I4V-MC-JAHG Protocol

Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis.

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Protocol I4V-MC-JAHG
A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis

Baricitinib

Parallel, double-blinded, randomized placebo-controlled multiple dose study in patients with moderate-to-severe atopic dermatitis

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Protocol Approval Date: 30-September-2015

LY3009104

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1. Protocol Synopsis

Title of Study:
A randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of baricitinib in patients with moderate-to-severe atopic dermatitis.

Rationale:
Baricitinib is a JAK1/JAK2 selective inhibitor that is currently in development for treatment of inflammatory diseases such as rheumatoid arthritis and psoriasis. Baricitinib has been administered to healthy subjects and patients with rheumatoid arthritis (RA), moderate-to-severe plaque stage psoriasis, and diabetic nephropathy (DN).

In addition, baricitinib is also being developed for the treatment of atopic dermatitis (AD). This study will evaluate the safety and efficacy of baricitinib in patients with moderate-to-severe atopic dermatitis.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	To compare the proportion of moderate-to-severe atopic dermatitis patients achieving a 50% or greater reduction in the Eczema Area and Severity Index (EASI-50) between each baricitinib dose group (2 mg and 4 mg) and placebo when treated daily for 16 weeks
Secondary	To evaluate the absolute and percent change from baseline of the EASI with baricitinib compared to placebo at weeks 1 and 4 and monthly intervals thereafter
	To evaluate the mean change from baseline of the SCORing Atopic Dermatitis (SCORAD) with baricitinib compared to placebo at weeks 1 and 4 and monthly intervals thereafter
	To evaluate the mean change from baseline of the Investigator's Global Assessment (IGA) with baricitinib compared to placebo for the at weeks 1 and 4 and monthly intervals thereafter
	To assess quality of life based on the Dermatologic Life Quality Index (DLQI) at baseline, weeks 1 and 4 and monthly intervals thereafter
	To assess itch using the itch numerical rating scale (NRS) at baseline, weeks 1 and 4 and monthly intervals thereafter
	To evaluate the pharmacokinetics of baricitinib in patients with moderate-to-severe atopic dermatitis

Summary of Study Design:

Study I4V-MC-JAHG is a multicenter, randomized, double-blind, parallel, placebo-controlled study designed to compare the efficacy and safety of baricitinib to placebo in patients with moderate-to-severe atopic dermatitis. Enrollment will be targeted at 90 patients to enable approximately 72 patients to complete the study. An interim analysis may be implemented and could result in up to an additional 30 patients being enrolled. Patients who meet all eligibility criteria will be randomized to receive either placebo or baricitinib, administered as once daily oral doses of 2 mg or 4 mg. Randomization will occur at the country level.

Treatment Arms and Duration:

Three arms will be randomized 4:3:3 to placebo, 2 mg baricitinib, or 4 mg baricitinib, respectively. Study drug will be administered as oral tablets to be taken once-daily (QD) for 16 weeks. A background therapy of a mid-potency topical corticosteroid (triamcinolone 0.1%) will be utilized during the 28 day standardization phase prior to randomization and continued throughout the study. This background therapy should be used according to the labeling provided by the manufacturer or as directed by the investigator.

Number of Patients: 90-120

Statistical Analysis:

Sample Size	The study will begin with a plan to enroll 90 patients that will be randomized 4:3:3 to placebo, 2 mg baricitinib, or 4 mg baricitinib, respectively. A maximum of 30 additional patients may be enrolled depending on the results of the interim analysis.
Primary Outcome & Methodology	The primary outcome parameter is the proportion of patients achieving EASI-50 in each treatment arm. The placebo arm will be compared to each of the baricitinib arms using a one-sided chi-square test with alpha=0.05. As this is a proof of concept study, there will not be any adjustment of alpha for multiple comparisons. Based on 72 patients and a 35% difference in response rates between placebo and either treatment, statistical power is estimated to be approximately 80%.
Interim Analysis	An interim analysis may be conducted to assess variability, effect size, and placebo effect during the course of the study in order to evaluate the potential need for an increase in the number of patients randomized (up to a total of 120) and/or a possible change in randomization ratio. Details around this potential interim analysis will be described in the statistical analysis plan (SAP) or in interim analysis planning documentation, as appropriate.

2. Introduction

2.1. Background

Atopic dermatitis (AD) is a common skin disorder characterized clinically by chronic inflammation and altered skin barrier function, and histologically by skin infiltration of inflammatory cells. AD is characterized by excessive T-cell activation, with significant skin infiltration by T-cells and dendritic cells. Both Th2 and Th22 activation are hallmarks of AD, with some Th17 and Th1 components. Patients with moderate-to-severe AD are afflicted with a heavy disease burden including medical as well as psycho-social abnormalities. Patients often have bacterial- or viral-mediated cutaneous complications. AD is the most common chronic inflammatory skin disease (Schmitt, 2013) with a prevalence of 2%–10% among adults in western geographies (Bieber, 2010) and a prevalence of about 3% in Japan (Muto et al, 2003).

Studies using genomic and histologic profiling of AD skin have defined sets of biomarkers for AD that include markers of epidermal hyperplasia (epidermal thickness, K16 and Ki67 staining), epidermal barrier components (filaggrin), specific cellular infiltrates, including T-cells (CD3+ and CD8+) and several dendritic cell subsets (CD11c+, CD1a+, inflammatory dendritic epidermal cells). Serum biomarkers that correlate with disease activity include IgE, eosinophils, eosinophilic cationic protein, as well as the Th2 chemokines CCL17, CCL18, CCL22, CCL11, and CCL26, and the cytokines IL-13, IL-31, and IL-22 (Mansouri, 2015).

Members of the Janus kinase (JAK) family of protein tyrosine kinases (JAK1, JAK2, JAK3, and TYK2), along with the signal transduction and activator of transcription (STAT) pathway, play an important role in signal transduction following cytokine and growth factor binding to their receptors (Pesu, 2008). Emerging data support the role of JAK and STAT in Th2 immunity, activating eosinophils, and suppressing regulatory T cells. The JAK-STAT pathway, activated by IL-4, plays a critical role in the pathogenesis of AD by upregulating epidermal chemokines, pro-inflammatory cytokines, and proangiogenic factors as well as by down-regulating antimicrobial peptides and factors responsible for skin barrier function (Bao, 2013). Consistent with the proposed role of IL-4 activation of the JAK-STAT pathway in AD, administration of a monoclonal antibody against the alpha subunit of the IL-4 receptor improved clinical endpoints associated with AD (Beck, 2014).

Baricitinib (also previously known as LY3009104 and INCB028050) is a potent and selective small molecule inhibitor of JAK1 and JAK 2 enzymes that is currently under development for the treatment of inflammatory conditions such as rheumatoid arthritis, diabetic kidney disease, psoriasis, and AD.

Through 04 June 2015, approximately 4300 subjects have received baricitinib. This group of subjects was comprised of healthy subjects, and patients with rheumatoid arthritis, psoriasis, diabetic kidney disease, rare auto-inflammatory syndromes, various degrees of renal impairment, and hepatic dysfunction. Baricitinib has been administered as single doses ranging from 1 to 40 mg, multiple doses of up to 20 mg QD for 10 days, 10 mg QD for 28 days or 5 mg twice daily for 28 days in healthy subjects; and as a single 10-mg or 5-mg dose to subjects with mild to moderate or severe renal impairment respectively, as well as a single 5-mg dose to patients with

end stage renal disease. Treatment duration has ranged from single doses in healthy volunteers to approximately 3.5 years in rheumatoid arthritis patients.

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).

2.2. Study Rationale

Inhibition of JAK-STAT signaling by targeting multiple AD-associated cytokine pathways has the potential to simultaneously reduce inflammation, cellular activation, and proliferation of key immune cells. Treatment of six patients with AD with a JAK1 and JAK3 inhibitor, tofacitinib, led to marked improvement in both objective measures of dermatitis and pruritus and patient-reported pruritus (Levy, 2015).

Baricitinib is a potent and selective small molecule inhibitor of JAK1/2 enzymes. *In vitro*, baricitinib inhibits JAK1 and JAK2 with IC_{50} values in the single-digit nM range, yet it does not significantly inhibit a diverse panel of 28 kinases when tested at 100-fold of the IC_{50} against JAK1 and JAK2. In healthy volunteers, baricitinib demonstrated dose and time-dependent inhibition of cytokine-induced pSTAT3 (Shi, 2014).

Study I4V-MC-JAHG will evaluate the safety and efficacy of baricitinib in patients with moderate-to-severe atopic dermatitis.

3. Objectives and Endpoints

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

Table JAHG.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the proportion of moderate-to-severe atopic dermatitis patients achieving a 50% or greater reduction in the Eczema Area and Severity Index (EASI-50) between each baricitinib dose group (2 mg and 4 mg) and placebo when treated daily for 16 weeks	• EASI-50 at 16 weeks
Secondary	
• To evaluate the absolute and percent change from baseline of the EASI with baricitinib compared to placebo	• EASI at Weeks 1, 4, 8, 12, and 16
• To evaluate the mean change from baseline compared to placebo for the SCORing Atopic Dermatitis (SCORAD)	• SCORAD at Weeks 1, 4, 8, 12, and 16
• To evaluate the mean change from baseline compared to placebo for the Investigator's Global Assessment (IGA)	• IGA at Weeks 1, 4, 8, 12, and 16
• To assess quality of life based on the Dermatologic Life Quality Index (DLQI)	• DLQI at Weeks 1, 4, 8, 12, and 16
• To assess itch using the itch numerical rating scale (NRS)	• Itch Numerical Rating Scale at Week 1, 4, 8, 12, and 16
• To characterize the pharmacokinetics of baricitinib in patients with moderate-to-severe atopic dermatitis	• Plasma pharmacokinetic data
Exploratory	
• To evaluate EASI response in patients based on their baseline total serum IgE	• EASI at Weeks 1, 4, 8, 12 and 16; Baseline total serum IgE
• To evaluate total serum IgE over the course of treatment	• Total serum IgE at baseline, Weeks 4 and 16

Exploratory (continued) • To evaluate changes in disease activity over the course of treatment	• Patient-Oriented Eczema Measure (POEM) at Weeks 1, 4, 8, 12, and 16
• To evaluate changes in sleep quality over the course of treatment	• Change from baseline with data from a wearable actigraphy device
• To evaluate changes in nocturnal itch patterns over the course of treatment	• Data from a wearable actigraphy device
• To evaluate EASI response relative to filaggrin genotype	• EASI-50 and filaggrin genotype data from peripheral baseline blood sample
• To assess tissue biomarkers from biopsies	• K16, Ki-67, and IL-4 will be assessed from each tissue biopsy (collected at baseline (lesion and non-lesion), at Week 4 (lesion), and at Week 16 (lesion and non-lesion)
• To assess peripheral biomarkers mechanistically related to inhibition of JAK 1/2 mechanism	• Peripheral biomarkers collected at baseline, Weeks 4 and 16
• To perform subgroup assessments of response based on patient and disease characteristics	• Ad hoc evaluation of potential prognostic and predictive disease characteristics

4. Study Design

4.1. Overview of Study Design

I4V-MC-JAHG is a randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of baricitinib in patients with moderate-to-severe atopic dermatitis. The study design is illustrated in Figure JAHG.1.

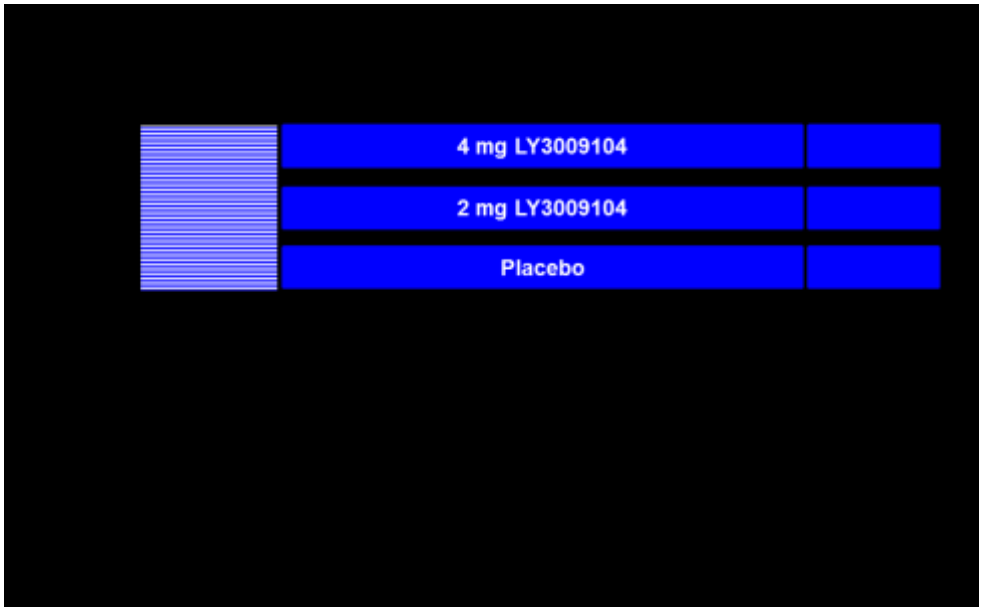

Figure JAHG.1. Illustration of study design for Clinical Protocol I4V-MC-JAHG.

4.2. Scientific Rationale for Study Design

This study will enroll moderate-to-severe atopic dermatitis patients for whom a systemic treatment such as baricitinib may be appropriate. A 16-week course of treatment is expected to enable an optimal assessment of efficacy based on previous baricitinib studies in an inflammatory skin condition.

Relatively high (20% to 50%) placebo responses have been observed in previously published atopic dermatitis studies (Bissonnette, 2012; Beck, 2014; Epstein and Pinski, 1964). Therefore, a 4:3:3 randomization scheme of placebo, 2 mg baricitinib and 4 mg baricitinib will be implemented. Increased placebo enrollment across treatment groups has been reported to decrease placebo response and to also increase statistical power (Mallinckrodt, 2011).

A standardization phase will be incorporated prior to randomization to minimize effects due to background treatment. Beginning at standardization and continuing throughout the study.

patients will be provided a topical corticosteroid to be used as prescribed and may continue use of other allowed study-specified palliative care measures as specified in Section 6.8.

The EASI and SCORAD are the best instruments available to measure clinical severity of AD (Schmitt, 2013). Several quality of life assessments are being utilized to evaluate the effect of baricitinib on patients' quality of life.

4.3. Justification for Dose

This study will evaluate the safety and efficacy of 2 mg and 4 mg doses of baricitinib in patients with moderate-to-severe atopic dermatitis. The dose justification for AD is based on the Phase 2 rheumatoid arthritis (RA) study (Study JADA), the reported Phase 3 RA studies (Study JADW and Study JADX) and the Phase 2 psoriasis study (Study JADP).

In these studies, all doses were generally well tolerated based on the observed adverse event profile and infrequent discontinuations of baricitinib dosing. The anticipated on-target, dose-limiting effect is a small decline in hemoglobin and hematocrit values. As described in Section 4.4, this likely results from inhibition of erythropoietin signals via the JAK2/STAT5 signal transduction pathway (Klingmüller, 1997; Vera, 2008). These hematologic effects occur in higher-dose groups (≥8 mg daily) upon initiation of treatment and then stabilize.

The 2-mg and 4-mg doses have shown efficacy in RA with an acceptable safety profile. There was no additional efficacy associated with an 8-mg dose in the Phase 2 RA study, thus only 4 mg and 2 mg have been studied in the RA Phase 3 program. Doses less than 2 mg were not clearly effective in RA.

In patients with moderate-to-severe plaque stage psoriasis, doses of 4 mg to 10 mg were found to be associated with statistically significant reductions in Psoriasis Area and Severity Index (PASI) score, with greater efficacy at the higher doses; however, the 8-mg and 10-mg doses were associated with a higher rate of AEs related to laboratory abnormalities (decreases in hemoglobin, neutrophils, and lymphocytes). The 2-mg and 4-mg dose groups had a pattern of AEs similar to placebo. The 2-mg dose did show numeric reductions in PASI score compared with placebo and statistically significant reductions in itch. Thus, in AD, the highest dose to be tested will be 4 mg, which would be anticipated to show efficacy together with an acceptable safety profile, and also provide the opportunity to cross reference to the large safety database from the RA Phase 3 program. The lower dose of 2 mg also has the opportunity to show efficacy in AD, where itch is a major component of the disease and may provide data that may be useful in the future for patients less than 18 years of age.

4.4. Benefit/Risk Assessment

Baricitinib is a specific inhibitor of JAK1/2 and may offer potential benefit to patients with moderate-to-severe AD. Increases in serum creatinine and in both LDL and HDL cholesterol have been observed in Phase 1 and 2 studies with baricitinib (see Investigator's Brochure).

Baricitinib is a specific inhibitor of JAK1/2 that has shown to be well-tolerated and effective in chronic inflammatory conditions such as rheumatoid arthritis (Keystone, 2015) and psoriasis

(Menter, 2014). baricitinib may offer potential benefit in a chronic inflammatory dermatologic condition such as AD.

Phase 1 and 2 studies with baricitinib showed increased levels of serum creatinine and LDL and HDL cholesterol (see Investigator's Brochure). Similar increased levels of creatinine and cholesterol were also seen in tofacitinib, a JAK1/3 inhibitor (Fleischmann, 2012; Kremer, 2012). In addition, reductions in absolute neutrophil counts have been reported with both baricitinib and tofacitinib. Other pathways that signal through JAK include granulocyte macrophage colony stimulating factor and granulocyte colony stimulating factor signal and erythropoietin (JAK2) (Parganas, 1998). The assessment of safety of baricitinib in this study will therefore also include, but will not be limited to, monitoring of creatinine, cholesterol, neutrophil and granulocyte counts, hemoglobin levels and rates of infection.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events may be found in the Investigator's Brochure. Information on adverse events expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the Investigator's Brochure. Information on serious adverse events expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate periodically during the course of the study and may be found in Section 6 (Effects in Humans) of the Investigator's Brochure.

5. Study Population

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

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

Type of Patient and Disease Characteristics

[1] Are at least 18 years of age at the time of Visit 1

[2] Have moderate-to-severe AD, as determined by all of the following:

- EASI ≥12 at Visits 1 and 2
- >10% of body surface area (BSA) involvement at Visits 1 and 2
- Were diagnosed with AD at least 2 years before Visit 1

With a history of inadequate clinical response, in the opinion of the investigator, to one or more of the three treatment categories listed below (used for at least 4 weeks):

- Category 1: Hydration plus topical steroids and/or antibiotics (e.g., tetracycline, trimethoprim and sulfamethoxazole, cephalosporins, etc.) and or topical immune modulators (e.g., tacrolimus/pimecrolimus)
- Category 2: Systemic steroids and/or phototherapy
- Category 3: Cyclosporine and/or other immunomodulators (e.g., methotrexate, mycophenolate mofetal, and azathioprine)

[3] Agree to discontinue use of the following excluded medications for at least 4 weeks prior to randomization (Visit 2) and throughout the study

- oral cyclosporine, steroids, and leukotriene inhibitors
- phototherapy
- potent topical steroids (e.g., clobetasol) or topical immune modulators (e.g.,tacrolimus/pimecrolimus).
- cyclosporine and/or other immunomodulators (e.g., methotrexate, mycophenolate mofetal, and azathioprine)

5.2. Exclusion Criteria

Patients will be excluded from participating in the study if they meet any of the following criteria:

Medical Conditions

[4] Are female subjects who are pregnant or nursing

[5] Are females of childbearing potential who do not agree to use 2 forms of highly effective methods of birth control or remain abstinent while enrolled in the study and for at least 28 days following the last dose of investigational product

Note: Females of nonchildbearing potential are defined as women ≥60 years of age, or women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, or women who are congenitally or surgically sterile (that is, have had a hysterectomy or bilateral oophorectomy or tubal ligation).

The following birth control methods are considered highly effective (the patient should choose 2):

- Oral, injectable, or implanted hormonal contraceptives
- Condom with a spermicidal foam, gel, film, cream, or suppository
- Occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository
- Intrauterine device
- Intrauterine system (for example, progestin-releasing coil)
- Vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

[6] Are males who do not agree to use 2 forms of highly effective birth control (see above) with female partners of childbearing potential while enrolled in the study, and for at least 28 days following the last dose of investigational product

Are currently experiencing or have a history of any of the following:

[7] Other concomitant skin conditions (e.g., psoriasis, or lupus erythematosus) that would interfere with evaluations of the effect of study medication on atopic dermatitis

[8] Erythrodermic, refractory or unstable skin disease that requires frequent hospitalizations and/or intravenous treatment for skin infections

[9] Immunocompromised and, in the opinion of the investigator, at an unacceptable risk for participating in the study

[10] Serious concomitant illness that could require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma)

[11] Organ transplant(s) (corneal transplant performed >3 months prior to screening may be allowed)

[12] Clinically important deviation, in the opinion of the investigator, from normal limits in physical examination, vital sign measurements, and/or electrocardiograms, that is not associated with a chronic, well-controlled medical condition

[13] Electrocardiogram (ECG) abnormalities at Visit 1 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 (Bazett's corrected QT interval >470 msec for men and women)

[14] Have evidence of active or latent TB as documented by a positive PPD test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), medical history, **or** chest x-ray at screening. Exceptions are patients with a history of latent TB who have documented evidence of completing a course of appropriate treatment.

- If the PPD test is positive or not conducted and the patient has no medical history or chest x-ray findings consistent with active or latent TB, the patient should have a QuantiFERON®-TB Gold test or the T-SPOT.TB® test. If either of these tests is positive or indeterminate (a single re-test is allowed), the patient is excluded from the study.

[15] Active or latent granulomatous disorders or a non-tuberculous mycobacterial infection or opportunistic systemic infection (e.g., *Pneumocystis carinii*, and aspergillosis) within 6 months prior to screening

[16] Uncompensated heart failure, fluid overload, myocardial infarction, or evidence of ischemic heart disease or other serious cardiac disease within 12 weeks of Visit 1

[17] Uncontrolled arterial hypertension characterized by a repeated systolic blood pressure >160mm Hg or diastolic blood pressure >100mm Hg at the time of Visit 1

[18] Malignancy (except for basal or squamous cell carcinoma completely excised without evidence of recurrence) or lymphoproliferative diseases or have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly including lymphoma

Note: Patients with cervical carcinoma *in situ* that has been resected with no evidence of recurrence or metastatic disease, or 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.

[19] Evidence of HIV infection or are positive for HIV antibodies (based on history or point-of-care testing (POCT)) at Visit 1

[20] Positive test for hepatitis B defined as:

a) positive for hepatitis B surface antigen (HbsAg), or

b) positive for anti-hepatitis B core antibody (HbcAb), but negative for hepatitis B surface antibody (HBsAb) or
c) HBcAb positive and are HBV DNA positive or
d) for patients enrolled in Japan, positive for HBcAb and/or anti-hepatitis B surface antibody (HbsAb) and positive for hepatitis B deoxyribonucleic acid (HBV DNA). If any of the hepatitis B tests have an indeterminate result, confirmatory testing will be performed by an alternate method.

[21] Positive for anti-hepatitis C antibody with confirmed presence of hepatitis C virus, or chronic liver disease with the most recent available AST or ALT >2X the ULN

[22] Serious and/or unstable mental and/or physical illness that, in the opinion of the investigator, poses an unacceptable risk for the patient's participation in the study

Prior/Concomitant Therapy

[23] Received any oral JAK inhibitor (e.g., Xeljianz) within the past 6 months

[24] Currently receiving any immunosuppressive therapy (e.g., cyclosporine)

[25] Received any monoclonal antibody intended for AD (e.g., ustekinumab or dupilumab) within the past 6 months.

[26] Currently using or expected to use concomitant medications or treatments for AD other than those allowed for use in the protocol

[27] Exposed to a live vaccine, including the nasal flu vaccine, within 12 weeks prior to planned enrollment (with the exception of herpes zoster vaccination; patients will be excluded if they were exposed to herpes zoster vaccination within 30 days of planned enrollment) or are expected to need/receive a live vaccine during the course of the study.

Prior/Concurrent Clinical Trial Experience

[28] Currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[29] Participated, within the last 30 days (for Japan, 4 months) in a clinical study involving an investigational product. If the previous investigational product has a long half-life (2 weeks or longer), at least 3 months or 5 half-lives (whichever is longer) should have passed.

[30] Previously completed or withdrawn from this study

Diagnostics Assessments

Have any of the following specific abnormalities on screening laboratory tests:

[31] AST or ALT >2X the ULN

[32] Total bilirubin ≥1.5X the ULN

[33] Hemoglobin <11.0 g/dL (100.0 g/L)

[34] Total white blood cell count <2500 cells/µL

[35] Neutropenia (absolute neutrophil count <1200 cells/µL)

[36] Lymphopenia (lymphocyte count <750 cells/µL)

[37] Thrombocytopenia (platelets <100,000/µL)

[38] eGFR <50 mL/min/1.73 m^2 (based on CKD EPI)

Note: In the case of any of the aforementioned laboratory abnormalities, they may be repeated once within 1 week of the initial values, and values resulting from repeat testing may be used to assess enrollment eligibility.

Other Exclusions

[39] Donated blood of more than 500 mL or blood products within 4 weeks prior to entry.

[40] Unwilling to commit to refrain from donating blood or blood products during the study.

[41] History of substance abuse (drug or alcohol) within the two years before screening.

[42] Unable or unwilling to be available for the duration of the study and/or are unwilling to follow study restrictions/procedures.

[43] Unable or unwilling to have skin biopsies performed, unless exempted by the investigator.

[44] 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.

[45] Employees of the sponsor.

[46] Unwilling or unable to comply with the use of all potential data collection devices.

5.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened once (time period from screen fail to re-screen to be determined by the investigator). If re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Additionally, all screening procedures must be conducted at re-screen to ensure all eligibility criteria are met.

6. Treatment

6.1. Treatments Administered

This study includes the treatment regimens outlined in Table JAHG.2 below. Doses of baricitinib or placebo will be administered orally.

Table JAHG.2. Treatment Regimens

Treatment Group	Dose (QD) Day 1 through Day 112
2 mg LY	(1 × 2-mg LY tab; 1 × 4-mg placebo tab)
4 mg LY	(1 × 2-mg placebo tab; 1 × 4-mg LY tab)
Placebo	(1 × 2-mg placebo tab; 1 × 4-mg placebo tab)

Abbreviations: tab = tablet; LY = baricitinib

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

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

6.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive response technology (IRT) system. The IRT system will be used to assign blister packs containing double-blind investigational product to each patient. The IRT system will dispense a number of blister packs adequate for each visit interval.

The randomization will be stratified by country.

6.2.1. Selection and Timing of Doses

Patient treatment assignments will be based on the randomization scheme as described above.

On PK sample collection days (Appendix 2), specific fasting and dose timing requirements are outlined in Table JAHG.5 (Section 8.5.1).

6.3. Blinding

This is a double-blind study in which the patients, investigator, and study site personnel will be blinded to treatment allocation.

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.

Emergency unblinding for AEs may be performed through an IRT system, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IRT system.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor CRP prior to unblinding a patient's treatment assignment.

If an investigator, site personnel performing assessments, or patient is unblinded to the treatment code assignment, the sponsor must be contacted immediately.

6.4. Packaging and Labelling

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

- tablets containing 2 mg of baricitinib
- tablets containing 4 mg of baricitinib
- placebo to match baricitinib 2 mg tablets
- placebo to match baricitinib 4 mg tablets

Additionally, the sponsor (or its designee) will also provide the following concomitant therapy product:

- triamcinolone 0.1% cream which should be used according to the labeling provided by the manufacturer or as directed by the investigator

Investigational products and triamcinolone 0.1% cream will be dispensed to the patient at the investigator's study site.

Investigational product will be packaged in blister packs. Investigational product packaging will be labeled with a unique identifier for drug dispensing by the IRT system. Blister packs will contain additional tablets to allow for sufficient administration of investigational product within the allowed visit internal window.

Investigational product will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Investigational products will be manufactured and tested by the sponsor or its representative in accordance with current Good Manufacturing Practices (cGMP)

requirements for clinical studies, and will be supplied with lot numbers, expiry dates, and certificates of analysis (as applicable).

6.5. Investigational Products Storage and Handling

Investigational products should be stored between 15°C and 30°C. All investigational products should be stored in a secure and locked area with strictly limited access and monitored for temperature and will be allocated and dispensed by appropriately trained personnel.

Investigational products will be packaged in blister packs. Patients will be provided with enough blister packs for their visit intervals. Detailed records of the amounts of study drug received, dispensed and remaining at the end of the study will be maintained.

Investigational products will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Investigational products will be supplied by the sponsor or its representative in accordance with current Good Manufacturing Practices, and will be supplied with lot numbers, expiry dates, and certificates of analysis (as applicable).

6.6. Dose Modification

No dose modifications will be allowed.

6.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

The patient will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses during the study. 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.

Patients found to be noncompliant with investigational product should be assessed to determine the reason for noncompliance, and educated and/or managed as deemed appropriate by the investigator to improve compliance.

6.8. Concomitant Therapy

The use of triamcinolone 0.1% cream will be allowed throughout the trial. Patients will be instructed to apply the triamcinolone 0.1% cream according to the labeling provided by the manufacturer or as directed by the investigator. The triamcinolone 0.1% cream container will be weighed at each visit to assess usage.

All concomitant medication taken during the study must be recorded on the Concomitant Medication case report form (CRF). Treatment with concomitant atopic dermatitis therapies during the study is permitted only as outlined in the inclusion/exclusion criteria (Section 5.1 and Section 5.2) and as described in the paragraphs below.

Additional systemic drugs are to be avoided during the study, unless required to treat an AE.

Non-live seasonal vaccinations and/or emergency vaccination (such as rabies or tetanus vaccinations) are allowed.

The following will be allowed as needed: use of topical antibiotics in the event of secondary infections of lesions; nonprescription shampoos; NSAIDs; diphenhydramine (≤50 mg); and topical moisturizers/emollients, bath oils, oatmeal bath preparations, bleach baths if using a stable regimen prior to enrollment, and salicylic acid preparations. Patients will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements.

6.9. Treatment after Study Completion

6.9.1. Continued Access

The Investigational Product will not be made available to patients after the conclusion of the study.

7. Discontinuation Criteria

7.1. Discontinuation of Investigational Product

7.1.1. Temporary Interruption of Investigational Product

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values as described in Table JAHG.3 that may have an unclear relationship to investigational product. Except in cases of emergency, it is recommended that the investigator consult with the sponsor (or its designee) before temporarily interrupting therapy.

The investigator must obtain approval from the sponsor (or its designee) before restarting investigational product that was temporarily discontinued because of an AE or abnormal laboratory value. Investigational product must be held in the following situations involving laboratory abnormalities and may be resumed as noted in Table JAHG.3.

Table JAHG.3. Criteria for Temporary Interruption from Study Treatment

Hold Investigational Product if the Following Laboratory Test Results Occur:	Investigational Product May Be Resumed after Approval from Lilly (or its Designee) and When:
WBC count <2000 cells/μL	WBC count ≥2500 cells/μL
ANC <1000 cells/μL	ANC >1200 cells/μL
Lymphocyte count <500 cells/μL	Lymphocyte count ≥750 cells/μL
Platelet count <75,000/μL	Platelet count ≥100,000/μL
eGFR <40 mL/min/1.73 m^2 (from serum creatinine)	eGFR ≥50 mL/min/1.73 m^2
ALT or AST >5 times the ULN	ALT and AST return to <2 times the ULN, and investigational product is not considered to be the cause of enzyme elevation
Hemoglobin <9 g/dL	Hemoglobin ≥10 g/dL
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Severe infection that, in the opinion of the investigator, merits the investigational product being discontinued	Resolution of infection

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; min = minute; ULN = upper limit of normal; WBC = white bloodcell.

7.1.2. Permanent Discontinuation of Investigational Product

Any patient who is permanently discontinued from investigational product for an AE or abnormal laboratory result should have the reason for investigational product discontinuation reported as the AE or abnormal laboratory value. If any of the criteria listed in Section 7.1.1. above recur after investigational product is restarted, the investigator must obtain approval from the sponsor (or its designee) before restarting investigational product. In addition, patients will

be permanently discontinued from investigational product if they experience any of the criteria listed in Table JAHG.4.

Table JAHG.4 Criteria for Permanent Discontinuation of Investigational Product

Permanently Discontinue Investigational Product if any of the Following are Observed:
ALT or AST >8 times the ULN
ALT or AST >5 times the ULN persisting for more than 2 weeks after temporary interruption of investigational product
ALT or AST >3 times the ULN and total bilirubin level >2 times the ULN
ALT or AST >3 times the ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
WBC count <1000 cells/μL
ANC <500 cells/μL
Lymphocyte count <200 cells/μL
Hemoglobin <8 g/dL
Pregnancy
Malignancy (except for successfully treated basal cell or squamous epithelial skin cancers)
HBV DNA ≥29 IU/mL[a]

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; HBV DNA = hepatitis B virus deoxyribonucleic acid; ULN = upper limit of normal; WBC = white bloodcell.

[a] If a HBV DNA result of 'target detected' 29 IU/mL or greater, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug in accordance with current immunomodulator management in the setting of HBV DNA positivity. This option may be considered in consultation with the sponsor (or its designee) and evaluation of individual patient risks and benefits. Refer to Section 8.4.5 for additional instruction on HBV DNA monitoring.

7.1.3. Discontinuation of Inadvertently Enrolled Patients

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

7.1.4. Permanent Discontinuation from the Study

Some possible reasons that may lead to permanent discontinuation include:

- 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

- Patient Decision

Patients who discontinue the study early will have early termination (ET) procedures performed as shown in the Schedule of Activities (Appendix 2).

7.1.5. Patients 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.

8. Study Assessments and Procedures

Appendix 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 3 lists the laboratory tests that will be performed for this study.

Appendix 4 provides the hepatic monitoring tests for treatment-emergent abnormalities.

Additionally, a study addendum will be compiled to detail the capture of photographs from selected lesions for patients enrolled at up to three selected study sites. These photographs will permit documentation of the clinical response through sequential photography of a selected lesion or involved area before and following study drug treatment.

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.

8.1. Efficacy Assessments

Study procedures and their timing are summarized in the Schedule of Activities (Appendix 2).

8.1.1. Primary Efficacy Assessments

The clinical outcome measure that will be used in this study is the EASI score (specifically, the proportion of patients achieving a 50% reduction in EASI or EASI-50).

- **Eczema Area and Severity Index (EASI) scores:** The EASI assesses extent of disease at four body sites and measures four clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification each on a scale of 0 to 3. EASI confers a maximum score of 72. EASI evaluates two dimensions of atopic dermatitis: disease extent and clinical signs.

8.1.2. Secondary Efficacy Assessments

- **Mean and Percentage change in Eczema Area and Severity Index (EASI) scores:** See above.

- **SCORing Atopic Dermatitis (SCORAD):** The SCORAD index uses the rule of nines to assess disease extent and evaluates five clinical characteristics to determine disease severity: (1) erythema, (2) edema/papulation, (3) oozing/crusts, (4) excoriation and (5) lichenification. SCORAD also assesses subjective symptoms of pruritus and sleep loss with Visual Analogue Scales (VAS). These three aspects: extent of disease, disease severity and subjective symptoms combine to give a maximum possible score of 103.

- **Investigator's Global Assessment (IGA):** The IGA consists of a 6-point severity scale from clear to very severe disease (0=clear, 1=almost clear, 2=mild disease, 3=moderate disease, 4=severe disease and 5=very severe disease). IGA uses clinical characteristics

of erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment.

- **Dermatology Life Quality Index (DLQI)**: The DLQI is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week." Response categories include "not at all," "a lot," and "very much," with corresponding scores of 1, 2, and 3 respectively and unanswered ("not relevant") responses scored as 0. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related quality of life, and a 5-point change from baseline is considered as the minimal clinically important difference threshold (Khilji, 2002; Hongbo, 2005).

- **Itch Numerical Rating Scale (NRS):** 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 circling the number that best describes the worst level of itching in the **past 24 hours.** Analyses were performed to support a responder definition that was defined as proportion of patients achieving an Itch NRS ≥4-point reduction from baseline for patients who had baseline Itch NRS ≥4.

8.1.2.2 Exploratory Efficacy Assessments

Data on the following exploratory efficacy measures will be collected at the times shown in the Schedule of Activities (Appendix 2):

- **Patient-Oriented Eczema Measure (POEM):** The Patient-Oriented Eczema Measure (POEM) was originally developed to help address the imbalance between physician and patient-based outcome measures in eczema research. Patients answer simple questions about the frequency of seven symptoms: itch, sleep disturbance, skin bleeding, skin weeping/oozing, skin cracking, skin flaking, and skin dryness/roughness over the last week. The total score from this assessment reflects overall disease activity. The POEM utilizes a 5-point Likert scale for each question and is intended for ages 1-60 years. POEM scores can range from 0 to 28 where lower total scores reflect lower disease activity and higher scores reflect higher disease activity (Charman, 2004).

- **Actigraphy Device:** A hypoallergenic wrist watch-like device that is used to collect sleep/wake patterns and quantify nocturnal scratching events (Ferguson, 2015).

8.1.3. Appropriateness of Primary Efficacy Measure

- **Eczema Area and Severity Index (EASI): The EASI is one of the best instruments** available to measure clinical signs of AD. EASI utilizes objective physician estimates of disease extent and severity. The EASI is valid and internally consistent and has adequate intraobserver reliability, intermediate interobserver reliability, and adequate responsiveness. One advantage of the EASI is its unidimensionality; that is, it only measures clinical signs of AD and does not include symptoms. Another advantage of the

EASI is that it measures the intensity of the lesions at multiple body parts (rather than relying on a representative lesion) (Schmitt, 2013).

8.2. Adverse Events

The investigator remains responsible for following, through an appropriate health care option, AEs that are (1) serious or otherwise medically important, (2) considered related to the investigational product or the study, or that (3) 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.

The sponsor has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. All AEs collected in the study CRF will be validated and reported in the final study report.

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 the CRF/electronic data entry, 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 their assessment of the potential relatedness of each AE to protocol procedure or investigational product.

Investigators must document their review of each laboratory safety report.

Any clinically significant findings from ECGs, laboratory tests, vital sign measurements, and other procedures that result in a diagnosis should be reported to the sponsor or its designee. In addition, all AEs occurring after the patient receives the first dose of the investigational product must be reported to the sponsor or its designee.

Investigators will be instructed to report to the sponsor or its designee their assessment of the potential relatedness of each AE to protocol procedure or investigational product via the case report form.

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

Cases of pregnancy that occur during maternal or paternal exposures to the investigational product should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel must alert the sponsor or its designee immediately of the investigator unblinding a patient's treatment group assignment for any reason.

If a patient's treatment is discontinued as a result of an AE, study site personnel must clearly report to the sponsor or its designee the circumstances and data leading to any such discontinuation of treatment.

8.2.1. Adverse Events/Laboratory Results of Special Interest

Adverse events or laboratory results of special interest include infections; myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia; thrombocytosis; hyperlipidemia; hypercholesterolemia; and elevations in ALT/AST (≥3X ULN) and total bilirubin (≥2X ULN).

8.2.2. Serious Adverse Events

Study site personnel must alert the sponsor or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms.

All SAEs will be reported in the study CRF and on the approved study-specific SAE form by the study site personnel. In addition, the study-specific SAE forms will be collected by sponsor/designee and subsequently entered into the clinical study database and the study safety database. Investigators will be required to update the study-specific SAE forms when new information becomes available, and address questions from the sponsor/designee until the SAE has been fully resolved or explained to the satisfaction of the sponsor. The SAE data from both CRF and study-specific SAE forms will be validated and included in the final CSR. If the SAE cases are closed after the completion of database lock, such information may not be included in the final study report. Such additional information will continue to be collected in the study-specific SAE form, and be reported either in an amendment to study report if such information lead to a clinically significant changes in the conclusion of the study; or in the annual Development Safety Update Report (DSUR) or IB update if the information from the SAE does not alter the overall conclusion of the study.

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
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Previously planned (prior to signing of ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

SAEs occurring after a patient has taken the last dose of the investigational product will be collected in the pharmacovigilance system and clinical data collection database for 30 days after the last dose of the investigational product, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product, drug delivery system, or a protocol procedure.

Sponsor/designee has the option to request follow up information or clarification of existing information from the investigators up to closure of the case. SAEs should be followed by the investigator until resolution of all queries, clinical recovery is complete or until a stable clinical endpoint has been reached. Follow up may therefore continue after the patient has been discharged from the study. The type and extent of follow up undertaken will be determined for each individual case and depends upon the nature, severity, and medical significance of the report. The follow up may include supplemental investigations, additional laboratory tests, histopathological examinations, or consultations with other health care professionals. If a patient dies during participation in the study, the follow up may include a copy of any post-mortem findings, if available.

The investigator site will be required to contact the patient in accordance with their procedures to obtain necessary information to provide updates to the study-specific SAE forms. Requests for outstanding information from the investigational site to patients should be maintained as part of the clinical study documents.

8.2.2.1. 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. The sponsor has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.2.3. Complaint Handling

The Sponsor 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.

8.3. Treatment of Overdose

Refer to the baricitinib Investigator's Brochure.

8.4. Safety Assessments

Safety assessments include vital signs, physical examination, electrocardiograms, AEs, patient-reported scale data, and safety laboratory testing.

8.4.1. Physical examination

A complete physical examination will be performed during Visit 1 (screening). Directed physical examinations will be performed according to the Schedule of Activities (Appendix 2) and may be repeated at the investigator's discretion any time a patient presents with physical complaints.

8.4.2. Electrocardiograms

For each patient, an electrocardiogram (ECG) should be performed according to the Schedule of Activities (Appendix 2) and as deemed necessary by the investigator.

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

8.4.3. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Appendix 2) and following study specific recommendations provided by the sponsor for the study.

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 the sponsor or its designee as an AE via designated data transmission methods.

8.4.4. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 3) should be conducted according to the Schedule of Activities (Appendix 2).

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 the sponsor or its designee as an AE via designated data transmission methods.

8.4.5. Hepatitis B virus (HBV) DNA monitoring

Patients who are HBcAb positive and HBV DNA negative (undetectable) at Visit 1 will require HBV DNA monitoring every 3 months and at the patient's last visit (V8 or ET), regardless of their HBsAb status. If the HBV DNA result is 'target detected' ≥29 IU/mL, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug in accordance with current immunomodulator management in the setting of HBV DNA positivity. This option may be considered in consultation with the sponsor (or its designee) and evaluation of individual patient risks and benefits. The following actions should be taken in response to HBV DNA test results:

- If a result of "target detected" is obtained at any time during the study with a value of ≥29 IU/mL, refer to Table JAHG.4.

For patients enrolled at study sites in Japan only, if a patient is HbsAb positive and negative for HBV DNA at Visit 1, HBV DNA needs to be checked at least monthly and at the patient's last visit (V8 or ET).

8.4.6. Quick Inventory of Depressive Symptomatology-Self Report 16 (QIDS-SR16)

For each patient, the QIDS-SR16 should be taken according to the Schedule of Activities (Appendix 2).

The QIDS-SR16 is a self-administered 16-item 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 (DSM-IV) (American Psychiatry Association [APA] 1994). The QIDS-SR16 scale is used to assess the potential impact of treatment on new onset or changes in depression, thoughts of death, and /or suicidal ideation severity. A patient is 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: (1) sad mood, (2) concentration, (3) self-criticism, (4) suicidal ideation, (5) interest, (6) energy/fatigue, (7) sleep disturbance (initial, middle, and late insomnia or hypersomnia), (8) decrease/increase in appetite/weight, and (9) psychomotor agitation/retardation (Rush, 2003).

8.4.7. Safety Monitoring

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

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

8.5. Pharmacokinetics

8.5.1. PK sample collection

A total of 6 venous blood samples (approximately 5 mL per sample) for the measurement of baricitinib concentrations will be drawn at visits scheduled within the time windows specified in the Schedule of Activities (Appendix 2). Specific dosing and fasting requirements for each PK visit are described in Table JAHG.5 below.

Table JAHG.5. Timing of Dosing and Fasting Requirements for PK Sample Collection Visits

Events	Visit					
	2	4	5	6	7	ET
Overnight (8-hr) fast	Yes	No	No	No	Yes	No
Take study drug	At clinic	At home	At home	At clinic	At clinic	N/A
Morning Fast	Until PK samples are taken	N/A	N/A	N/A	Until PK sample is taken	N/A
Sample time windows relative to dose	• Pre-dose • 15-30min post-dose	1.5 – 4 hr post-dose	4 – 8 hr post-dose	Pre-dose	30-90 min post-dose	N/A

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On all PK sample collection days, patients should take all study medication within 5 minutes. At Visits 2 and 7, patients will be asked to arrive at the study site after an overnight fast. Patients will receive an oral dose of placebo or baricitinib at the study site and will remain fasted until PK blood samples have been collected. A light snack will be provided after PK samples have been collected.

At Visits 4 and 5, patients will be advised to take the study drug at home. Patients will then go to the study site in the scheduled time window for study assessments.

At Visit 6, patients will be advised to NOT take study drug prior to visiting the study site. A single blood sample will be collected prior to the patient taking their drug at the study site.

A single PK sample will be obtained, whenever possible, at the early termination visit. In the event of an SAE, up to 2 additional blood samples may be taken at the investigator's discretion, up to 6 hours after the reported event and within 24 hours of the patient's last dose.

For any PK sample taken, the actual date and time (24-hour clock) of PK sample collection as well as the date and time of the last 2 dose administrations prior to the PK sample should be recorded.

The sponsor, or its designee, will provide instructions for the collection and handling of blood samples.

8.5.2. PK sample assay

Plasma samples will be assayed for baricitinib using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method at a laboratory approved by the sponsor. Samples from patients receiving baricitinib will be assayed. PK samples from patients on placebo are not planned to be assayed.

8.5.3. PK sample storage and retention

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last patient visit for the study. Pharmacokinetic samples will be kept in storage at a laboratory facility designated by the sponsor and may also be assayed for additional exploratory analyses. Pharmacokinetic results will not be provided to investigative sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

Further pharmacodynamic data, beyond efficacy and biomarker data, will not be collected.

8.7. Genetics

A blood sample (approximately 10 mL) will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Appendix 2) where local regulations and ethical review boards (ERBs) allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to baricitinib and to

investigate genetic variants thought to play a role in atopic dermatitis or other inflammatory skin disorders. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to evaluate their association with observed response to baricitinib.

All pharmacogenetic samples will be coded with the patient number. Only investigator site personnel can link these samples, and any data generated, back to the patient. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described here.

8.8. Biomarkers

Skin biopsies, serum, plasma, and whole blood ribonucleic acid (RNA) samples for non-genetic biomarker research will be collected at the times specified in the Schedule of Activities (Appendix 2) where local regulations and ERBs allow.

Samples may be used for research on the drug target, disease process, pathways associated with atopic dermatitis, mechanism of action of baricitinib, and/or research method or in validating diagnostic tools or assay(s) related to atopic dermatitis.

All biomarker samples will be coded with the patient number. Only investigator site personnel can link these samples, and any data generated, back to the patient. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

8.8.1. Skin Biopsies

Patients will be required to provide skin punch biopsy samples collected per the Schedule of Activities (Appendix 2), unless exempted by the investigator.

Skin biopsy samples from atopic dermatitis lesions and adjacent normal tissue will be collected and used to study biomarkers related to atopic dermatitis and/or related to the mechanism of action of baricitinib. Techniques used may include but are not limited to immunohistochemistry

and microarray expression profiling. Samples will be de-identified as described in International Conference on Harmonisation (ICH) guideline E15, and may be used for exploratory microarray expression profiling or transcriptome sequencing. Detailed instructions for sample collection and handling will be provided by the sponsor. Samples will be sent to a sponsor-designated lab for immunohistochemistry.

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8.8.2. Nonpharmacogenetic Biomarkers

Peripheral serum samples (approximately 10 mL) will be collected at pre- and post-treatment time points for the assessment of biomarkers expected to be mechanistically related to JAK 1/2 inhibition and/or the atopic dermatitis disease state. A blood sample for genotyping of filaggrin will also be collected. Sample processing and handling instructions will be provided by the sponsor. Samples will be sent to a sponsor-designated lab for evaluation.

Exploratory biomarker serum, plasma, and blood for mRNA samples will also be collected and stored at a sponsor-designated vendor.

8.9. Health Economics

The self-reported questionnaires will be administered according to the Schedule of Activities (Appendix 2). The questionnaires will be administered in countries where they have been translated into the native language of the region and linguistically validated.

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

Approximately 90 patients will be enrolled using a 4:3:3 randomization scheme of placebo, 2 mg baricitinib, or 4 mg baricitinib, respectively. Assuming a drop-out rate no greater than 20%, approximately 72 patients will complete the study.

This sample size provides 80% power to see a difference in EASI-50 between placebo and either baricitinib treatment group of 35%, assuming a placebo response rate of 40%, using a 1-sided chi-square test with alpha = 0.05.

An interim analysis may be conducted to assess variability, effect size, and placebo effect to evaluate the need for an increase in the number of patients randomized up to a total of 120 and/or a possible change in randomization ratio. Details around this potential interim analysis will be described in the statistical analysis plan (SAP) or in interim analysis planning documentation, as appropriate.

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee. A detailed statistical analysis plan (SAP) will be provided by the sponsor or its designee, and will be finalized prior to database lock and unblinding.

Investigator site data will be pooled for statistical analysis purposes.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.05, unless otherwise stated.

Data analyses will be provided by treatment groups and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages.

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

9.3. Treatment Group Comparability

9.3.1. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. Data tabulations will summarize the following patient numbers, per treatment group:

- Enrolled

- Received treatment
- Violated the protocol
- Completed the protocol
- Withdrew because of:
  - Adverse event
  - Lack of efficacy
  - Consent withdrawal
  - Other reasons, as applicable

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

9.3.2. Patient Characteristics

Baseline and demographic characteristics will be summarized descriptively by treatment group and overall.

9.3.3. Concomitant Therapy

Concomitant use of topical corticosteroids will be summarized by treatment group.

9.4. Primary and Secondary Analyses

9.4.1. Primary Analyses

The primary outcome will be the proportion of patients achieving EASI-50 in each treatment arm. The primary analysis will be performed using all randomized patients utilizing a Non-Responder Imputation (NRI) analysis. The proportion of patients achieving EASI-50 in the placebo arm will be compared to proportion of patients in each of the baricitinib arms using a one-sided chi-square test with alpha=0.05. As this is a proof of concept study, there will not be any adjustment of alpha for multiple comparisons.

For EASI-50 endpoint, all Non-Responders, as well as all patients who discontinue study treatment at any time prior to the time point of interest or discontinue from the study for any reason, will be defined as Non-Responders for the NRI analysis. Randomized patients without at least 1 post-baseline observation will also be defined as Non-Responders for the NRI analysis.

9.4.2. Secondary Analyses

Continuous secondary endpoints will be summarized and analyzed using treatment groups by use of a mixed effects model with treatment as the main factor and baseline values as covariates. The treatment (intercept) effects and their standard errors from the mixed effects model will be used to produce p-values and 90% confidence intervals for the treatment comparison.

For continuous endpoints collected longitudinally, missing data will assumed to be missing at random and a mixed model repeated measures (MMRM) approach will be used. Other imputation techniques, such as multiple imputation, may be utilized in sensitivity analyses.

Categorical secondary endpoints will be summarized and analyzed using a chi-square test or Fisher's exact test, if needed.

9.4.3. Tertiary/Exploratory Analyses

Continuous secondary endpoints will be summarized and may be analyzed by use of a mixed effects model with treatment as the main factor and baseline values as covariates. The treatment (intercept) effects and their standard errors from the mixed effects model will be used to produce p-values and 90% confidence intervals for the treatment comparison.

Categorical secondary endpoints will be summarized and may be analyzed using a chi-square test or Fisher's exact test, if needed.

9.5. Safety Analyses

Safety analyses will be conducted on all patients who received at least one dose of study drug. No statistical comparisons of treatment groups will be completed for safety endpoints.

All adverse events will be summarized and listed. The incidence of symptoms for each treatment will be presented by severity and by association with study drug as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study.

Additional safety parameters that will be assessed include safety lab parameters and vital signs. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

9.6. Pharmacokinetic/Pharmacodynamic Analyses

The pharmacokinetics of baricitinib will be assessed using population PK analysis techniques. The relationship between the primary and secondary efficacy endpoints and plasma exposure, race, and age of onset may be explored. PK and PD data may be combined with prior data for an integrated analysis.

9.7. Other Analyses

9.7.1. Health Economics

Patient reported outcome endpoints will be summarized and analyzed using treatment groups by use of a mixed effects model with treatment as the main factor and baseline values as covariates. The treatment (intercept) effects and their standard errors from the mixed effects model will be used to produce p-values and 90% confidence intervals for the treatment comparison.

9.7.2. Biomarkers

Biomarker data from all patients undergoing biomarker assessments will be analyzed. Biomarker data will be summarized and listed, and may be displayed graphically.

9.8. Interim Analyses

A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population pharmacokinetics/pharmacodynamics (PK/PD) model development processes

for interim or 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.

An interim analysis may be conducted to assess variability of response, effect size, and placebo effect during the course of the study in order to evaluate the potential need for an increase in the number of patients randomized up to a total of 120 and/or a possible change in randomization ratio. Details around this potential interim analysis will be described in the statistical analysis plan (SAP) or in interim analysis planning documentation, as appropriate.

10. Study Governance Considerations

10.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1.1. Informed Consent

The investigator is responsible for ensuring that:

- the patient understands the potential risks and benefits of participating in the study
- informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- any questions the patient may have throughout the study are answered and shares, 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.

10.1.2. Ethical Review

The investigator or designee must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to the sponsor before the study may begin at the investigative site(s). The sponsor 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 GCP.

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

- current IB and updates during the course of the study
- ICF
- relevant *curricula vitae*

10.1.3. Regulatory Considerations

This study will be conducted in accordance with:

- 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

The investigator or designee will promptly submit the protocol to applicable ERB(s).

All or some of the obligations of the Sponsor may be assigned to a Contract Research Organization (CRO).

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other study-related data.

10.1.4. Investigator Information

Physicians with a specialty in dermatology will participate as investigators in this clinical study.

10.1.5. 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 sponsor representative.

10.1.6. 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 investigator with the most enrolled patients will be requested to serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by the sponsor to serve as the CSR coordinating investigator.

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

10.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, the sponsor/designee will perform 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 CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax

- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, the sponsor/designee will periodically check a sample of the patient data recorded against source documents at the study site. The sponsor/designee and/or regulatory agencies may audit the study 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.

10.2.1. Data Capture System

An electronic data capture (EDC) system will be used in this study. The site maintains a source for the data entered into the sponsor-designated EDC system, if collected external to the EDC system.

Electronic patient-reported outcome (ePRO) measures (for example, a rating scale) or other data reported directly by the patient (for example, daily dosing schedule, event diary) may be entered into an ePRO instrument (for example, personal digital assistant [PDA]), or by means of an interactive response technology system (IRT) at the time the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

If ePRO records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical study database.

Case report form data collected by a third-party will be encoded by the third-party and stored electronically in the third-party's database system. Validated data will subsequently be transferred to the sponsor designated database.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the sponsor designated database.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, a rating scale), a daily dosing schedule, or an event diary.

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

10.3. Study and Site Closure

10.3.1. Discontinuation of Study Sites

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

10.3.2. Discontinuation of the Study

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

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Appendix 1. Abbreviations and Definitions

Term	Definition
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.
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
Blinding/masking	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 patients are aware of the treatment received.
BSA	body surface area
Chorus	A semi-autonomous clinical development organization within Eli Lilly and Company.
CIOMS	Council for International Organizations of Medical Sciences
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

Confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF/eCRF	case report form/electronic case report form (sometimes referred to as clinical report form): A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRO	contract research organization
CRP	Clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CS	corticosteroid
CSE	clinically significant event. A moderate-to-severe adverse event (AE), abnormal clinical sign, or clinical laboratory finding that may pose a risk to the well-being of the patient.
CSR	clinical study report
DLQI	Dermatologic Life Quality Index
DMC	data monitoring committee
DN	Diabetic Nephropathy
DNA	deoxyribonucleic acid
DSUR	Development Safety Update Report
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
End of study	Date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study
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.
ePRO	electronic patient-reported outcome
ERB/IRB	ethical review board/institutional review board: a board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
e-source	electronic source documentation
FSH	follicle stimulating hormone
GCP	good clinical practice
GGT	gamma glutamyltransferase
H_2 receptor	histamine H_2 receptor
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV DNA	hepatitis B virus DNA
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IFN-γ	interferon-gamma
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	interleukin
INR	international normalized ratio
Informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Interim analysis	An interim analysis is an analysis of clinical 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 study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
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 treatment group irrespective of their compliance to the planned course of treatment.
IRT	interactive response technology system
JAK	Janus kinase
JAK1, JAK2, JAK3	kinases belonging to the Janus kinase family
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
Lilly	Eli Lilly and Company
LRL	Lilly Research Laboratories
MMRM	mixed model repeated measures
MOS	margin of safety
NRI	non-responder imputation
NRS	numerical rating scale
PASI	Psoriasis Area and Severity Index
Patient	A study participant who has the disease or condition for which the investigational product is targeted.
PK/PD	pharmacokinetics/pharmacodynamics
PO	per os; oral administration
POCT	point-of-care testing
POEM	Patient-Oriented Eczema Measure

PPD	purified protein derivate
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QIDS-SR16	Quick Inventory of Depressive Symptomatology-Self Report 16
QD	once daily
Randomize	the process of assigning subjects to an experimental treatment group according to the randomization schedule for the study.
RA	Rheumatoid Arthritis
RNA	ribonucleic acid
SAE	serious adverse event; any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.
SAP	statistical analysis plan
SCORAD	SCORing of Atopic Dermatitis
Screening	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.
SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
Th1, Th 2	subsets of T helper cells; T lymphocytes expressing CD4 are also known as helper T cells
TSH	thyroid stimulating hormone.
ULN	upper limit of normal

Appendix 2. Schedule of Activities

Study Schedule of Activities Protocol I4V-MC-JAHG

Procedure	Screening		Treatment Period						Washout Period	Early Term
Study Visit	V1	V1a [a]	V2	V3	V4	V5	V6	V7	V8 (LPV)	
Study Week relative to Start of Investigational Product			0	1	4	8	12	16	20	ET
Study Day Relative to Start of Investigational Product	-38 to -28	1 to 3 days after V1	0	7	28	56	84	112	140	ET
Visit Tolerance Window (days)				±2	±4	±4	±4	±4	±4	
Study Site/CRU Visit	X	X (applicable for PPD only)	X	X	X	X	X	X	X	X
ICF	X									
Clinical Assessments										
Demographics, Height	X									
Weight	X		X		X	X	X	X	X	X
QuantiFERON®-TB Gold, or T-SPOT.TB® test or PPD (read 48-72 hrs later)	X									
Read PPD (if applicable)		X								
ECG (single)-Taken prior to all other assessments at V1	X									
Chest x-ray[b] (posterior-anterior view)	X									
Inclusion/Exclusion Review for Entry	X									
Inclusion/Exclusion Review for Enrollment			X							
Randomization			X							
Medical History and PE	X									
Symptom Directed PE			X	X	X	X	X	X	X	X
Previous AD Therapy	X									
Habits	X									

continued on next page

[a] If the QuantiFERON-TB Gold test or T-SPOT.TB test is available and, if, in the judgment of the investigator, it is preferred as an alternative to the PPD skin test for the evaluation of tuberculosis infection, it may be used instead of the PPD skin test and may be read locally. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient will be excluded from the study.

[b] A posterior-anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available.

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Procedure	Screening		Treatment Period						Washout Period	Early Term
Study Visit	V1	V1a	V2	V3	V4	V5	V6	V7	V8 (LPV)	
Study Week relative to Start of Investigational Product			0	1	4	8	12	16	20	ET
Study Day Relative to Start of Investigational Product	-38 to -28	1 to 3 days after V1	0	7	28	56	84	112	140	ET
Visit Tolerance Window (days)				±2	±4	±4	±4	±4	±4	
Clinical Assessments (continued)										
Vital Signs (BP and pulse)	X		X	X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X		X
Dispense topical corticosteroid (as needed)	X		X	X	X	X	X	X		
Weigh and record topical corticosteroid container with cap	X		X	X	X	X	X	X	X	X
Discontinue all excluded AD medications	X									
Pre-existing Conditions	X									
AEs	X	X	X	X	X	X	X	X	X	X
Investigational Product Package Dispensed			X	X	X	X	X			
Investigational Product Package Returned/Compliance Assessed				X	X	X	X	X		X
Dose administration at site			X				X	X		
EASI	X		X	X	X	X	X	X		X
SCORAD	X		X	X	X	X	X	X		X
IGA	X		X	X	X	X	X	X		X
Itch NRS			X	X	X	X	X	X		X
DLQI			X	X	X	X	X	X		X
POEM			X	X	X	X	X	X		X

continued on next page

Procedure	**Screening**		**Treatment Period**						**Washout Period**	**Early Term**
Study Visit	V1	V1a	V2	V3	V4	V5	V6	V7	V8 (LPV)	
Study Week relative to Start of Investigational Product			0	1	4	8	12	16	20	ET
Study Day Relative to Start of Investigational Product	-38 to -28	1 to 3 days after V1	0	7	28	56	84	112	140	ET
Visit Tolerance Window (days)				±2	±4	±4	±4	±4	±4	
Clinical Assessments (continued)										
QIDS-SR16			X	X	X	X	X	X		X
Actigraphy Device Download				X	X	X	X	X		X
Biopsy performed (NL: non-lesion and L: lesion to be performed following Investigator and Patient rating scale assessments)			X (NL, L)		X (L)			X (NL, L)		
Laboratory Assessments-(collect all non-PK samples pre-dose, as applicable)										
Hematology	X		X		X	X	X	X		X
Serum Chemistry	X		X		X	X	X	X		X
Lipids (fasting)			X					X		
eGFR (CKD EPI)	X		X		X	X	X	X		X
Urinalysis	X		X		X	X	X	X		X
HBsAg, HBcAb, HbsAb (including Quantitative HBsAb load assessment)	X									
HBV DNA	X									

continued on next page

Procedure	Screening		Treatment Period						Washout Period	Early Term
Study Visit	**V1**	**V1a**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8** (LPV)	
Study Week relative to Start of Investigational Product			0	1	4	8	12	16	20	ET
Study Day Relative to Start of Investigational Product	-38 to -28	1 to 3 days after V1	0	7	28	56	84	112	140	ET
Visit Tolerance Window (days)				±2	±4	±4	±4	±4	±4	
Laboratory Assessments (cont.-collect all non-PK samples pre-dose, as applicable)										
Hep C Antibody	X									
HIV	X									
Thyroid Function Tests	X									
Serum Pregnancy Test	X									
Urine Pregnancy Test			X	X	X	X	X	X		X
FSH	X									
Stored serum and plasma for /Exploratory Biomarkers			X		X			X		X
Stored blood for RNA and Exploratory Biomarkers			X		X			X		X
Blood for DNA (filaggrin genotyping)			X							
Plasma for baricitinib Concentration (See PK Sample Collection Visits Table JAHG.5)			X		X	X	X	X		X
Stored blood for pharmacogenetics			X							
Serum for Disease State Biomarkers			X		X			X		

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Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**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
Reticulocyte	Alanine aminotransferase (ALT/SGPT)
Absolute counts of:	Aspartate aminotransferase (AST/SGOT)
Neutrophils, segmented	Blood urea nitrogen (BUN)
Neutrophils, juvenile (bands)	Creatinine
Lymphocytes	Uric acid
Monocytes	Calcium
Eosinophils	Glucose
Basophils	Albumin
Platelets	Total protein
Cell morphology	Estimated glomerular filtration rate (eGFR)[e]
	Creatine phosphokinase (CPK)
Urinalysis[a,b,d]	
Color	**Other Tests**[a]
Specific gravity	Hepatitis B Surface antigen[f]
pH	Anti-Hepatitis B Core antibody[f]
Protein	Quantitative HBsAb load assessment[a]
Glucose	Hepatitis B Surface antibody[f]
Ketones	Human immunodeficiency virus[f]
Bilirubin	Hepatitis C antibody[f,g]
Urobilinogen	Thyroid-stimulating hormone[f]
Blood	Thyroxine[f]
Leukocyte esterase	Pregnancy Test[h]
Nitrite	FSH[f,i]
	Serum immunoglobulin (IgA, IgG, and IgM)
Lipid (Fasting) [a,c]	PPD, QuantiFERON®-TB Gold or T-SPOT.TB® [j]
Total cholesterol	
Low-density lipoprotein	baricitinib
High-density lipoprotein	HBV DNA
Triglycerides	

Abbreviations: CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; DNA = deoxyribonucleic acid; FSH = folliclestimulatinghormone; HBV = Hepatitis B virus;; RBC = red blood cells; RNA = ribonucleic acid; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; TB = tuberculosis; WBC = white blood cells.

a Assayed by sponsor-designated laboratory.

b Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.

c Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test.

d Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.

e eGFR for serum creatinine calculated by the central laboratory using the -CKD EPI method.

f Test required at Visit 1 only to determine eligibilityof patient for the study.

g A positive hepatitis C antibody (Hep C antibody) result will be confirmed with an alternate hepatitis C method.
h For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a local urine pregnancy test will be performed at all visits thereafter.
i To confirm postmenopausal status for women ≥40 and <60 years of age who have had a cessation of menses, an FSH test will be performed. Non-childbearing potential is defined as an FSH ≥40 mIU/mL and a cessation of menses for at least 12 months.
j The QuantiFERON®-TB Gold test is the preferred alternative to the PPD test for the evaluation of TB infection, and it may be used instead of the PPD test or T-SPOT.TB® test and may be read locally. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

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 sponsor, its designee, or clinical research physician.

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	
	Anti-smooth muscle antibody[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by sponsor-designated or local laboratory.

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

Appendix 5. Protocol 14V-MC-JAHG Signature Page

I confirm that I have read this protocol; I understand it and I will work according to this protocol. I will also work consistently with the ethical principles that have their 01igin in tlte Declaration of Helsinki and that are consistent with good clinical practices and applicable laws and regulations. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my Agreement with the sponsor (Choms, Eli Lilly and Company) or designee. I will promptly submit the protocol to applicable ethical review board(s). I confirm that ifl or any of mystaff are members of tlte ethical review board, we will abstain from voting on this protocol.

Instructionsto the Investigator. Please SIGN and DATE this signature page. PRINT your name, title andthe nameof thefacility in which thestudy willbe cooducted oo bothcopies. **Return** 1 ***ot*** the ·s nedc ·esto the sponsor (Chorus, Eli Lilly and Company) or designee.

Signatme of Investigator

Date

Investigator Name (Title)

Name of Facility

Location of Facility
(City, State (if applicable), Country)

Signatme of sponsor

Date (dd-mmm-yyyy)

PD (Chief Medical Officer, Choms-Eli Lilly and Company)

Sponsor name (Title)

Eli Lilly and Company

Name

Lilly Corporate Center, Indianapolis, Indiana, USA

Location (City, State (if applicable), Country)

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