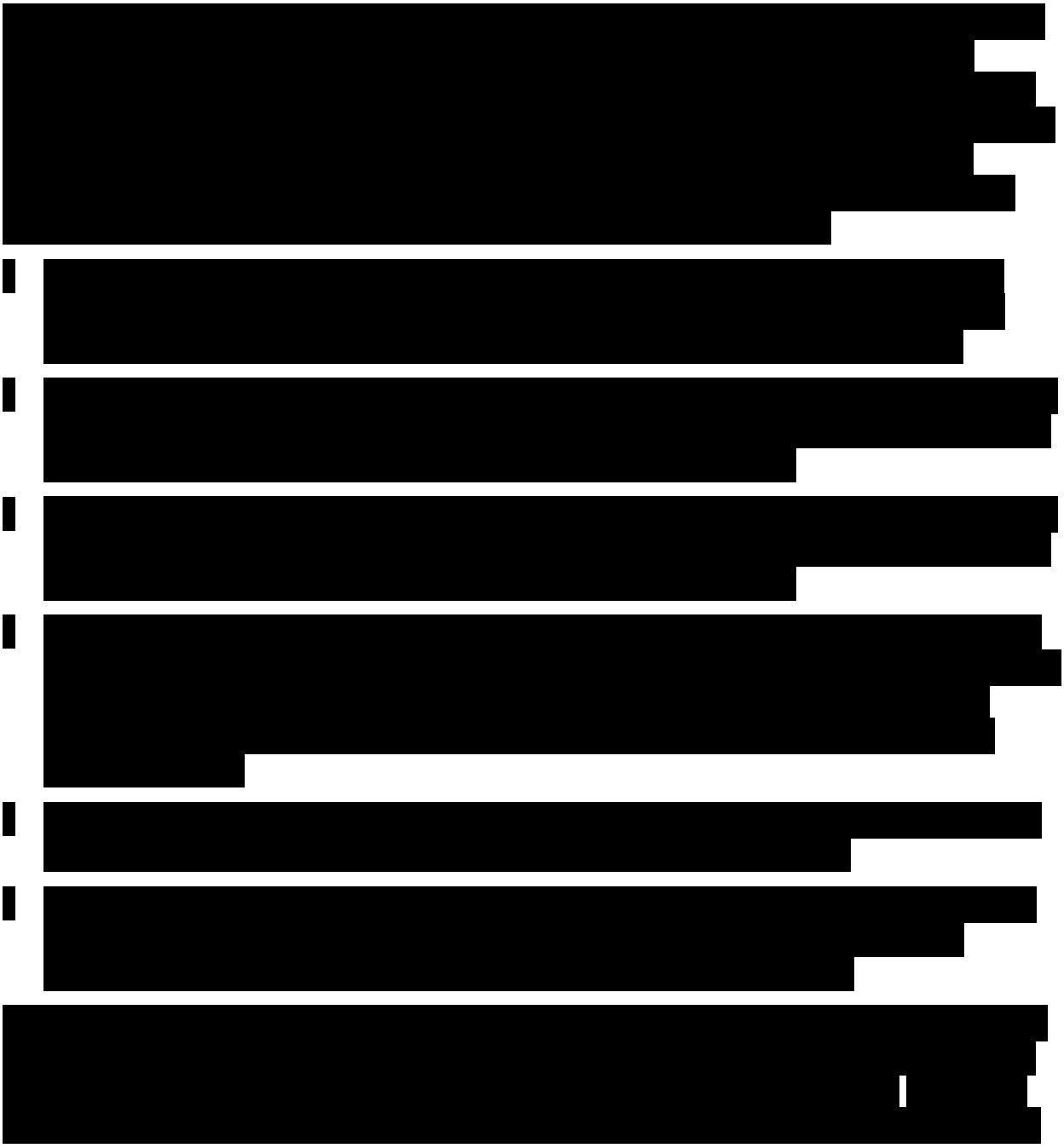
Access to the unblinded interim data will be limited to the statisticians who conduct the interim analyses and the DMC. The statisticians conducting the interim analyses will be independent from the study team. The study team will not have access to the unblinded data.

Data that the DMC will review include, but are not limited to, reasons for study discontinuation, AEs including SAEs, clinical laboratory data and vital signs. The DMC may recommend continuation of the study as designed, temporary suspension of enrollment, or discontinuation of a particular dose regimen or discontinuation of the entire study. The DMC may request to review efficacy data to investigate the benefit/risk relationship in the context of safety

observations for ongoing patients in the study. Details of the DMC and interim safety analyses will be documented in a DMC charter.

In addition to the DMC members, a limited number of prespecified individuals may gain access to the unblinded PK, safety, and efficacy data (as specified in the unblinding plan) prior to the final database lock to initiate the exploration and/or final population of the PK/PD model development processes. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the database is locked.

9.5. Pharmacokinetics



[redacted]

9.6. Pharmacodynamics

[redacted]

9.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target

[redacted]

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 20 patients will be randomized to the baricitinib 2-mg and placebo treatment groups for Cohort A. Twelve patients will be randomly assigned to the 2-mg treatment group and 8 patients to the placebo treatment group. This sample size is appropriate to provide sufficient preliminary safety and tolerability information for baricitinib 2-mg dose in patients with PBC prior to studying 4-mg baricitinib.

For Cohort B, 32 patients will be randomized to the baricitinib 4-mg and placebo treatment groups. Twenty patients will be randomized to the baricitinib 4-mg treatment group and 12 patients to placebo.

Overall, 20 patients per group will be assigned to the baricitinib 4-mg and placebo dose groups. Based on this sample size, this study will have approximately 81% power to detect a difference in ALP change from baseline between baricitinib 4-mg and placebo at Week 12 assuming that the true difference is 65 U/L. The sample size was determined based on a 2-sample t-test with 2-sided alpha level of 0.1 and a standard deviation of 80 U/L for the change from baseline in ALP. The sample size calculation was performed using nQuery® Advisor 7.0 software.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All patients who sign informed consent
Randomized	All patients who are randomized at Week 0.
Modified Intent-to-Treat (mITT)	The mITT population is defined as all randomized patients who take at least one dose of study treatment. Patients will be included if they do not receive the correct treatment, or otherwise do not follow the protocol. Subjects will be analyzed according to the treatment to which they were randomized.
Safety	The safety population is defined as all randomized patients who receive at least 1 dose of study treatment and who did not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit with no safety post-baseline data. Patients will be analyzed according to the treatment to which they were randomized.

Additional subpopulations may be identified. Full details will be provided in the study statistical analysis plan (SAP).

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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

Unless otherwise specified, the efficacy, health outcomes, and safety analyses will be conducted on the modified intent-to-treat (mITT) population.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.1, unless otherwise stated. No multiplicity adjustment will be used in this study.

Baseline will be defined as the last available value before the first dose of investigational product for both efficacy and safety analyses. In most cases, this will be the measure recorded at Week 0 (Visit 3). Change from baseline will be calculated as the visit value of interest minus the baseline value.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1.1. Analysis Methods

The primary analysis for all continuous efficacy and health outcomes variables will use a mixed-effects models for repeated measures (MMRM) with treatment, [redacted] An unstructured covariance matrix will be used to model the within-patient variance-covariance errors. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III sums of squares for the least-squares (LS) means will be used for all the statistical comparisons; the 90% confidence interval (CI) will also be reported. The LS mean difference, standard error, p-value, and CIs will also be reported. Treatment group comparisons at specific study visits will be tested using the t-test obtained from the MMRM results. Additional details of the MMRM method are described in Section 10.3.1.2.

The primary analysis for all categorical efficacy and health outcomes variables will use a logistic regression analysis with treatment, cohort, [redacted] The p-value and 90% (unless otherwise specified) CI for the odds ratio from the logistic regression model will be used for primary statistical inference. When logistic regression sample size requirements are not met, (<5 responders in any category for any factor), the p-value from the Cochran-Mantel-Haenszel (CMH) test with [redacted] as factors will be used instead of the odds ratio and CI. Missing data imputation is described in Section 10.3.1.2.

10.3.1.2. Missing Data Imputation

As with any clinical study, patient dropouts and consequently missing data are expected. While every effort will be made to reduce missing data, the missing data imputation methods described below will be used to provide a conservative approach for assessing efficacy endpoints when patients have missing data.

The following imputation rules will be used:

- Last-observed-value-carried forward (LOCF): For analysis of categorical efficacy and health outcomes variables, LOCF will be used to assess a patient's response when data are missing at that endpoint. Randomized subjects without at least 1 postbaseline observation will be defined as non-responders for this analysis.
- Mixed-model repeated measures (MMRM): For continuous variables, the primary analysis will be a MMRM analysis with a missing-at-random assumption for handling missing data. This analysis takes into account both missingness of data and the correlation of the repeated measurements. No additional imputation methods will be applied to the MMRM analysis. Any observed data after permanent discontinuation of investigational product will be excluded from the MMRM analysis.

Full details of these analyses including missing data imputation methods and covariates will be provided in the SAP. Additional sensitivity analyses will be described in the SAP.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

All patients who discontinue from the study or the study treatment will be identified, along with their reason for discontinuation. Reasons for discontinuation from the study will be summarized by treatment group.

A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Descriptive statistics including the number of patients, mean, standard deviation, median, minimum, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures. No formal statistical comparisons will be made among treatment groups unless otherwise stated.

10.3.2.3. Concomitant Therapy

Concomitant medications will be descriptively summarized by treatment group in terms of frequencies and percentages using the safety population. The medications will be coded accordingly.

10.3.2.4. Treatment Compliance

Treatment compliance with the randomly assigned study medication will be evaluated at every clinic visit through the counts of returned investigational product tablets. A patient will be considered significantly noncompliant if he or she misses more than 20% (i.e., compliance <80%) of the prescribed doses during the study, unless the patient's investigational product is withheld by the investigator for safety reasons. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy measure is the change from baseline in ALP at Week 12. An MMRM (as described in Section 10.3.1.1) will be used to test the treatment difference between baricitinib and placebo.

10.3.3.2. Secondary Analyses

Secondary efficacy and health outcomes variables will be assessed using the methods stated in Sections 10.3.1.1 and 10.3.1.2.

10.3.4. Safety Analyses

All safety data will be descriptively summarized by treatment groups and analyzed using the safety population.

Treatment-emergent adverse event (TEAEs) are defined as AEs that first occurred or worsened in severity after the first dose of study treatment. The number of TEAEs as well as the number and percentage of patients who experienced at least 1 TEAE will be summarized using the Medical Dictionary for Regulatory Activities for each system organ class (or a body system) and each preferred term by treatment group. SAEs and AEs that lead to discontinuation of investigational product will also be summarized by treatment group. Fisher's exact test will be used to perform comparisons between the baricitinib and placebo groups.

All clinical laboratory results will be descriptively summarized by treatment group. Individual results that are outside of normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables obtained at the baseline to postbaseline visits will be summarized as changes from baseline by treatment group and analyzed using analysis of covariance (ANCOVA) with treatment and baseline value in the model. Categorical variables, including the incidence of abnormal values and incidence of AEs of special interest, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures.

Observed values and changes from baseline (predose or screening if missing) for vital signs and physical characteristics will be descriptively summarized by treatment group and time point. Change from baseline to postbaseline in vital signs and body weight will be analyzed using ANCOVA with treatment and baseline value in the model.

The incidence and average duration of investigational product interruptions will be summarized and compared descriptively among treatment groups. Further analyses may be performed and will be planned in the SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

All plasma baricitinib concentration-time data will be pooled and evaluated using population PK methods. A covariate screen of patient and study-specific factors will be included in the analyses based on factors investigated in previous and (if any) ongoing PK analyses, and on their relevance to the target population. Exploratory and/or model-based analyses, examining the

relationships between baricitinib exposure and efficacy and response endpoints will be conducted. Other analyses of efficacy and safety outcome measures may also be assessed as scientifically appropriate and warranted by available data. Details about the analyses to be conducted will be contained in the PK/PD analysis plan.

10.3.6. Other Analyses

Not Applicable.

10.3.6.1. Subgroup Analyses

Not Applicable.

10.3.7. Interim Analyses

A limited number of preidentified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the final database lock, in order to initiate the final population PK/PD model development processes for final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded; this applies to Cohort A and Cohort B.

Data from patients in Cohort A will be summarized after all the patients have completed the study. These data will be available to Lilly and the DMC. No additional interim analyses are planned.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AASLD	American Association for the Study of Liver Disease
AD	atopic dermatitis
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 adverse event 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
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
blinding	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CANDLE	Chronic Atypical Neutrophilic Dermatosis With Lipodystrophy and Elevated Temperatures
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK-18	cytokeratin 18
CMH	Cochran-Mantel-Haenszel
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 study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRP	C-reactive protein
DN	diabetic nephropathy
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
EASL	European Association for Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FGF	fibroblast growth factor
GCP	good clinical practice
HBcAb	hepatitis B core antibody

HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assay
IL	interleukin
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	International Normalized Ratio
interim analysis	An interim analysis is an analysis of clinical study 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.
IRB/ERB	institutional review board /ethics review board
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
JAK	Janus kinase
LOCF	last-observed-value-carried forward
LS mean	least squares mean
MELD	Model for End Stage Liver Disease
mITT	modified intent-to-treat
MMRM	mixed-effects models for repeated measures
NRI	nonresponder imputation
NRS	Numeric Rating Scale
PBC	primary biliary cholangitis
PBC-40	Quality of Life for Primary Biliary Cirrhosis
PE	pulmonary embolism
PK/PD	pharmacokinetics/pharmacodynamics
PPD	purified protein derivative
PTM	placebo to match
QD	once daily
QIDS-SR16	Quick Inventory of Depressive Symptomatology
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event

SAP	statistical analysis plan
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 study.
SoC	Standard of care
SAVI	stimulator of interferon genes-associated vasculopathy with onset in infancy
SLE	systemic lupus erythematosus
STAT	signal transducers and activators of transcription
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An 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.
TNF	Tumor necrosis factor
TSH	thyroid-stimulating hormone
TST	tuberculin skin test
TYK	tyrosine kinase
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
VAS	visual analog scale
VTE	venous thromboembolic events
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase (ALP)
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
Mean Platelet Volume	TSH
INR (prothrombin time)[c]	Glucose[d]
ESR	Albumin
	Creatine phosphokinase (CPK)
Urinalysis[a]	
Specific gravity	**Markers**
pH	IgM, IgG, IgA
Protein	CRP
Glucose	FGF 19
Ketones	CK-18 M30
Blood	CK-18 M65
Urine leukocyte esterase	
	Cytokine Panel
Hepatitis Serology	IL-1 beta
HBsAg[c], HBcAb[c], HBsAb[c]	IL-2
HCV antibody[c]	IL-4
HIV serology[c]	IL-6
ANA[c] and ASMA[c]	IL-8
	IL-10
Lipid Profile[d]	IL-12 (p70)
Total Cholesterol	IL-13
High-density lipoprotein	TNF alpha
Low-density lipoprotein	IFN gamma
Triglycerides	
	ELF
Pregnancy Test (females only)[e]	Hyaluronic acid (HA)
	Procollagen type III amino N-terminal peptide (P3NP)
Alkaline Phosphatase Isoenzymes[f]	Tissue inhibitor of metalloproteinase 1 (TIMP-1)

Abbreviations: ANA = antinuclear antibody; ASMA = antismooth muscle antibody; CK= cytokeratin; CRP = C reactive protein; ELF = enhanced liver fibrosis; ESR = erythrocyte sedimentation rate; FGF = fibroblast growth factor; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody test; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; HCV antibody = hepatitis C virus antibody; HIV = human immunodeficiency virus; IFN = interferon; Ig = Immunoglobulin; IL = interleukin; INR = International Normalized Ratio.; RBC = red blood cells; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; WBC = white blood cells.

[a] All laboratories will be assayed/calculated by a Lilly-designated laboratory unless otherwise noted.

[b] Refer to the Schedule of Activities: Abbreviated chemistry includes total bilirubin, direct bilirubin, ALT, BUN, and serum creatinine.

[c] Only at screening visit.

[d] Fasting laboratory values for glucose and lipids will be required at baseline and Week 12. Patients should not eat or drink anything except water for 12 hours prior to test. Lipid panel consists of direct HDL-C, triglycerides, cholesterol, and LDL-C (calculation from Friedewald et al. 1972).

[e] For all women of child-bearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will also be performed at each subsequent study visit per the Schedule of Activities.

[f] Assayed by Lilly-designated laboratory.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient 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 investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Investigator(s) will be responsible for subject recruitment through local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonization (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, 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 protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- 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
- applicable ICH GCP Guidelines
- applicable laws and regulations

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

Appendix 3.1.5. Investigator Information

Physicians with a specialty in gastroenterology or hepatology will participate as investigators in this clinical trial.

Appendix 3.1.6. 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.

Appendix 3.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of their knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. 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
- sponsor start-up 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 verify data reported to detect potential errors

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, 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 original source documents.

Appendix 3.2.1. Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (questionnaires, scales, rating scales etc.) will be collected by the patient and investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture system will be stored at a third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. 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.

Appendix 3.3.2. 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 3.4. Publication Policy

The publication policy for Study F1K-MC-JAIV is described in Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, designated medical monitor.

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = International Normalized Ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Monitoring Tests for Confirmed VTE

Selected tests may be obtained in the event of a confirmed venous thromboembolic event (VTE) and may be required in follow-up with patients in consultation with Eli Lilly and Company, its designee, or the designated medical monitor. The choice and optimal timing of these tests will be directed by the patient's management and may require ongoing follow-up after study discontinuation.

Protein C Functional
Protein S Clottable
Antithrombin III
APC Resistance
PT
APTT
Fibrinogen
Cardiolipin Antibodies
PT Gene
Factor VIII C Assay
Hexagonal Phase Phospholipid Neutralization
C-Reactive Protein
PTT Incubated Mixing
Dilute Russell Viper Venom
Platelet Neutralization
Factor V Leiden
MTHFR
Thrombin Time
Reptilase
Fibrinogen Antigen
Protein C Immunologic
Protein S Immunologic
Heparin fXa Inhibition

Abbreviations: APC = activated protein C; APTT = activated partial thromboplastin time; MTHFR = methylene tetrahydrofolate reductase; PT = prothrombin time; PTT = partial thromboplastin time.

Appendix 6. Protocol Amendment History

Overview

Protocol I4V-MC-JAIV, A Randomized, Double Blind, Placebo Controlled, Proof of Concept Study Evaluating the Efficacy and Safety of Baricitinib (LY3009104) in Patients with Primary Biliary Cholangitis Who Have an Inadequate Response or Are Intolerant to UDCA, has been amended. The new protocol is indicated by amendment (b) 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 described in the following table:

Section # and Name	Description of Change	Brief Rationale
Section 6. Study Population	Added a note on number system used for inclusion and exclusion criteria	To avoid confusion for the reader who may think there has been a mistake with numbering.
Section 6.2 Exclusion Criteria Exclusion Criterion 8c	Added clarifying language that cirrhosis should include complications	Without this language the reader could interpret this as cirrhosis without complications was an exclusion criterion – it is not.
Section 7.2 Method of Treatment Assignment	Changed method from stratification to dynamic minimization	The method was changed to increase the likelihood of balanced randomization.
Section 8.1.2 Permanent Discontinuation from Study Treatment	Added the discontinuation criterion of eGFR $\leq$40mL/min/1.73m^2	The study team intended for this to be added in amendment (a); however, it was inadvertently not included.
Throughout	Minor editorial changes	Changes made for clarity.

The following section includes content changes to Protocol JAIV. The following section does not include minor edits to grammar, capitalization, and formatting.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

6. Study Population

Note: The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion which is maintained in the case of a protocol amendment. Specifically, if a criterion removed as a result of an amendment, the number and the criterion will be removed and will not be reused. If an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of where it is located in the list.

6.2. Exclusion Criteria

Medical Conditions

[8] Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:

c. Cirrhosis with complication, i.e., decompensated cirrhosis, including history or presence of one or more of the following:

- spontaneous bacterial peritonitis
- hepatocellular carcinoma
- hepatorenal or hepatopulmonary syndrome

~~d. Hepatorenal syndrome (type I or II)~~

7.2. Method of Treatment Assignment

[redacted]

8.1.2. Permanent Discontinuation from Study Treatment

Discontinuation due to other laboratory abnormalities:

- White blood cell count <1000 cells/μL (1.00 x 10^3/μL or 1.00 GI/L)
- Absolute neutrophil count <500 cells/μL (0.50 x 10^3/μL or 0.50 GI/L)
- Lymphocyte count <200 cells/μL (0.20 x 10^3/μL or 0.20 GI/L)
- Hemoglobin <6.5 g/dL (<65.0 g/L)
- Creatine phosphokinase >5x ULN
- eGFR ≤40mL/min/1.73m^2.