Protocol I4V-MC-JAIX(c)

A Multicenter, Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Moderate to Severe Atopic Dermatitis

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BREEZE-AD6

Baricitinib (LY3009104)

Study I4V-MC-JAIX is a Phase 3, multicenter, open-label, outpatient, 204-week study designed to evaluate the efficacy and safety of baricitinib 2-mg in patients with moderate to severe atopic dermatitis.

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1. Synopsis

Title of Study:
A Multicenter, Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Moderate to Severe Atopic Dermatitis

Rationale:
Atopic dermatitis (AD) is a pruritic, chronic or chronically relapsing, highly symptomatic inflammatory skin disease characterized by excessive T cell activation leading to significant skin infiltration by T cells and dendritic cells (Bieber 2010). Presentation is varied, but includes skin manifestations and pruritus, with associated sleep disturbances and subsequent skin infections. The course of disease includes relapses of varying duration and severity.

Baricitinib is an orally available, selective Janus kinase (JAK) inhibitor with potency and selectivity for JAK1 and JAK2 and less potency for JAK3 or tyrosine kinase 2 (TYK2) (Fridman et al. 2010). The pathogenesis of AD is thought to be modulated through thymic stromal lymphopoietin (TSLP), interleukin (IL)-13, IL-4, IL-5, IL-22, and IL-31, many of which activate receptors with downstream signaling through intracellular JAK1/JAK2/TYK2 (Nomura and Kabashima 2016). This activity profile suggests that baricitinib would inhibit many of the cytokines involved in AD pathogenesis.

Clinical studies have established that baricitinib is effective in autoimmune/autoinflammatory diseases involving the joints, kidneys, and skin. Baricitinib was effective at reducing swollen and tender joints in patients with rheumatoid arthritis (Genovese et al. 2016; Dougados et al. 2017; Fleischmann et al. 2017; Taylor et al. 2017); was effective at reducing disease severity in patients with moderate to severe plaque psoriasis (Papp et al. 2016); was effective at reducing the urinary albumin-to-creatinine ratio in patients with diabetic kidney disease (Tuttle et al. 2015); and in a recently completed Phase 2 study (Study I4V-MC-JAHG) was effective at reducing disease severity in patients with moderate to severe AD. The mechanism of action, combined with demonstration of clinical benefit in inflammatory diseases involving joints, kidneys, and skin, provides the rationale for evaluating baricitinib in moderate to severe AD.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To describe the clinical response to baricitinib 2-mg QD in patients with moderate to severe AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) and responder status achieved in Study I4V-MC-JAIW (JAIW).	• Proportion of patients achieving EASI75 from baseline of originating study, assessed at Week 16
Secondary	
To describe the clinical response to baricitinib 2-mg QD in AD as measured by improvement in signs and symptoms of AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) and responder status achieved in Study JAIW.	• Proportion of patients achieving IGA of 0 or 1 assessed at Week 16 • Proportion of patients achieving IGA of 0 or 1 assessed at or before Week 16 • Proportion of patients achieving EASI75 from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline in EASI score from baseline of originating study, assessed at Week 16 • Proportion of patients achieving a BSA of ≤3% assessed at or before Week 16
To describe the clinical response to baricitinib 2-mg QD in AD as assessed by patient-reported outcome measures by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) and responder status achieved in Study JAIW.	• Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of originating study, assessed at Week 16 • Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline of originating study, in Itch NRS assessed at Week 16

Abbreviations: AD = atopic dermatitis; BSA = body surface area EASI = Eczema Area and Severity Index; EASI75 = 75% improvement from baseline in EASI; IGA = Investigator's Global Assessment; NRS = numeric rating scale; QD = once daily.

Summary of Study Design:

Study I4V-MC-JAIX (JAIX) is a Phase 3, multicenter, open-label outpatient study evaluating the efficacy and safety of baricitinib 2-mg once daily (QD) in adult patients with moderate to severe AD. The study population will include patients 18 years or older with a history of inadequate response or intolerance to existing topical therapies, and who have completed protocol-defined minimal participation in Study JAIW based on responder status.

The study duration will be up to 204 weeks over 2 study periods:

- Period 1: Open-Label Treatment Period, lasting from Week 0 (baseline, Visit 1) through Week 200 (Visit 17).
- Period 2: Post-Treatment Follow-Up Period (Visit 801), spanning the period from the last treatment visit at Week 200 (Visit 17) or Early Termination Visit (ETV) to approximately 4 weeks following the last dose of investigational product.

Treatment Arms and Duration:

Patients will be assigned at baseline to open-label treatment with baricitinib 2-mg QD. The study duration will be up to 204 weeks (Open-Label Treatment Period: 200 weeks; Post-Treatment Follow-Up Period: approximately 4 weeks after the last dose of investigational product).

Number of Patients:

This study will include up to 450 patients with AD who will be treated with baricitinib 2-mg QD.

Statistical Analysis:

Unless otherwise specified, the efficacy and health outcomes summaries will be conducted on all enrolled patients who receive at least 1 dose of investigational product in Study JAIX, even if the patient does not follow the protocol, and safety analyses will be conducted on all enrolled patients who receive at least 1 dose of investigational product and who do not discontinue from the study for the reason "Lost to Follow-up" at the first postbaseline visit.

Treatment comparisons of discrete efficacy variables between prior-treatment-received groups may be performed using group percentages. All patients who discontinue the study or study treatment at any time for any reason will be defined as nonresponders for the nonresponder imputation (NRI) analysis for categorical variables after discontinuation onward.

Continuous efficacy variables will be descriptively summarized in terms of number of patients, mean, standard deviation, median, minimum, and maximum.

Frequencies and percentages will be computed for adverse event (AE), discontinuation, and other categorical safety data.

2. Schedule of Activities

Table JAIX.1. Schedule of Activities

	Period 1: Open-Label Treatment Period																	Period 2: PTFU
Visit Number	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ET[b]**	**801[c]**
Weeks from entry into JAIX	**0**	**4**	**8**	**16**	**24**	**36**	**52**	**64**	**76**	**88**	**104**	**120**	**136**	**152**	**168**	**184**	**200**	**204**
Visit tolerance interval (days) from entry into JAIX	**0[d]**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28±4 after last dose**
Procedures																		
Inclusion and exclusion review	X																	
Informed consent	X																	
Abbreviated demographics	X																	
Clinical Assessments																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP and pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ePRO (patient diary) dispensed	X	X	X															
ePRO (patient diary) returned		X	X	X[e]														
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP dispensed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IP returned and compliance assessed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense TCS[f]	X	X	X	X	X	X	X	X	X	X								
Weigh (tube with cap) and record returned TCS (as needed)		X	X	X	X	X	X	X	X	X	X						X[b]	X
Scales																		
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Period 1: Open-Label Treatment Period																	Period 2: PTFU
Visit Number	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ET[b]**	**801[c]**
Weeks from entry into JAIX	**0**	**4**	**8**	**16**	**24**	**36**	**52**	**64**	**76**	**88**	**104**	**120**	**136**	**152**	**168**	**184**	**200**	**204**
Visit tolerance interval (days) from entry into JAIX	**0[d]**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28±4 after last dose**
Health Outcomes Measures and Other Questionnaires[g]																		
Itch NRS	X	X	X	X[e]														
Skin Pain NRS	X	X	X	X[e]														
ADSS	X	X	X	X[e]														
PGI-S-AD	X	X	X	X[e]														
POEM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X	X	X	X	X						X[b]	X
EQ-5D-5L		X	X	X							X						X[b]	X
WPAI-AD		X	X	X							X						X[b]	X
C-SSRS and Self-Harm Supplement[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-Up Form[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																		
Lipids (fasting)[j]	X[k]			X		X	X		X		X	X	X	X	X	X	X[l]	X
Clinical chemistry[m]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA[n]	X[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X[k]	X	X	X	X	X	X	X	X	X	X						X[o]	X
Urine pregnancy[p]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunoglobulin (IgE)	X			X			X				X						X[o]	
Exploratory storage samples (serum and plasma)	X			X			X				X						X[o]	
RNA and biomarkers: blood	X			X			X				X						X[o]	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale 11 categories suicidal ideation/suicidal behavior; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D-5L = the European Quality of Life–5 Dimensions 5 Levels; ET = early termination; ePRO = electronic patient-reported outcomes (device); HADS = Hospital Anxiety Depression Scale; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibody; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; IP = investigational product; IWRS = interactive web-response system; NRS = numeric rating scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PTFU = post-treatment follow-up; SCORAD = SCORing Atopic Dermatitis; TCS = topical corticosteroids; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

[a] Any assessments/procedures conducted during the final visit of the patient's originating study (Study JAIW) should not be repeated during their first visit for Study JAIX.

[b] An ET visit should be conducted if a patient discontinues from the study before Week 200. Early termination visit activities do not need to be duplicated if occurring at the time of a scheduled visit. Weighing of TCS and collection of HADS, EQ-5D-5L, and WPAI-AD are not to be performed at Study Visit 17; these activities should only be performed at the ET visit if it occurs at or before Week 104.

[c] Visit 801 is the PTFU visit, which occurs after the patient has been off baricitinib/IP for approximately 4 weeks. Patients who have permanently discontinued IP but remain in the study for more than 28 days without IP will only complete Visit 17/ET; Visit 801 (follow-up visit) is not required.

[d] Screening should occur during the LPV of the originating study. It may be permissible for screening to occur after the last visit of the originating study if needed, upon approval from the sponsor.

[e] Applies to ET visit if conducted prior to Week 16 only.

[f] Only required at investigator discretion. Sponsor provided low potency TCS will be available to dispense to patients at anytime prior to study visit 11. At visit 11 and after, low potency TCS is allowed as background therapy but will not be provided by the sponsor or reimbursed by the sponsor.

[g] The following measures (POEM, DLQI, HADS, EQ-5D-5L, WPAI-AD) should be completed prior to any clinical assessments being performed on days when study visits occur.

[h] Suicidal ideation and behavior subscales excerpt—adapted for the assessment of 11 preferred ideation and behavior categories.

[i] The Self-Harm Follow-Up Form is required only if triggered by the Self-Harm Supplement Form.

[j] Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Unscheduled lipid testing can be performed at the discretion of the investigator.

[k] If laboratory examinations have been performed ≤4 weeks from previous study visit, then they do not need to be repeated.

[l] For ET visits, collect fasting lipids when possible.

[m] Clinical chemistry will include the following value calculated from serum creatinine: estimated glomerular filtration rate (eGFR; calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine 2009 equation).

[n] Patients who are positive for HBcAb and negative for HBV DNA may be enrolled. Any enrolled patient who is HBcAb positive as determined at screening of originating study, Study JAIW, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule.

[o] Urinalysis, serum IgE, exploratory storage samples, and RNA and biomarker samples are only collected for ET visits occurring at or before Week 104. These samples are not collected as a component of Visit 17.

[p] For all women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at all specified visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

3. Introduction

3.1. Background

Atopic dermatitis (AD), also known as eczema or atopic eczema, is a common, chronic, relapsing, highly symptomatic inflammatory skin disease (Bieber 2010). Patients with AD may present with skin lesions that can be acute with oozing, crusted, eroded vesicles or papules on erythematous plaques. Patients may also present with lesions that have a subacute appearance, with thick and excoriated plaques, or chronic appearance, with lichenified, slightly pigmented, excoriated plaques (Bieber 2010). AD causes pruritus attacks throughout the day, which is the primary source of morbidity in this disorder (Simpson 2012). Pruritus often leads to an "itch–scratch" cycle, further compromising the epidermal barrier and resulting in dry skin, microbial colonization, and secondary infections (Krakowski et al. 2008), with 36% of patients reporting that they often or always scratch until their skin bleeds (Langenbruch et al. 2014). Pruritus from AD can worsen at night, resulting in sleep disturbances, with approximately 27% of adult patients with AD experiencing sleep disturbance as a result of itching (Langenbruch et al. 2014). In adult patients with moderate to severe AD, poor sleep quality and latency were significantly associated with poor quality of life (Yano et al. 2013).

In clinical practice, AD is classified as mild, moderate, or severe based on a variety of clinical features, including severity of skin lesions and pruritus and extent of disease (body surface area [BSA] involved).

Until recently, there were no US Food and Drug Administration-approved systemic treatments for patients with moderate to severe AD, with the exception of systemic corticosteroids. In March 2017, Dupixent® (dupilumab) injection, an IgG4 monoclonal antibody that inhibits IL-4 and IL-13, was approved by the US Food and Drug Administration for this patient population. In the European Union, only cyclosporine has been approved for the treatment of patients with severe AD (Bieber and Straeter 2015). A recently completed Phase 2 study (Study I4V-MC-JAHG [JAHG]) evaluated the safety and efficacy of baricitinib (a JAK inhibitor) in AD, and results showed significant improvement in disease severity compared to placebo, and no new safety concerns were identified.

In addition to AD, baricitinib has also been studied in Phase 3 in patients with rheumatoid arthritis (RA) and in Phase 2 in patients with diabetic nephropathy, moderate to severe psoriasis, and systemic lupus erythematosus.

Through 13 February 2019, baricitinib has been studied in more than 548 healthy volunteers and 6555 patients have received baricitinib in clinical studies. As of 13 February 2018, more than 2700 patients have been treated with baricitinib for more than a year and more than 1800 patients have been treated with baricitinib for more than 2 years at doses of 2-mg once daily or 4-mg once daily across the RA clinical program. Baricitinib has been administered as single doses ranging from 1- to 40-mg and as repeat oral doses ranging from 2- to 20-mg to healthy subjects. Baricitinib has also been administered to patients with RA at doses up to 15-mg daily for 4 weeks, 10-mg daily for 24 weeks, 8-mg daily for 76 weeks, and lower doses up to 4-mg daily for up to approximately 7 years.

3.2. Study Rationale

The underlying cause of AD is not completely understood. Loss of function mutations in the gene for *filaggrin* (filament aggregating protein), a key protein in terminal differentiation of the epidermis contributing to barrier function, has been identified as the strongest genetic risk factor for AD in European populations (Palmer et al. 2006). At a cellular level, AD is characterized by excessive T cell activation caused by genetic and environmental factors, leading to significant skin infiltration by T cells and dendritic cells. The cytokine TSLP is thought to act as a master switch that triggers the initiation and maintenance of AD (Moniaga et al. 2013; Ziegler et al. 2013). Overexpression of TSLP in keratinocytes, the most prevalent cell type in the skin, triggers robust itch-evoked scratching and the development of an AD-like skin phenotype in mice (Li et al. 2005). In addition to directly inducing itch by activating sensory neurons in the skin, TSLP also enhances maturation and differentiation of dendritic cells and naive CD4+ T cells and induces production of Th2-related cytokines involved in AD pathogenesis (Wilson et al. 2013; Divekar and Kita 2015). TSLP and other key cytokines involved in AD pathogenesis, such as IL-13, IL-5, IL-22, and IL-31, signal through receptors associated with intracellular JAK1/JAK2/TYK2 signaling (Ziegler et al. 2013; Nomura and Kabashima 2016).

JAKs are a family of tyrosine kinases that mediate cytokine receptor signalling through phosphorylation and activation of signal transducers and activators of transcription proteins. There are 4 known JAK family members: JAK1, JAK2, JAK3, and TYK2 (Clark et al. 2014). The relative affinity of JAK inhibitors for different members of the JAK kinase family allows for differentiation of JAK inhibitors in relation to their enzymatic inhibitory profile. In vitro assays indicate that baricitinib is a selective inhibitor of JAKs with potency and selectivity for JAK1/2 and less potency for JAK3 or TYK2 (Fridman et al. 2010). The balanced JAK1/JAK2 inhibitory profile of baricitinib suggests that baricitinib will have the greatest modulatory effect in cytokines signalling through a JAK1/JAK2 heterodimer intracellularly (or a JAK1/JAK2/TYK2), such as IL-6, TSLP, IL-13, or IL-31 (Vaddi and Luchi 2012).

The recently completed Phase 2 study of baricitinib in AD, Study JAHG, met its primary objective of proportion of patients achieving a 50% improvement from baseline in Eczema Area and Severity Index (EASI50) scores compared to placebo. Baricitinib also showed statistically significant improvements for other disease severity analyses as well as multiple different patient-reported outcome scales compared to placebo, further validating the hypothesis that JAK1/JAK2 signaling plays a key role in AD pathogenesis. Phase 3 placebo-controlled studies are ongoing to define baricitinib efficacy in AD. This open-label, long-term extension study is designed to further assess long-term efficacy and safety of baricitinib in patients with moderate to severe AD, who did not achieve Investigator's Global Assessment [IGA] 0 or 1 in the originating study, Study I4V-MC-JAIW (JAIW). This will allow patients originally randomized to baricitinib 1-mg or placebo in Study JAIW to have the opportunity for treatment with baricitinib 2-mg QD, and also assess the longer-term clinical utility of the 2-mg dose beyond achieving an IGA 0,1. In addition, this study will give patients completing Study JAIW as responders the opportunity for ongoing access to baricitinib 2-mg.

3.3. Benefit/Risk Assessment

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

Additional information about the known and expected benefits, risks, serious AEs (SAEs), and reasonably anticipated AEs of baricitinib can be found in the investigator's brochure (IB).

4. Objectives and Endpoints

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

Table JAIX.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe the clinical response to baricitinib 2-mg QD in patients with moderate to severe AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) and responder status achieved in Study I4V-MC-JAIW (JAIW)	• Proportion of patients achieving EASI75 from baseline of originating study, assessed at Week 16
Secondary	
To describe the clinical response to baricitinib 2-mg QD in AD as measured by improvement in signs and symptoms of AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) and responder status achieved in Study JAIW.	• Proportion of patients achieving IGA of 0 or 1 assessed at Week 16 • Proportion of patients achieving IGA of 0 or 1 assessed at or before Week 16 • Proportion of patients achieving EASI75 from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline in EASI score from baseline of originating study, assessed at Week 16 • Proportion of patients achieving a BSA of ≤3% assessed at or before Week 16
To describe the clinical response to baricitinib 2-mg QD in AD as assessed by patient-reported outcome measures by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) and responder status achieved in Study JAIW.	• Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of originating study, assessed at Week 16 • Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline of originating study, in Itch NRS assessed at Week 16
Exploratory Objectives/Endpoints	
• Exploratory objectives may include evaluating the response to baricitinib treatment regimens on clinical measures and patient reported outcomes. These endpoints may include dichotomous endpoints or change from baseline for the following measures: IGA, EASI, SCORAD, POEM, HADS, DLQI, WPAI-AD, EQ-5D-5L, Itch NRS, ADSS Item 2 score, Skin Pain NRS, PGI-S-AD.	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI75 = 75% improvement from baseline in EASI; EQ-5D-5L = the European Quality of Life–5 Dimensions–5 Levels; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; NRS = numeric rating scale; QD = once daily; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; WPAI-AD = Work Productivity and Activity Impairment – Atopic Dermatitis.

5. Study Design

5.1. Overall Design

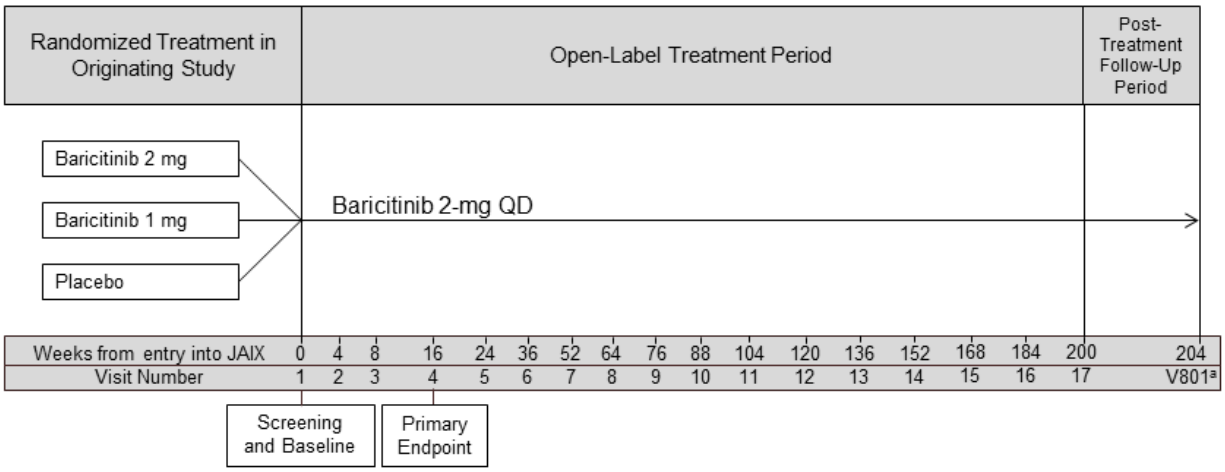
Study I4V-MC-JAIX (JAIX) is a Phase 3, multicenter, open-label, outpatient study evaluating the efficacy and safety of baricitinib 2-mg QD in adult patients with moderate to severe AD. The study is divided into 2 periods; a 200-week Open-Label Treatment period, and a 4-week Post-Treatment Follow-Up period. The following patients will be eligible to participate in this study:

- Partial Responders (IGA 2 at Week 16 of Study JAIW)
- Previous Responders at Week 16 of Study JAIW (IGA 0 or 1): Patients who were responders at Week 16 of Study JAIW, and thus remain in Study JAIW but later experience loss of response resulting in an IGA ≥3 (or requiring more than low-potency TCS after Week 16 to manage symptoms)
- Nonresponders (IGA 3 or 4 at Week 16 of Study JAIW or rescued with topical [e.g. TCS, TCNI] or systemic therapies prior to Week 16)
- Responders who completed Study JAIW through Week 104 (Visit 15)

Approximately 300 patients who have been discontinued from Study JAIW may be eligible to enroll in this study. Patients who complete Study JAIW through Visit 8 (Week 16) can enter Study JAIX. In addition, patients who complete Study JAIW as responders may be eligible to enroll in this study. For most patients, the last visit of the originating study will be the first visit and screening/baseline period for Study JAIX. Patients will have been using emollients daily in their originating study and this will continue during Study JAIX participation. Starting at baseline, patients will be treated with open-label baricitinib 2-mg QD for up to 200 weeks.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Section 2). Section 9.4.3 describes collection of laboratory samples; Appendix 2, Appendix 4, Appendix 5, and Appendix 6 list the specific laboratory tests that will be performed for this study. Study governance considerations are described in detail in Appendix 3. The IGA tool to be used in this study is included in Appendix 8.

Figure JAIX.1 illustrates the study design. The dosing regimen is described in Section 7.1.



Abbreviations: AD = atopic dermatitis; QD = once daily; V = visit; W = week.
[a] Occurs approximately 28 days after the last dose of investigational product.

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

5.1.1. Period 1: Open-Label Treatment, Weeks 0 to 200

Screening should occur during the last visit of the originating study. Study eligibility for each patient will be reviewed based on all enrollment criteria (Section 6). Patients who meet all criteria will have treatment allocated by interactive web-response system (IWRS) and begin their treatment period at Visit 1. Patients who meet all of the inclusion and none of the exclusion criteria (Section 6) will be enrolled in the study. It may be permissible for screening to occur after the last visit of the originating study if needed, upon approval from the sponsor. For example, patients requiring elective procedures may want to have those in between studies, or responders who complete Visit 15 of Study JAIW have the option to delay enrollment into open-label Study JAIX to assess response while off investigational product.

Patients who received oral systemic AD treatment and/or topical rescue therapy during the originating study must discontinue use of the prohibited medications listed in Section 7.7.1 prior to initiating IP in Study JAIX. Low-potency TCS (e.g., hydrocortisone 2.5% ointment) is permitted (Section 7.7.2).

Patients will receive open-label baricitinib 2–mg QD. Investigational product will be administered daily for a maximum of 200 weeks (treatment period Visits 1 through 17; see Section 7). All patients will be required to use emollients daily. Daily diaries will continue to be utilized through Week 16. Download of this data will be required at study visits. Patients are allowed to use low potency TCS (e.g., hydrocortisone 2.5% ointment) in combination with investigational product. Rescue with higher potency TCS, topical calcineurin inhibitors (TCNIs), or systemic therapies is not allowed. Assessments of disease severity will be performed by the investigator as described in the Schedule of Activities (Section 2).

The primary efficacy endpoint will be at Week 16 (Visit 4). All patients who permanently discontinue investigational product prior to the primary endpoint should complete an ETV and post-treatment follow-up visit.

At Week 16, all patients should be formally assessed to determine if sufficient clinical benefit has been observed to justify continuing in this study. Clinical benefit is defined as meeting at least 1 of the following criteria during the first 16 weeks:

- IGA score of 0 or 1 with a ≥2-point improvement from baseline of originating study,
- ≥4-point improvement from baseline of originating study in Itch NRS,
- EASI-75 from baseline of originating study, or
- BSA involvement of ≤3%.

If a patient achieves any of these treatment goals during the first 16 weeks of the treatment period, the patient will be allowed to continue in the study. Although formal criteria for sufficient clinical benefit should be assessed at Week 16, investigators are strongly encouraged to discontinue patients who have not shown signs of clinical benefit by Week 8 of Study JAIX, defined as improvement in IGA, itch NRS, EASI, or BSA. Attention should be given to patients treated continuously for 16 weeks during Study JAIW (no IP discontinuation for systemic rescue therapy) and who then show no benefit in Study JAIX, to avoid exposing patients to a potentially ineffective therapy for an additional 16 weeks before discontinuation. Since no rescue therapies are available during this study, patients requiring more than low-potency TCS at any time during the study will be discontinued.

5.1.2. Period 2: Post-Treatment Follow-Up

Patients who complete the study through Visit 17 (Week 200) will have a post-treatment follow-up visit (Visit 801) approximately 28 days after the last dose of investigational product.

Patients who have received at least 1 dose of investigational product and discontinue early from the study should have an ETV, and return for the post-treatment safety follow-up visit (Visit 801) approximately 28 days after the last dose of investigational product.

Patients who have discontinued investigational product but remain in the study for more than 28 days without investigational product will have an ETV if they choose to discontinue early; however, a separate follow-up visit (V801) is not required.

Patients should not initiate new systemic AD treatment during this period. However, if patients or investigators must initiate treatment, investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any new treatment. An unscheduled visit can be used for this purpose if necessary.

5.2. Number of Participants

Up to 450 participants may be enrolled.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

This open-label long-term extension study will enroll moderate to severe AD patients who have completed Visit 8, Week 16 of Study JAIW but who did not achieve IGA 0,1, or who experience loss of response after Week 16, or who complete Study JAIW as responders at Visit 15, Week 104. This study will further assess long-term efficacy and safety of baricitinib in this population. This will allow patients originally randomized to baricitinib 1-mg or placebo in Study JAIW to have the opportunity for treatment with baricitinib 2-mg QD, and also assess the longer-term clinical utility of the 2-mg dose beyond achieving an IGA 0,1.

During the open-label treatment period, patients will be treated with baricitinib 2-mg, which has been shown to be efficacious in the Phase 2 study in AD (JAHG). Patients will also be allowed to use low-potency TCS (e.g., hydrocortisone 2.5% ointment) as background therapy for comfort if needed. Daily treatment with emollient will continue. To avoid confounding effect of topical therapies, higher-potency TCS, as well as TCNIs and topical phosphodiesterase type 4 (PDE-4) inhibitors are not allowed at any time during the study. If a patient does not experience sufficient clinical benefit during the study, the patient should be discontinued. The criteria for determining sufficient clinical benefit are discussed in Section 5.1.1. This 4-year-long study will generate important long-term efficacy and safety data in AD.

The post-treatment follow-up period (Period 2) is for safety monitoring after the patient has been off investigational product for approximately 28 days.

5.5. Justification for Dose

The dose used in Study JAIX is baricitinib 2-mg QD. This dose was chosen primarily on the basis of the recently completed Phase 2 AD study, Study JAHG, and is additionally supported by pharmacokinetic, safety, and efficacy data for baricitinib in Phase 2 and Phase 3 RA studies and a Phase 2 psoriasis study.

In the Phase 2 Study JAHG, baricitinib 2-mg showed benefit on the clinically important endpoints (EASI, IGA, SCORAD, POEM, and DLQI) as compared to placebo, and had an acceptable safety profile at Week 16. To ensure that all patients participating in the originating study, Study JAIW, have the opportunity to receive the highest dose proposed in the study, this open-label study will treat all patients with the 2-mg dose.

6. Study Population

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

Study investigator(s) will determine if the patient meets all inclusion criteria and none of the exclusion criteria to qualify for enrollment in the study. All screening activities must be completed and reviewed before the patient is enrolled.

6.1. Inclusion Criteria

Type of Patient and Disease Characteristics

[1] have completed the minimum number of visits based on responder status in Study JAIW

- nonresponder/partial responder: have completed at least 16 weeks of treatment in Study JAIW (i.e., Visit 8, Week 16)

  A nonresponder/partial responder is defined as a patient who met at least 1 of the following in Study JAIW:

  - did not achieve an IGA of 0 or 1 at Week 16, or
  - achieved an IGA ≥3 after Week 16, or
  - required rescue therapy at any time.

or

- responder: have completed the full treatment period of Study JAIW (i.e., Visit 15, Week 104)

  A responder is defined as a patient who achieved IGA 0 or 1 and who did not require rescue therapy at or before Week 16 in Study JAIW.

[2] are able to read, understand, and give documented (electronic or paper signature) informed consent.

[3] are male or nonpregnant, nonbreastfeeding female patients, and

a. Male patients will either remain abstinent (if this is their preferred and usual lifestyle) or agree to use 2 forms of birth control (1 must be highly effective, see below) while engaging in sexual intercourse with female partners of childbearing potential while enrolled in the study and for at least 4 weeks following the last dose of investigational product.

   Men who are in exclusively same sex relationships (when it is their preferred and usual lifestyle) are not required to use contraception.

b. Female patients of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

   Otherwise, female patients of childbearing potential must agree to use 2 forms of birth control when engaging in sexual intercourse with a male partner while enrolled in the study and for at least 4 weeks following the last dose of investigational product.

   The following birth control methods are considered acceptable (the patient should choose 2 to be used with their male partner, and 1 must be highly effective):

   - Highly effective birth control methods: oral, injectable, or implanted hormonal contraceptives (combined estrogen/progesterone or progesterone only, associated with inhibition of ovulation); intrauterine device or intrauterine system (for example, progestin-releasing coil); or, vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
   - Effective birth control methods: 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; or, oral hormonal contraceptives.

     Note: When local guidelines concerning highly effective or effective methods of birth control differ from the above, the local guidelines must be followed.

c. Females of nonchildbearing potential are not required to use birth control. They are defined as:

   - women aged ≥60 years or women who are congenitally sterile, or
   - women aged ≥40 and <60 years who have had a cessation of menses for ≥12 months and a follicle-stimulating hormone test confirming nonchildbearing potential (≥40 mIU/mL or ≥40 IU/L), or women who are surgically sterile (that is, have had a hysterectomy or bilateral oophorectomy or tubal ligation).

6.2. Exclusion Criteria

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

[4] are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[5] have significant uncontrolled cerebro-cardiovascular (e.g., myocardial infarction [MI], unstable angina, unstable arterial hypertension, severe heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that developed during a previous baricitinib study that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered.

[6] have a history of VTE, or are considered at high risk of VTE as deemed by the investigator.

[7] Have a known hypersensitivity to baricitinib or any component of this investigational product.

[8] Had investigational product permanently discontinued at any time during a previous baricitinib study, except for patients who had investigational product discontinued during originating study because of rescue with an oral systemic AD therapy (e.g., corticosteroid, cyclosporine, methotrexate).

[9] Had temporary investigational product interruption continue at the final study visit of a previous baricitinib study and, in the opinion of the investigator, this poses an unacceptable risk for the patient's participation in the study.

[10] Have any other condition that, in the opinion of the investigator, renders the patient unable to understand the nature, scope, and possible consequences of the study or precludes the patient from following and completing the protocol.

[11] Are unwilling or unable to comply with the use of a data collection device to directly record data from the subject.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. Treatments

7.1. Treatments Administered

This study involves baricitinib 2-mg administered orally QD. Table JAIX.3 shows the treatment regimen.

Table JAIX.3. Treatment Regimen

Regimen	Investigational Product Supplied	Dose
Baricitinib 2–mg QD	Baricitinib 2-mg tablet	1 tablet per day

Abbreviation: QD = once daily.

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

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

7.1.1. Packaging and Labeling

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

- tablets containing 2-mg of baricitinib

Investigational product tablets will be provided in bottles. Clinical trial materials will be labeled according to the country's regulatory requirements. **Patients will be instructed to take 1 tablet each day.**

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will receive baricitinib 2-mg at Visit 1 (Week 0). Site personnel will confirm that they have located the correct bottles by entering the confirmation number found on the bottle into an interactive web-response system (IWRS).

7.2.1. Selection and Timing of Doses

The investigational product (1 tablet) should be taken once daily without regard to food and, if possible, at approximately the same time every day, usually at the start of the patient's day, to aid patient compliance.

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

All investigational product (used and partially used) will be returned to the sponsor or destroyed at site level with the sponsor's written approval. In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Follow storage and handling instructions on the investigational product packaging.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit during the treatment period (Visit 2 through Visit 17) by counting returned tablets.

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

Patients will be counseled by study staff on the importance of taking the investigational product as prescribed, as appropriate.

Patients' compliance will be further defined in the statistical analysis plan (SAP).

7.7. Concomitant Therapy

All concomitant medication, whether prescription or over the counter, used at baseline and/or during the course of the study, must be recorded on the Concomitant Medication electronic case report form (eCRF). Patients will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study. For AD therapies permitted as part of rescue therapy, see Section 7.7.3.

7.7.1. Prohibited Medications and Procedures

Prohibited Medications and Procedures Not Requiring Interruption of Investigational Product

The following therapies will not be allowed during the study.

- Medium-potency TCS or higher potency TCS, TCNIs (for example, tacrolimus and pimecrolimus), or topical PDE-4 inhibitor (that is, crisaborole) are not allowed. Low-potency TCS is allowed (see Section 7.7.2).
- Allergen immunotherapy.
- Phototherapy including PUVA (psoralen and ultraviolet A), ultraviolet B, tanning booth and excimer laser.
- Bleach baths

Prohibited Medications Requiring Temporary Interruption of Investigational Product

The following therapies will not be allowed during the course of the study and, if taken by or administered to the patient, temporary interruption of investigational product is required.

- Live vaccines (including Bacillus Calmette-Guérin [BCG] or herpes zoster)
    - For BCG vaccination, investigational product should be temporarily interrupted for 12 weeks.
    - For herpes zoster vaccination, investigational product should be temporarily interrupted for 4 weeks.
- Probenecid: if a patient is inadvertently started on probenecid, investigational product should be temporarily interrupted and can be resumed after patient has discontinued probenecid. If a patient is not able to discontinue probenecid, then investigational product should be permanently discontinued.
- Systemic corticosteroids may be used for the treatment of an AE (for example, worsening of existing condition, such as asthma flare). Investigational product may be restarted if systemic corticosteroids were used for a short duration (<30 days). If used for >30 days, sponsor approval to restart investigational product is required. Systemic corticosteroids may not be used to treat AD.

Prohibited Medications Requiring Permanent Discontinuation of Investigational Product

- Any systemic therapy, investigational or commercial (approved or off-label use), used for the treatment of AD or symptoms of AD (except for antihistamines, as specified below).
- Other JAK inhibitors (for example, tofacitinib and ruxolitinib).
- Systemic immunosuppressive/immunomodulatory substances, including, but not limited to cyclosporine, methotrexate, mycophenolate mofetil, interferon γ, azathioprine, or biologic agents.

7.7.2. Permitted Medications and Procedures

Treatment with concomitant AD therapies during the study is permitted only as described below.

- Daily use of emollients is required as background treatment. Moisturizers with additives such as antipruritics or antiseptics are not permitted. If daily applications are missed, it will not be considered a protocol violation.
  - Patients should not apply emollients on the day of their study visit before study procedures to allow adequate assessment of skin dryness.
- Antihistamines are allowed.
- Intra-articular or soft tissue (bursa, tendons, and ligaments) corticosteroid injection: No more than 1 intra-articular or soft tissue (bursa, tendons, and ligaments) corticosteroid injection is allowed up until Week 16 (Visit 4). After Week 16, such injections are permitted.
- Intranasal or inhaled steroid use is allowed.
- Topical anesthetics and topical and systemic anti-infective medications are allowed.
- Nonlive seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed.
- Low-potency TCS (for example, hydrocortisone 2.5% ointment) is permitted.
  - Patients should not apply TCS on the day of their study visit before study procedures to allow adequate assessment of skin dryness.

Any changes of these concomitant medications must be recorded in the Concomitant Therapy of Special Interest eCRF.

Treatment with concomitant therapies for other medical conditions such as diabetes and hypertension is permitted during the study.

7.7.3. Rescue Therapy

No rescue therapy options are available during the study. Patients are allowed to use low-potency TCS as background therapy for comfort if needed. Patients who experience worsening and unacceptable symptoms of AD should consider discontinuing from the study. Patients requiring more than low-potency TCS to manage their symptoms should also be discontinued.

Hydrocortisone 2.5% ointment will be supplied by the sponsor for use during the first 2 years of the treatment period (dispensed at Visits 1-10 only). In the event that providing this topical formulation during the first 2 years is not possible, an alternate, equivalent potency TCS cream and/or ointment may be provided by the sponsor. Use of sponsor-supplied TCS should be recorded via weight of returned tubes as indicated in the Schedule of Activities (Section 2). Sponsor will not provide or reimburse the cost of TCS at Visit 11 or after.

In the event that the sponsor is unable to supply TCS during the first 2 years of the treatment period, commercially available hydrocortisone 2.5% ointment or an equivalent-potency TCS cream and/or ointment that is in line with local practices can be supplied by the sponsor or the sites. Refer to Appendix 7 for guidance on potency equivalence.

On the days of study visits, topical therapy should not be applied before the patient has undergone all study procedures and clinical evaluations to allow adequate assessment of skin dryness.

7.8. Treatment after the End of the Study

7.8.1. Continued Access

After the conclusion of the study, continued access to baricitinib will not be provided to patients. Patients will be referred to their local treatment centers for AD therapy as clinically indicated.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Temporary Interruption from Investigational Product

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. For example, investigational product should be temporarily interrupted if the patient experiences a cardiovascular AE considered to be related to study treatment, is graded as moderate (Grade 2 according to Common Terminology Criteria for Adverse Events [CTCAE] Version 3.0), and that does not resolve promptly with supportive care. Except in cases of emergency, it is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting therapy for reasons other than those defined in Table JAIX.4.

Patients who met criteria for temporary interruption of investigational product during the originating study or during screening may be enrolled in Study JAIX, but will remain on temporary interruption until the criteria for resuming investigational product has been met.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table JAIX.4, specific guidance is provided for temporarily interrupting treatment and determining when treatment may be restarted. Retest frequency and timing of follow-up laboratory tests to monitor the abnormal finding is at the discretion of the investigator. Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value not specifically covered in Table JAIX.4 may be restarted at the discretion of the investigator.

Table JAIX.4. Criteria for Temporary Interruption of Investigational Product

Hold Investigational Product if the Following Laboratory Test Results or Clinical Events Occur:	Investigational Product May Be Resumed When:
WBC count <2000 cells/µL (<2.00x10^3/µL or <2.00 GI/L)	WBC count ≥2500 cells/µL (≥2.50x10^3/µL or ≥2.50 GI/L)
ANC <1000 cells/µL (<1.00x10^3/µL or <1.00 GI/L)	ANC ≥1200 cells/µL (≥1.20x10^3/µL or ≥1.20 GI/L)
Lymphocyte count <500 cells/µL (<0.50x10^3/µL or <0.50 GI/L)	Lymphocyte count ≥750 cells/µL (≥0.75x10^3/µL or ≥0.75 GI/L)
Platelet count <75,000/µL (<75x10^3/µL or <75 GI/L)	Platelet count ≥100,000/µL (≥100x10^3/µL or ≥100 GI/L)
eGFR <50 mL/min/1.73 m^2 (from serum creatinine)	eGFR ≥60 mL/min/1.73 m^2
ALT or AST >5 x ULN	ALT and AST return to <2 x ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥10 g/dL (≥100.0 g/L)
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection

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

For specific guidance on temporary interruption of investigational product after use of a prohibited medication, please refer to Section 7.7.1.

Lastly, investigational product should be temporarily interrupted for suicidal ideation or any suicide-related behaviors as assessed by the following patient responses on the C-SSRS:

- A "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) **or**
- A "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS **or**
- A "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS.

Note: Prior to resumption of investigational product, it is recommended that a patient be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the patient should remain on investigational product and ultimately continue participation in the study. A patient does not necessarily have to have investigational product interrupted if they have self-injurious behavior that would be classified as non-suicidal self-injurious behavior.

8.1.2. Permanent Discontinuation from Investigational Product

Investigational product should be permanently discontinued if the patient requests to discontinue investigational product.

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:

- ALT or AST >8 x upper limit of normal (ULN)
- ALT or AST >5 x ULN for >2 weeks
- ALT or AST >3 x ULN and total bilirubin level (TBL) >2 x ULN or international normalized ratio >1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, and/or rash
- alkaline phosphatase (ALP) >3 x ULN
- ALP >2.5 x ULN and TBL >2 x ULN
- ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, and/or rash

Note: Patients who are discontinued from investigational product because of a hepatic event or liver test abnormality should have additional hepatic safety data collected via the hepatic safety eCRF.

Investigational product should be permanently discontinued if any of the following laboratory abnormalities are observed:

- white blood cell count <1000 cells/µL (1.00×10^3/µL or 1.00 GI/L)
- absolute neutrophil count <500 cells/µL (0.50×10^3/µL or 0.50 GI/L)
- lymphocyte count <200 cells/µL (0.20×10^3/µL or 0.20 GI/L)
- hemoglobin <6.5 g/dL (<65.0 g/L)

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

In addition, patients will be discontinued from investigational product in the following circumstances:

- pregnancy
- malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- HBV DNA is detected with a value above limit of quantitation or 2 sequential tests return a value below the limit of quantitation (see Section 9.4.6)
- certain prohibited medications are taken per Section 7.7.1
- develop a VTE

  Note: Patients who develop a VTE may have additional follow up and testing recommended (see Section 9.4.8. and Appendix 6).

If a patient develops multiple risk factors for a VTE during the conduct of the study, the investigator may consider study discontinuation if he/she believes the risk outweighs the benefits of continuing therapy. It is recommended that the investigator consult with Lilly (or its designee) before discontinuing therapy for this reason.

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

8.1.3. Discontinuation of Inadvertently Enrolled Patients

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

8.2. Discontinuation from the Study

Patients may choose to withdraw from the study for any reason at any time, and the reason for early withdrawal will be documented.

Some possible reasons that may lead to permanent discontinuation include the following:

- 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
- study termination may occur in a specific country or region when baricitinib is approved for the treatment of AD and becomes reimbursed or commercially available in that country or region, or a negative regulatory opinion is received in that country or region
- 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 (not allowed as part of rescue therapy [Section 7.7.3]) 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
    - The patient requests to be withdrawn from the study.

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

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

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

Appendix 2 and Appendix 4 list the laboratory tests that will be performed for this study.

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

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

Eczema Area and Severity Index Scores (EASI): The EASI assesses extent of disease at 4 body regions and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale of 0 to 3. The EASI confers a maximum score of 72. The EASI evaluates 2 dimensions of AD: disease extent and clinical signs (Hanifin et al. 2001).

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD)

The IGA used in this study, the vIGA-AD (referred to as the IGA throughout the protocol) measures the IGA of the patient's overall severity of their AD, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification.

9.1.2.2. Eczema Area and Severity Index scores

The EASI assesses extent of disease at 4 body regions and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale of 0 to 3. The EASI confers a maximum score of 72. The EASI evaluates 2 dimensions of AD: disease extent and clinical signs (Hanifin et al. 2001).

BSA affected by AD will be derived from data collected as part of the EASI assessment.

9.1.2.3. SCORing Atopic Dermatitis

The SCORAD index uses the rule of nines to assess disease extent and evaluates 6 clinical characteristics to determine disease severity: (1) erythema, (2) edema/papulation, (3) oozing/crusts, (4) excoriation, (5) lichenification, and (6) dryness. The SCORAD index also assesses subjective symptoms of pruritus and sleep loss. These 3 aspects (extent of disease, disease severity, and subjective symptoms) combine to give a maximum possible score of 103 (Stalder et al. 1993; Kunz et al. 1997; Schram et al. 2012).

9.1.2.4. Hospital Anxiety Depression Scale

The Hospital Anxiety Depression Scale (HADS) is a 14-item self-assessment scale that determines the levels of anxiety and depression that a patient is experiencing over the past week. The HADS utilizes a 4-point Likert scale (for example, 0 to 3) for each question and is intended for ages 12 to 65 years (Zigmond and Snaith 1983; White et al. 1999). Scores for each domain (anxiety and depression) can range from 0 to 21, with higher scores indicating greater anxiety or depression (Zigmond and Snaith 1983; Snaith 2003).

9.1.3. Health Outcomes and Quality-of-Life Measures

The patient self-reported questionnaires will be administered via either an electronic patient diary or via an electronic tablet. Questionnaires will have been translated into the native language of the country and/or region and linguistically validated.

9.1.3.1. Patient-Oriented Eczema Measure

The POEM is a simple, 7-item, patient-administered scale that assesses disease severity in children and adults. Patients respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the last week. Response categories include "No days," "1-2 days," "3-4 days," "5-6 days," and "Every day" with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0-28 with higher total scores indicating greater disease severity (Charman et al. 2004).

9.1.3.2. Itch Numeric Rating Scale

The Itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016).

9.1.3.3. Atopic Dermatitis Sleep Scale

The Atopic Dermatitis Sleep Scale (ADSS) is a 3-item, patient-administered questionnaire developed to assess the impact of itch on sleep including difficulty falling asleep, frequency of waking, and difficulty getting back to sleep the previous night. Patient's rate their difficulty falling asleep and difficulty getting back to sleep, items 1 and 3, respectively, using a 5-point Likert-type scale with response options ranging from 0 "not at all" to 4 "very difficult." Patients report their frequency of waking the previous night, item 2, by selecting the number of times they woke up each night, ranging from 0 to 29 times. The ADSS is designed to be completed each day with respondents thinking about sleep "last night." Each item is scored individually.

9.1.3.4. Skin Pain Numeric Rating Scale

Skin Pain NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the previous 24 hours.

9.1.3.5. Patient Global Impression of Severity

The Patient Global Impression of Severity–Atopic Dermatitis (PGI-S-AD) is a single-item question asking the patient how they would rate their overall AD symptoms over the past 24 hours. The 5 categories of responses range from "no symptoms" to "severe."

9.1.3.6. Dermatology Life Quality Index

The DLQI is a simple, patient-administered, 10-item, 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 little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered ("not relevant") responses scored as 0 as applicable. Scores range from 0-30 with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related quality of life (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

9.1.3.7. European Quality of Life–5 Dimensions–5 Levels

The European Quality of Life–5 Dimensions–5 Levels (EQ-5D-5L) is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his or her current health state using a 0 to 100 mm Visual Analog Scale (VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his or her health state by checking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as an ordinal score. The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension (Herdman et al. 2011; EuroQol Group 2015 [WWW]).

9.1.3.8. Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis

The Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis (WPAI-AD) records impairment due to AD during the past 7 days. The WPAI-AD consists of 6 items grouped into 4 domains: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. Scores are calculated as impairment percentages (Reilly et al. 1993), with higher scores indicating greater impairment and less productivity.

9.1.4. Appropriateness of Assessments

All assessments utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant except ADSS and Skin Pain NRS, which are currently being developed and validated according to regulatory guidances.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

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

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the investigational product, study device, and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

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

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

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death

- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines if it is considered reasonably possibly related to study procedure.

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Adverse Events of Special Interest

AEs of special interest will include the following:

- infections (including tuberculosis, herpes zoster, or opportunistic infections)
- malignancies
- hepatic events (see Section 9.4.7)
- major adverse cardiovascular events (MACE) (see Section 9.4.9)
- thrombotic events (such as deep vein thrombosis and pulmonary embolism) (see Section 9.4.8).

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

9.2.3. Complaint Handling

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

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

9.3. Treatment of Overdose

Refer to the IB.

9.4. Safety

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

9.4.1. Vital Signs

For each patient, vital signs should be measured according to the Schedule of Activities (Section 2).

9.4.2. Physical Exam

For each patient, a symptom-directed physical examination will be performed at all visits. A complete physical examination may be performed at the investigator's discretion at any time a patient presents with physical complaints.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2). Lilly or its designee will provide the investigator with the

results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

9.4.4. Columbia Suicide Severity Rating Scale

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by an appropriately trained health care professional with at least 1 year of patient care/clinical experience. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception and the SAE and/or AE leading to discontinuation should be included on the AE form, and the process for reporting SAEs should be followed.

9.4.5. Self-Harm and Follow-Up Supplement Forms

Suicide-related events (behavior and/or ideations) will be assessed and evaluated at every visit with the administration of the C-SSRS and the Self-Harm Supplement Form. The Self-Harm Supplement Form is a single question to enter the number of suicidal behavior events, possible suicide behaviors, or nonsuicidal self-injurious behaviors. If the number of behavioral events is greater than zero, it will lead to the completion of the self-harm follow-up form. The self-harm follow-up form is a series of questions that provides a more detailed description of the behavior cases.

9.4.6. Hepatitis B Virus DNA Monitoring

Hepatitis B virus DNA testing will be performed in enrolled patients who tested positive for anti-hepatitis B core antibody (HBcAb) at screening in the originating study (Study JAIW).

Patients who are HBcAb positive and HBV DNA negative (undetectable) at screening (Visit 1) in the originating study (Study JAIW) will require measurement of HBV DNA per Schedule of Activities (Section 2), regardless of their hepatitis B surface antibody (HBsAb) status.
The following actions should be taken in response to HBV DNA test results:

- If a single result is obtained with a value “below limit of quantitation,” the test should be repeated within approximately 2 weeks. If the repeat test result is “target not detected,” monitoring will resume as specified in the Schedule of Activities (Section 2).

- If the patient has 2 or more test results with a value "below limit of quantitation" or a test result above the limit of quantitation, the patient will be permanently discontinued from investigational product (see Section 8.1.2) and should be referred to a hepatology specialist.

9.4.7. Hepatic Safety Monitoring and Data Collection

If a study patient experiences elevated ALT ≥3 x ULN, ALP ≥2 x ULN, or elevated TBL ≥2 x ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Criteria for discontinuation of investigational products (either temporary interruption or permanent discontinuation) due to abnormal ALT, AST, TBL, or ALP are detailed in Section 8.1.

Additional safety data should be collected via the hepatic eCRF if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5 x ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2 x ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2 x ULN on 2 or more consecutive blood tests
- patient discontinued from treatment because of a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

See Appendix 4 and Appendix 5 for a description of hepatic laboratory values that warrant exclusion from the study, temporary or permanent discontinuation of investigational product, or additional safety collection via the hepatic eCRF.

9.4.8. VTE Assessment

If a patient develops the signs and symptoms of a deep vein thrombosis or pulmonary embolism, appropriate local laboratory tests and imaging should be performed, as necessary, for diagnosis of the event. For confirmed cases, additional laboratory testing should be performed as outlined in Appendix 6. All suspected VTE events will be independently adjudicated by a Clinical Event Committee (see Section 10.3.6.1).

9.4.9. Safety Monitoring

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

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

All deaths and SAE reports will be reviewed by Lilly during the clinical trial.

Investigators will monitor vital signs and carefully review findings that may be associated with cardiovascular and VTEs. AE reports and vital signs will be collected at each study visit. The cardiovascular monitoring plan includes the following:

- regular monitoring of lipid levels
- potential MACE (cardiovascular death, MI, stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization such as coronary artery bypass graft or percutaneous coronary intervention), VTEs and noncardiovascular deaths will be identified by the investigative site or through medical review and will be sent to a blinded Clinical Event Committee for adjudication at regular intervals.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenetics

Not applicable.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Blood samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

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

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

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 ethical review boards (ERBs) impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of baricitinib or after baricitinib becomes commercially available.

9.9. Medical Resource Utilization and Health Economics

Health Economics will be evaluated in this study utilizing the EQ-5D-5L and WPAI-AD (see Section 9.1.3). Medical Resource Utilization parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

The study is descriptive in nature and the sample size is not based on any statistical power calculations. All of the approximate 450 patients participating in the originating study can be assessed for eligibility to participate in Study JAIX.

10.2. Populations for Analyses

Unless otherwise specified, the efficacy and health outcome analyses will be conducted on all enrolled patients who receive at least 1 dose of investigational product in Study JAIX, even if the patient does not follow the protocol. Significant protocol violations will be described in the SAP.

Unless otherwise specified, safety analyses will be performed on all enrolled patients who receive at least 1 dose of investigational product and who do not discontinue from the study for the reason "Lost to Follow-up" at the first postbaseline visit. Further details of other populations will be described in the SAP.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

As this study is open-label and all patients are receiving baricitinib 2-mg, no hypothesis testing will be performed. Data will be summarized both overall and by prior-treatment-received in Study JAIW. Data from this trial may be integrated with other trials.

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by Lilly or its designee.

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

All discrete efficacy variables will be summarized using frequencies and percentages. Continuous efficacy and health outcome variables will be summarized using number of patients, mean, standard deviation, median, minimum, and maximum.

The methods used to handle missing data will be specified in the SAP.

Frequencies and percentages will be computed for AEs, discontinuation, and other categorical safety data.

All patients who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the NRI summary of categorical efficacy variables such as IGA 0/1 or EASI 50/75/90 after discontinuation and onward.

10.3.2. Descriptive Population Analyses

10.3.2.1. Patient Disposition

All patients who discontinue from the study or the study treatment will be identified, along with their reason for discontinuation. Reasons for discontinuation from the study will be summarized. Additional summary may be produced by prior treatment received.

10.3.2.2. Patient Characteristics

Descriptive statistics for continuous variables will be produced including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

10.3.2.3. Concomitant Therapy

Concomitant medications will be descriptively summarized in terms of frequencies and percentages using the safety population. Additional summary may be produced by prior treatment received. The medications will be coded accordingly.

10.3.2.4. Treatment Compliance

Treatment compliance with study medication will be evaluated at every clinic visit through the counts of returned investigational product tablets. A patient will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses during the study, unless the patient's investigational product is withheld by the investigator for safety reasons; that is, compliance <80%. 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, that is, compliance ≥120%.

10.3.3. Efficacy Analyses

Categorical efficacy variables will be summarized in terms of frequencies and percentages. Nonresponder imputation will be used as described in Section 10.3.1. Continuous efficacy variables will be descriptively summarized in terms of number of patients, mean, standard deviation, median, minimum, and maximum.

10.3.4. Safety Analyses

All safety data will be summarized overall and by prior therapy received using the safety population.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the first dose of study treatment. The number of TEAEs as well as the number and percentage of patients who experienced at least 1 TEAE will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) for each system organ class (or a body system) and each preferred term. Serious adverse events and AEs that lead to discontinuation of investigational product will also be summarized.

Categorical variables, including the incidence of AEs of special interest, together with individual analyses of clinical laboratory results and vital signs are not planned for this Study, but will be included in an integrated database.

Further summaries may be performed and will be planned in the SAP.

Data collected after initiation of rescue therapy will be summarized as appropriate.

10.3.5. Other Analyses

10.3.5.1. Health Outcome Measures

The health outcome measures will be summarized using methods described for continuous or categorical data as described for efficacy measures in Section 10.3.3.

10.3.6. Interim Analyses

10.3.6.1. Adjudication Committee

A Clinical Event Committee will adjudicate potential MACE (cardiovascular death, MI, stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization such as coronary artery bypass graft or percutaneous coronary intervention), VTEs, and noncardiovascular deaths. Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the Charter.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AD	atopic dermatitis
ADSS	Atopic Dermatitis Sleep Scale
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
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BCG	Bacillus Calmette Guérin
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 subjects are aware of the treatment received.
BSA	body surface area
CI	confidence interval
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	50% improvement from baseline in EASI
EASI75	75% improvement from baseline in EASI
eCOA	electronic clinical outcome assessment

eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcomes
EQ-5D-5L	European Quality of Life–5 Dimensions–5 Levels
ERB	ethical review board
ETV	early termination visit
GCP	good clinical practice
HADS	Hospital Anxiety Depression Scale
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBV	hepatitis B virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IL	interleukin
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.
INR	international normalized ratio
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IWRS	interactive web-response system
JAK	Janus kinase
LSM	least squares mean

MACE	major adverse cardiovascular events
MI	myocardial infarction
MMRM	mixed-effects model of repeated measures
NRI	nonresponder imputation
NRS	Numeric Rating Scale
PDE-4	phosphodiesterase type 4
POEM	Patient-Oriented Eczema Measure
QD	once daily
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
TCNI	topical calcineurin inhibitor
TCS	topical corticosteroids
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which does not necessarily have to have a causal relationship with this treatment.
TSLP	thymic stromal lymphopoietin
TYK2	tyrosine kinase 2
VAS	Visual Analog Scale
vIGA-AD	validated Investigator's Global Assessment for Atopic Dermatitis
VTE	venous thromboembolic event
WPAI-AD	The Work Productivity and Activity Impairment–Atopic Dermatitis

Appendix 2. Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Absolute reticulocyte count	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin	Alkaline phosphatase
Mean cell hemoglobin concentration	Alanine aminotransferase (ALT)
Leukocytes (WBC)	Aspartate aminotransferase (AST)
Platelets	Blood urea nitrogen (BUN)
	Creatinine
Absolute counts of:	Cystatin C
Neutrophils, segmented	Uric acid
Neutrophils, juvenile (bands)	Calcium
Lymphocytes	Glucose
Monocytes	Albumin
Eosinophils	Total protein
Basophils	Estimated glomerular filtration rate (eGFR)[d]
	Creatine phosphokinase (CPK)
Urinalysis[a,b,c]	
Color	**Lipids**[a,e]
Specific gravity	Total cholesterol
pH	Low-density lipoprotein
Protein	High-density lipoprotein
Glucose	Triglycerides
Ketones	
Bilirubin	**Other Tests**[a]
Urobilinogen	HBV DNA[f]
Blood	Exploratory storage samples (serum, plasma and mRNA)
Leukocyte esterase	Pregnancy test[g]
Nitrite	Serum immunoglobulin (IgE)

Abbreviations: HBcAb+ = hepatitis B core antibody positive; HBV = hepatitis B virus; RBC = red blood cell; WBC = white blood cell.

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

[d] eGFR for serum creatinine calculated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine 2009 equation.

[e] Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

[f] HBV DNA testing will be done in those patients who are HBcAb+ at screening of originating study, Study JAIW.

[g] For all women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at all specified visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for ensuring the following:

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

Appendix 3.1.2. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Eli Lilly and Company (Lilly) before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

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

- the current investigator brochure (IB) and updates during the course of the study
- ICF
- relevant curricula vitae.

Appendix 3.1.3. 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.

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

Appendix 3.1.4. Investigator Information

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

Appendix 3.1.5. 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 Lilly representative.

Appendix 3.1.6. Final Report Signature

Lilly will select a qualified investigator(s) from among investigators participating in the design, conduct, and/or analysis of the study to serve as the clinical study report (CSR) coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

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

Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide 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, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic patient-reported outcome (ePRO) measures (e.g., a rating scale) and electronic clinical outcome assessments (eCOAs) are entered into an ePRO/eCOA instrument at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO/eCOA instrument record will serve as the source.

If ePRO/eCOA 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/eCOA 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 InForm. 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 Lilly data warehouse.

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 Lilly data warehouse.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, its designee, or the 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	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Liver Function Testing and Hepatic Safety Monitoring

Liver Function Testing and Hepatic Safety Monitoring

Analyte	Exclusion Criteria	Additional Hepatic Testing	Hepatic eCRF Reporting	Temporary Interruption of IP	Permanent Discontinuation of IP after Consultation with the Lilly-Designated Medical Monitor
Protocol Section	Section 6.2	Section 9.4.7	Section 9.4.7	Section 8.1.1	Section 8.1.2
ALT/AST	≥2 x ULN	ALT only ≥3 x ULN	ALT only ≥5 x ULN on ≥2 consecutive tests	≥5 x ULN	• >8 x ULN • >5 x ULN for >2 weeks • >3 x ULN AND TBL >2 x ULN or INR >1.5 • >3 x ULN with symptoms[a]
ALP	≥2 x ULN	≥2 x ULN	≥2 x ULN on ≥2 consecutive tests	No applicable criteria	• >3 x ULN • >2.5 x ULN AND TBL >2 x ULN • >2.5 x ULN with symptoms[a]
TBL	≥1.5 x ULN	≥2 x ULN	≥2 x ULN (excluding Gilbert's syndrome)	No applicable criteria	• ALT or AST >3 x ULN AND TBL >2 x ULN • ALP >2.5 x ULN AND TBL >2 x ULN

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; IP = investigational product; TBL = total bilirubin level; ULN = upper level of normal.

[a] Fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, and/or rash.

Appendix 6. Monitoring Tests for Confirmed VTE

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

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

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

Appendix 7. Classification of Potency for Topical Corticosteroids

Potency	Class	Topical Corticosteroid	Formulation
Ultra high	I	Clobetasol propionate	Cream 0.05%
		Diflorasone diacetate	Ointment 0.05%
High	II	Amcinonide	Ointment 0.1%
		Betamethasone dipropionate	Ointment 0.05%
		Desoximetasone	Cream or ointment 0.025%
		Fluocinonide	Cream, ointment or gel 0.05%
		Halcinonide	Cream 0.1%
	III	Betamethasone dipropionate	Cream 0.05%
		Betamethasone valerate	Ointment 0.1%
		Diflorasone diacetate	Cream 0.05%
		Triamcinolone acetonide	Ointment 0.1%
Moderate	IV	Desoximetasone	Cream 0.05%
		Fluocinolone acetonide	Ointment 0.025%
		Fludroxycortide	Ointment 0.05%
		Hydrocortisone valerate	Ointment 0.2%
		Triamcinolone acetonide	Cream 0.1%
	V	Betamethasone dipropionate	Lotion 0.02%
		Betamethasone valerate	Cream 0.1%
		Fluocinolone acetonide	Cream 0.025%
		Fludroxycortide	Cream 0.05%
		Hydrocortisone butyrate	Cream 0.1%
		Hydrocortisone valerate	Cream 0.2%
		Triamcinolone acetonide	Lotion 0.1%
Low	VI	Betamethasone valerate	Lotion 0.05%
		Desonide	Cream 0.05%
		Fluocinolone acetonide	Solution 0.01%
	VII	Dexamethasone sodium phosphate	Cream 0.1%
		Hydrocortisone	Lotion, cream, or ointment 2.5%
		Hydrocortisone acetate	Cream 1%
		Methylprednisolone acetate	Cream 0.25%

Source: WHO (1997) and Tadicherla et al. 2009.

Appendix 8. Investigator Global Assessment

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

Appendix 9. Protocol I4V MC JAIX(c) Summary - A Multicenter, Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Moderate to Severe Atopic Dermatitis

Overview

Protocol I4V-MC-JAIX, A Multicenter, Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Moderate to Severe Atopic Dermatitis, has been amended. The new protocol is indicated by amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

There are 3 main changes in this protocol amendment:

1. Study duration extended for all participating patients
2. Study design updated to allow patients who complete Study JAIW to subsequently enter Study JAIX
3. Primary efficacy endpoint changed.

Amendment Summary for Protocol I4V-MC-JAIX Amendment (c)

Section #	Description of Change	Brief Rationale
Section 1,4 and 5	Primary efficacy endpoint was changed.	To reflect the change made in the originating study, Study JAIW, where the primary endpoint was changed from IGA 0,1 to EASI75.
	Updated language to reflect the change in eligibility criteria that will allow responders who completed Study JAIW through Week 104 to be enrolled.	To allow all patients participating in Study JAIW the opportunity to receive IP (2-mg QD), the study design has been updated to allow "responders" from Study JAIW to enter this study (Study JAIX) after completing the full treatment period of that study.
	Objectives were updated to clarify that analyses will consider treatment received and responder status.	The change was made to align with the study design change which now allows inclusion of Study JAIW responders. Data for these patients may be analyzed separately from the data for nonresponders and partial responders.
	Exploratory objectives/endpoints were updated to reflect the fact that changes in IgE and	Specific analysis of changes in IgE and eosinophil levels are not currently planned

Section #	Description of Change	Brief Rationale
	eosinophil levels will not be considered.	to be considered as exploratory objectives/endpoints.
Section 1	Extended treatment duration by approximately 2 years.	The treatment period was extended to allow for continued efficacy and safety data collection as well as to allow patients to continue to receive baricitinib treatment for up to another 2 years.
Section 2, Table JAIX.1. Schedule of Activities	Added scheduled study visits every 4 months to the end of the study treatment period for a total of 6 new visits (Visits 12 through 17) during the 2-year extension.	Treatment visits were added at a frequency of every 4-months to allow for appropriate ongoing safety monitoring during the study.
Section 5 and Figure JAIX 1	Updated to reflect the 2-year treatment extension and associated visit schedule. Figure was updated to include the additional visits.	As described above, the treatment period was extended to allow for continued efficacy and safety data collection as well as to allow patients to continue to receive baricitinib treatment for up to another 2 years.
Section 1, 3.2, 5.1, 5.2, 5.4, 6 and 10.1	Updated the number of patients that may be enrolled. Updated language to reflect the change in eligibility criteria that will allow responders who completed Study JAIW through Week 104 to be enrolled.	The study design has been updated to allow "responders" from Study JAIW to enter this study (Study JAIX) after completing the full treatment period of that study. This change, in effect, makes all patients enrolled in Study JAIW eligible for assessment to enter Study JAIX at some point at or after JAIW Visit 8. The approximate sample size in Study JAIW is 450 patients. To allow all patients participating in Study JAIW the opportunity to receive IP (2-mg QD), the study design has been updated to allow "responders" from Study JAIW to enter this study (Study JAIX) after completing the full treatment period of that study.
Section 5.1.1	Added text that will allow Study JAIW "responders" to take a voluntary drug interruption between Study JAIW Visit 15 and Study JAIX Visit 1.	Some patients who have achieved and maintained treatment response in Study JAIW may be receiving placebo or 1-mg baricitinib QD. This voluntary interruption will give patients and investigators time to see if the patients' condition changes after stopping treatment which may inform their decision to enter into Study JAIX.
Section 6.1	Eligibility criteria were updated to include responders who completed Study JAIW through Week 104.	To allow all patients participating in Study JAIW the opportunity to receive IP (2-mg QD), the study design has been updated to allow "responders" from Study JAIW to enter this study (Study JAIX) after

Section #	Description of Change	Brief Rationale
		completing the full treatment period of that study.
Section 7.6	Treatment period was updated.	Section was updated to reflect the extension of the treatment period for the reasons described above. There is no change to how treatment compliance is assessed nor what is considered significant noncompliance.
Section 7.7.3	Updated language to reflect that TCS will not be provided or reimbursed by the sponsor for visit 11 and after (i.e., dispensed at Visits 1-10 only).	The purpose for this extension is to allow patients the opportunity to continue to receive baricitinib while allowing clinicians and patients freedom to use a low potency TCS product/dosing form (e.g., cream, ointment) that is preferred and is available as part of local standard of care.
Section 8.2	Added that study termination may occur based on regulatory disapproval, or approval and reimbursement and commercial availability of baricitinib for the treatment of AD, in a country or region.	Early termination of the study in a country/region as a result of a favorable or unfavorable regulatory opinion will allow patients to receive treatment that is in line with what the local or regional regulatory agency consider appropriate standard of care.
Section 9.1.1 and 9.1.2	Updated efficacy assessment descriptions and section heading numbering.	To reflect the change made in the originating study, Study JAIW, where the primary endpoint was changed from IGA 0,1 to EASI75.
Section 10.3.1 and 10.3.4	Updated safety analyses description.	Safety endpoints are better assessed in the context of combining the safety data from the originating study with the safety data from an extension study. Therefore, some of the planned safety analyses (e.g., clinical laboratory analysis, vital signs, and AEs of special interest) will now be conducted as part of the integrated safety database and not at the study level.

Revised Protocol Sections

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

1. Synopsis

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To describe the clinical response to baricitinib 2-mg QD in patients with moderate to severe AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) ~~received~~ and responder status achieved in Study I4V-MC-JAIW (JAIW).	• Proportion of patients achieving ~~IGA~~EASI75 from baseline of ~~0 or 1~~originating study, assessed at Week 16
Secondary	
To describe the clinical response to baricitinib 2-mg QD in AD as measured by improvement in signs and symptoms of AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) ~~received~~ and responder status achieved in Study JAIW.	• Proportion of patients achieving IGA of 0 or 1 assessed at Week 16 • Proportion of patients achieving IGA of 0 or 1 assessed at or before Week 16 • ~~Proportion of patients achieving EASI75 from baseline of originating study, assessed at Week 16~~ • Proportion of patients achieving EASI75 from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline in EASI score from baseline of originating study, assessed at Week 16 • Proportion of patients achieving a BSA of ≤3% assessed at or before Week 16
To describe the clinical response to baricitinib 2-mg QD in AD as assessed by patient-reported outcome measures by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) ~~received~~ and responder status achieved in Study JAIW.	• Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of originating study, assessed at Week 16 • Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline of originating study, in Itch NRS assessed at Week 16

Abbreviations: AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; EASI75 = 75% improvement from baseline in EASI; IGA = Investigator's Global Assessment; NRS = numeric rating scale; QD = once daily.

Summary of Study Design:

Study I4V-MC-JAIX (JAIX) is a Phase 3, multicenter, open-label outpatient study evaluating the efficacy and safety of baricitinib 2-mg once daily (QD) in adult patients with moderate to severe AD. The study population will include patients 18 years or older with a history of inadequate response or intolerance to existing topical therapies, and who have completed ~~at least Visit 8~~protocol-defined minimal participation in Study JAIW based on responder status.

The study duration will be up to ~~108~~204 weeks over 2 study periods:

- Period 1: Open-Label Treatment Period, lasting from Week 0 (baseline, Visit 1) through Week ~~104~~200 (Visit ~~11~~17).

Period 2: Post-Treatment Follow-Up Period (Visit 801), spanning the period from the last treatment visit at Week ~~104~~200 (Visit ~~11~~17) or Early Termination Visit (ETV) to approximately 4 weeks following the last dose of investigational product

Treatment Arms and Duration:

Patients will be assigned at baseline to open-label treatment with baricitinib 2-mg QD. The study duration will be up to ~~108~~204 weeks (Open-Label Treatment Period: ~~104~~200 weeks; Post-Treatment Follow-Up Period: approximately 4 weeks after the last dose of investigational product).

Number of Patients:

This study will include ~~approximately 300~~up to 450 patients with AD who will be treated with baricitinib 2-mg QD.

Statistical Analysis:

Unless otherwise specified, the efficacy and health outcomes summaries will be conducted on all enrolled patients who receive at least 1 dose of investigational product in Study JAIX, even if the patient does not follow the protocol, and safety analyses will be conducted on all enrolled patients who receive at least 1 dose of investigational product and who do not discontinue from the study for the reason "Lost to Follow-up" at the first postbaseline visit.

Treatment comparisons of discrete efficacy variables between prior-treatment-received groups may be performed using group percentages. All patients who discontinue the study or study treatment at any time for any reason will be defined as nonresponders for the nonresponder imputation (NRI) analysis for categorical variables after discontinuation onward.

Continuous efficacy variables will be descriptively summarized in terms of number of patients, mean, standard deviation, median, minimum, and maximum.

Frequencies and percentages will be computed for adverse event (AE), discontinuation, and other categorical safety data. ~~Continuous vital signs, body weight, and other safety variables including laboratory variables will be summarized by mean, standard deviation, median, minimum and maximum.~~

Table JAIX.1. Schedule of Activities

	Period 1: Open-Label Treatment Period																	Period 2: PTFU
Visit Number	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11/~~ET~~[b]**	**12**	**13**	**14**	**15**	**16**	**17/ET[b]**	**801[c]**
Weeks from entry into JAIX	**0**	**4**	**8**	**16**	**24**	**36**	**52**	**64**	**76**	**88**	**104**	**120**	**136**	**152**	**168**	**184**	**200**	**~~108~~204**
Visit tolerance interval (days) from entry into JAIX	**0[d]**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28±4 after last dose**
Procedures																		
Inclusion and exclusion review	X																	
Informed consent	X																	
Abbreviated demographics	X																	
Clinical Assessments																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP and pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ePRO (patient diary) dispensed	X	X	X															
ePRO (patient diary) returned		X	X	X[e]														
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP dispensed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IP returned and compliance assessed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense TCS[f]	X	X	X	X	X	X	X	X	X	X	~~X~~							
Weigh (tube with cap) and record returned TCS (as needed)		X	X	X	X	X	X	X	X	X	X						X[b]	X
Scales																		
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Outcomes Measures and Other Questionnaires[g]																		
Itch NRS	X	X	X	X[e]														
Skin Pain NRS	X	X	X	X[e]														

	Period 1: Open-Label Treatment Period																	Period 2: PTFU
Visit Number	**1[a]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11~~/ET~~[b]**	**12**	**13**	**14**	**15**	**16**	**17/ET[b]**	**801[c]**
Weeks from entry into JAIX	**0**	**4**	**8**	**16**	**24**	**36**	**52**	**64**	**76**	**88**	**104**	**120**	**136**	**152**	**168**	**184**	**200**	**~~108~~204**
Visit tolerance interval (days) from entry into JAIX	**0[d]**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28±4 after last dose**
ADSS	X	X	X	X[e]														
PGI-S-AD	X	X	X	X[e]														
POEM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X	X	X	X	X						X[b]	X
EQ-5D-5L		X	X	X							X						X[b]	X
WPAI-AD		X	X	X							X						X[b]	X
C-SSRS and Self-Harm Supplement[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-Up Form[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																		
Lipids (fasting)[j]	X[k]			X		X	X		X		X	X	X	X	X	X	X[l]	X
Clinical chemistry[m]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA[n]	X[k]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X[k]	X	X	X	X	X	X	X	X	X	X						X[o]	X
Urine pregnancy[~~e~~p]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunoglobulin (IgE)	X			X			X				X						X[o]	
Exploratory storage samples (serum and plasma)	X			X			X				X						X[o]	
RNA and biomarkers: blood	X			X			X				X						X[o]	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale 11 categories suicidal ideation/suicidal behavior; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D-5L = the European Quality of Life–5 Dimensions 5 Levels; ET = early termination; ePRO = electronic patient-reported outcomes (device); HADS = Hospital Anxiety Depression Scale; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibody; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; IP = investigational product; IWRS = interactive web-response system; NRS = numeric rating scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PTFU = post-treatment follow-up; SCORAD = SCORing Atopic Dermatitis; TCS = topical corticosteroids; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

[a] Any assessments/procedures conducted during the final visit of the patient's originating study (Study JAIW) should not be repeated during their first visit for Study JAIX.

[b] An ET visit should be conducted if a patient discontinues from the study before Week ~~104~~200. Early termination visit activities do not need to be duplicated if occurring at the time of a scheduled visit. Weighing of TCS and collection of HADS, EQ-5D-5L, and WPAI-AD are not a component of study visit 17, only the ETV at or before Week 104.

[c] Visit 801 is the PTFU visit, which occurs after the patient has been off baricitinib/IP for approximately 4 weeks. Patients who have permanently discontinued IP but remain in the study for more than 28 days without IP will only complete Visit ~~11~~17/ET; Visit 801 (follow-up visit) is not required.

[d] Screening should occur during the LPV of the originating study. It may be permissible for screening to occur after the last visit of the originating study if needed, upon approval from the sponsor.

[e] Applies to ET visit if conducted prior to Week 16 only.

[f] Only required at investigator discretion. Sponsor provided low potency TCS will be available to dispense to patients at anytime prior to study visit 11. At visit 11 and after, low potency TCS is allowed as background therapy but will not be provided by the sponsor or reimbursed by the sponsor.

[g] The following measures (POEM, DLQI, HADS, EQ-5D-5L, WPAI-AD) should be completed prior to any clinical assessments being performed on days when study visits occur.

[h] Suicidal ideation and behavior subscales excerpt—adapted for the assessment of 11 preferred ideation and behavior categories.

[i] The Self-Harm Follow-Up Form is required only if triggered by the Self-Harm Supplement Form.

[j] Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Unscheduled lipid testing can be performed at the discretion of the investigator.

[k] If laboratory examinations have been performed ≤4 weeks from previous study visit, then they do not need to be repeated.

[l] For ET visits, collect fasting lipids when possible.

[m] Clinical chemistry will include the following value calculated from serum creatinine: estimated glomerular filtration rate (eGFR; calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine 2009 equation).

[n] Patients who are positive for HBcAb and negative for HBV DNA may be enrolled. Any enrolled patient who is HBcAb positive as determined at screening of originating study, Study JAIW, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule.

[o] Urinalysis, serum IgE, exploratory storage samples, and RNA and biomarker samples are only collected for ET visits occurring at or before Week 104. These samples are not collected as a component of Visit 17~~For all women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at all specified visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period~~.

[p] For all women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at all specified visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

3.2 Study Rationale

The recently completed Phase 2 study of baricitinib in AD, Study JAHG, met its primary objective of proportion of patients achieving a 50% improvement from baseline in Eczema Area and Severity Index (EASI50) scores compared to placebo. Baricitinib also showed statistically significant improvements for other disease severity analyses as well as multiple different patient reported outcome scales compared to placebo, further validating the hypothesis that JAK1/JAK2 signaling plays a key role in AD pathogenesis. Phase 3 placebo-controlled studies are ongoing to define baricitinib efficacy in AD. This open-label, long-term extension study is designed to further assess long-term efficacy and safety of baricitinib in patients with moderate to severe AD, who did not achieve ~~the primary end point (~~Investigator's Global Assessment [IGA] 0~~,~~ or 1~~)~~ in the originating study, Study I4V-MC-JAIW (JAIW). This will allow patients originally randomized to baricitinib 1-mg or placebo in Study JAIW to have the opportunity for treatment with baricitinib 2-mg QD, and also assess the longer-term clinical utility of the 2-mg dose beyond achieving an IGA 0,1. In addition, this study will give patients completing Study JAIW as responders the opportunity for ongoing access to baricitinib 2-mg.

4. Objectives and Endpoints

Table JAIX.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe the clinical response to baricitinib 2-mg QD in patients with moderate to severe AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) ~~received~~ and responder status achieved in Study I4V-MC-JAIW (JAIW~~).~~)	• Proportion of patients achieving ~~IGA~~EASI75 from baseline of ~~0 or 1~~originating study, assessed at Week 16
Secondary	
To describe the clinical response to baricitinib 2-mg QD in AD as measured by improvement in signs and symptoms of AD by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) ~~received~~ and responder status achieved in Study JAIW.	• Proportion of patients achieving IGA of 0 or 1 assessed at Week 16 • Proportion of patients achieving IGA of 0 or 1 assessed at or before Week 16 • ~~Proportion of patients achieving EASI75 from baseline of originating study, assessed at Week 16~~ • Proportion of patients achieving EASI75 from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline in EASI score from baseline of originating study, assessed at Week 16 • Proportion of patients achieving a BSA of ≤3% assessed at or before Week 16
To describe the clinical response to baricitinib 2-mg QD in AD as assessed by patient-reported outcome	• Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of

Objectives	Endpoints
measures by prior treatment received (ie., baricitinib 2-mg, 1-mg, or placebo) ~~received~~ and responder status achieved in Study JAIW.	originating study, assessed at Week 16 • Proportions of patients achieving a ≥4-point improvement in Itch NRS from baseline of originating study, assessed at or before Week 16 • Mean percent change from baseline of originating study, in Itch NRS assessed at Week 16
Exploratory Objectives/Endpoints	
• Exploratory objectives may include evaluating the response to baricitinib treatment regimens on clinical measures and patient reported outcomes. These endpoints may include dichotomous endpoints or change from baseline for the following measures: IGA, EASI, SCORAD, POEM, HADS, DLQI, WPAI-AD, EQ-5D-5L, Itch NRS, ADSS Item 2 score, Skin Pain NRS, PGI-S-AD. • ~~To evaluate changes from baseline in IgE levels during the study.~~ • ~~To evaluate changes from baseline in eosinophil levels during the study.~~	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BSA = body surface area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI75 = 75% improvement from baseline in EASI; EQ-5D-5L = the European Quality of Life–5 Dimensions–5 Levels; HADS = Hospital Anxiety Depression Scale; IGA = Investigator's Global Assessment; ~~IgE = immunoglobulin E;~~ NRS = numeric rating scale; QD = once daily; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; WPAI-AD = Work Productivity and Activity Impairment – Atopic Dermatitis.

5. Study Design

5.1 Overall Design

Study I4V-MC-JAIX (JAIX) is a Phase 3, multicenter, open-label, outpatient study evaluating the efficacy and safety of baricitinib 2-mg QD in adult patients with moderate to severe AD. The study is divided into 2 periods; a ~~104~~200-week Open-Label Treatment period, and a 4-week Post-Treatment Follow-Up period. The following patients will be eligible to participate in this study:

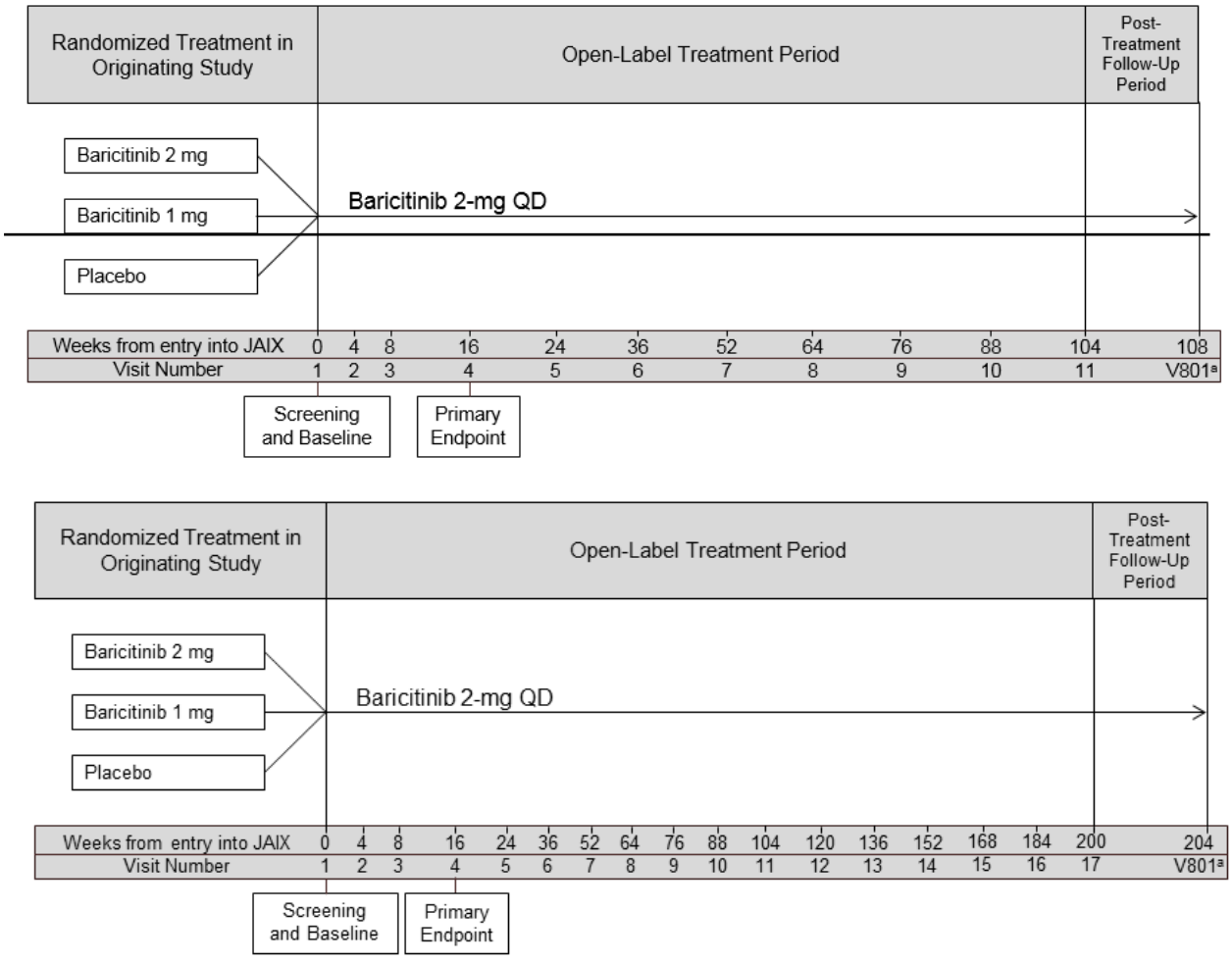
- Partial Responders (IGA 2 at Week 16 of Study JAIW)
- Previous Responders at Week 16 of Study JAIW (IGA 0 or 1): Patients who were responders at Week 16 of Study JAIW, and thus remain in Study JAIW but later experience loss of response resulting in an IGA ≥3 (or requiring more than low-potency TCS after Week 16 to manage symptoms)
- Nonresponders (IGA 3 or 4 at Week 16 of Study JAIW or rescued with topical [e.g. TCS, TCNI] or systemic therapies prior to Week 16)
- Responders who completed Study JAIW through Week 104 (Visit 15)

Approximately 300 patients who have been discontinued from Study JAIW may be eligible to enroll in this study. Patients who complete Study JAIW through Visit 8 (Week 16) can enter Study JAIX. In addition, patients who complete Study JAIW as responders may be eligible to enroll in this study. For most patients, the last visit of the originating study will be the first visit and screening/baseline period for Study JAIX. Patients will have been using emollients daily in

their originating study and this will continue during Study JAIX participation. Starting at baseline, patients will be treated with open-label baricitinib 2-mg QD for up to ~~104~~200 weeks.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Section 2). Section 9.4.3 describes collection of laboratory samples; Appendix 2, Appendix 4, Appendix 5, and Appendix 6 list the specific laboratory tests that will be performed for this study. Study governance considerations are described in detail in Appendix 3. The IGA tool to be used in this study is included in Appendix 8.

Figure JAIX.1 illustrates the study design. The dosing regimen is described in Section 7.1.



Abbreviations: AD = atopic dermatitis; QD = once daily; V = visit; W = week.

[a] Occurs approximately 28 days after the last dose of investigational product.

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

5.1.1. Period 1: Open-Label Treatment, Weeks 0 to 200~~104~~

Screening should occur during the last visit of the originating study. Study eligibility for each patient will be reviewed based on all enrollment criteria (Section 6). Patients who meet all criteria will have treatment allocated by interactive web-response system (IWRS) and begin their treatment period at Visit 1. Patients who meet all of the inclusion and none of the exclusion criteria (Section 6) will be enrolled in the study. It may be permissible for screening to occur after the last visit of the originating study if needed, upon approval from the sponsor. For example, patients requiring elective procedures may want to have those in between studies~~.~~, or responders who complete Visit 15 of Study JAIW have the option to delay enrollment into open-label Study JAIX to assess response while off investigational product.

Patients who received oral systemic AD treatment and/or topical rescue therapy during the originating study must discontinue use of the prohibited medications listed in Section 7.7.1 prior to initiating IP in Study JAIX. Low-potency TCS (e.g., hydrocortisone 2.5% ointment) is permitted (Section 7.7.2).

Patients will receive open-label baricitinib 2–mg QD. Investigational product will be administered daily for a maximum of ~~104~~200 weeks (treatment period Visits 1 through ~~11~~17; see Section 7). All patients will be required to use emollients daily. Daily diaries will continue to be utilized through Week 16. Download of this data will be required at study visits. Patients are allowed to use low potency TCS (e.g., hydrocortisone 2.5% ointment) in combination with investigational product. Rescue with higher potency TCS, topical calcineurin inhibitors (TCNIs), or systemic therapies is not allowed. Assessments of disease severity will be performed by the investigator as described in the Schedule of Activities (Section 2).

The primary efficacy endpoint will be at Week 16 (Visit 4). All patients who permanently discontinue investigational product prior to the primary endpoint should complete an ETV and post-treatment follow-up visit.

At Week 16, all patients should be formally assessed to determine if sufficient clinical benefit has been observed to justify continuing in this study. Clinical benefit is defined as meeting at least 1 of the following criteria during the first 16 weeks:

- IGA score of 0 or 1 with a ≥2-point improvement from baseline of originating study,
- ≥4-point improvement from baseline of originating study in Itch NRS,
- EASI-75 from baseline of originating study, or
- BSA involvement of ≤3%.

If a patient achieves any of these treatment goals during the first 16 weeks of the treatment period, the patient will be allowed to continue in the study. Although formal criteria for sufficient clinical benefit should be assessed at Week 16, investigators are strongly encouraged to discontinue patients who have not shown signs of clinical benefit by Week 8 of Study JAIX, defined as improvement in IGA, itch NRS, EASI, or BSA. Attention should be given to patients treated continuously for 16 weeks during Study JAIW (no IP discontinuation for systemic rescue

therapy) and who then show no benefit in Study JAIX, to avoid exposing patients to a potentially ineffective therapy for an additional 16 weeks before discontinuation. Since no rescue therapies are available during this study, patients requiring more than low-potency TCS at any time during the study will be discontinued.

5.1.2. Period 2: Post-Treatment Follow-Up

Patients who complete the study through Visit ~~11~~17 (Week ~~104~~200) will have a post-treatment follow-up visit (Visit 801) approximately 28 days after the last dose of investigational product.

Patients who have received at least 1 dose of investigational product and discontinue early from the study should have an ETV, and return for the post-treatment safety follow-up visit (Visit 801) approximately 28 days after the last dose of investigational product.

Patients who have discontinued investigational product but remain in the study for more than 28 days without investigational product will have an ETV if they choose to discontinue early; however, a separate follow-up visit (V801) is not required.

Patients should not initiate new systemic AD treatment during this period. However, if patients or investigators must initiate treatment, investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any new treatment. An unscheduled visit can be used for this purpose if necessary.

5.2. Number of Participants

~~Approximately 300~~Up to 450 participants ~~will~~may be enrolled~~, although final number of patients will be determined by response rate observed in the originating Study JAIW~~.

5.4. Scientific Rationale for Study Design

This open-label long-term extension study will enroll moderate to severe AD patients who have completed ~~treatment visits until at least the primary endpoint of an originating study (i.e.,~~ Visit 8, Week 16 of Study JAIW~~)~~ but who did not achieve ~~the primary endpoint of~~ IGA 0,1, or who experience loss of response after Week 16, or who complete Study JAIW as responders at Visit 15, Week 104. This study will further assess long-term efficacy and safety of baricitinib in this population. This will allow patients originally randomized to baricitinib 1-mg or placebo in Study JAIW to have the opportunity for treatment with baricitinib 2-mg QD, and also assess the longer-term clinical utility of the 2-mg dose beyond achieving an IGA 0,1.

During the open-label treatment period, patients will be treated with baricitinib 2-mg, which has been shown to be efficacious in the Phase 2 study in AD (JAHG). Patients will also be allowed to use low-potency TCS (e.g., hydrocortisone 2.5% ointment) as background therapy for comfort if needed. Daily treatment with emollient will continue. To avoid confounding effect of topical therapies, higher-potency TCS, as well as TCNIs and topical phosphodiesterase type 4 (PDE-4) inhibitors are not allowed at any time during the study. If a patient does not experience sufficient clinical benefit during the study, the patient should be discontinued. The criteria for determining sufficient clinical benefit are discussed in Section 5.1.1. This ~~2~~4-year-long study will generate important long-term efficacy and safety data in AD.

The post-treatment follow-up period (Period 2) is for safety monitoring after the patient has been off investigational product for approximately 28 days.

6. Study Population

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

~~The study population will comprise patients diagnosed with AD who have completed at least Visit 8 (Week 16) of Study JAIW.~~ Study investigator(s) will determine if the patient meets all inclusion criteria and none of the exclusion criteria to qualify for enrollment in the study. All screening activities must be completed and reviewed before the patient is enrolled.

6.1. Inclusion Criteria

Type of Patient and Disease Characteristics

[1] have completed the minimum number of visits based on responder status in Study JAIW

- nonresponder/partial responder: have completed at least 16 weeks of treatment in Study JAIW (i.e., Visit 8, Week 16) ~~and~~

  A nonresponder/partial responder is defined as a patient who met at least 1 of the following in Study JAIW:

  - did not achieve an IGA of 0 or 1 at Week 16, or
  - achieved an IGA ≥3 after Week 16, or
  - required rescue therapy at any time.

or

- responder: have completed the full treatment period of Study JAIW (i.e., Visit 15, week 104)

  A responder is defined as a patient who achieved IGA 0 or 1 and who did not require rescue therapy at or before Week 16 in Study JAIW.

7.6 Treatment Compliance

Patient compliance with study medication will be assessed at each visit during the treatment period (Visit 2 through Visit ~~11~~17) by counting returned tablets.

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

Patients will be counseled by study staff on the importance of taking the investigational product as prescribed, as appropriate.

Patients' compliance will be further defined in the statistical analysis plan (SAP).

7.7.3. Rescue Therapy

No rescue therapy options are available during the study. Patients are allowed to use low-potency TCS as background therapy for comfort if needed. Patients who experience worsening and unacceptable symptoms of AD should consider discontinuing from the study. Patients requiring more than low-potency TCS to manage their symptoms should also be discontinued.

Hydrocortisone 2.5% ointment will be supplied by the sponsor~~.~~ for use during the first 2 years of the treatment period (dispensed at Visits 1-10 only). In the event that providing this topical formulation during the first 2 years is not possible, an alternate, equivalent potency TCS cream and/or ointment may be provided by the sponsor. Use of sponsor-supplied TCS should be recorded via weight of returned tubes as indicated in the Schedule of Activities (Section 2). Sponsor will not provide or reimburse the cost of TCS at Visit 11 or after.

In the event that the sponsor is unable to supply TCS during the first 2 years of the treatment period, commercially available hydrocortisone 2.5% ointment or an equivalent-potency TCS cream and/or ointment that is in line with local practices can be supplied by the sponsor or the sites. Refer to Appendix 7 for guidance on potency equivalence.

On the days of study visits, topical therapy should not be applied before the patient has undergone all study procedures and clinical evaluations to allow adequate assessment of skin dryness.

8.2 Discontinuation From the Study

Patients may choose to withdraw from the study for any reason at any time, and the reason for early withdrawal will be documented.

Some possible reasons that may lead to permanent discontinuation include the following:

- 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
- study termination may occur in a specific country or region when baricitinib is approved for the treatment of AD and becomes reimbursed or commercially available in that country or region, or a negative regulatory opinion is received in that country or region
- 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 (not allowed as part of rescue therapy [Section 7.7.3]) 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
  - The patient requests to be withdrawn from the study.

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

9.1.1 Primary Efficacy Assessments

Eczema Area and Severity Index Scores (EASI): The EASI assesses extent of disease at 4 body regions and measures 4 clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale of 0 to 3. The EASI confers a maximum score of 72. The EASI evaluates 2 dimensions of AD: disease extent and clinical signs (Hanifin et al. 2001).~~**Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD):** The IGA used in this study, the vIGA-AD (referred to as the IGA throughout the protocol) measures the IGA of the patient's overall severity of their AD, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification.~~

9.1.2 Secondary Efficacy Assessments

9.1.2.1. ~~Eczema Area and Severity Index scores~~Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD)

The IGA used in this study, the vIGA-AD (referred to as the IGA throughout the protocol) measures the IGA of the patient's overall severity of their AD, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification.

9.1.2.~~1~~2. Eczema Area and Severity Index scores

9.1.2.~~2~~3. SCORing Atopic Dermatitis

9.1.2.~~3~~4. Hospital Anxiety Depression Scale

10.1. Sample Size Determination

~~It is anticipated that approximately 90% of enrolled patients will complete Week 16 of Study JAIW; of these patients, it is expected that approximately 75% will roll over into Study JAIX. Assuming that approximately 90% of the nonresponders and partial responders join Study JAIX, then the planned enrollment will be approximately 300 patients.~~ The study is

descriptive in nature and the sample size is not based on any statistical power calculations. ~~The final sample size will depend on the response rate in Study JAIW.~~All of the approximate 450 patients participating in the originating study can be assessed for eligibility to participate in Study JAIX.

10.3.1 General Statistical Considerations

As this study is open-label and all patients are receiving baricitinib 2-mg, no hypothesis testing will be performed. Data will be summarized both overall and by prior-treatment-received in Study JAIW. Data from this trial may be integrated with other trials.

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by Lilly or its designee.

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

All discrete efficacy variables will be summarized using frequencies and percentages. Continuous efficacy and health outcome variables will be summarized using number of patients, mean, standard deviation, median, minimum, and maximum.

The methods used to handle missing data will be specified in the SAP.

Frequencies and percentages will be computed for AEs, discontinuation, and other categorical safety data. ~~Continuous vital signs, body weight, and other safety variables including laboratory variables will be summarized using mean, standard deviation, median, minimum and maximum. Shift tables for categorical safety analyses (e.g., "high" or "low" laboratory results) will also be produced.~~

All patients who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the NRI summary of categorical efficacy variables such as IGA 0/1 or EASI 50/75/90 after discontinuation and onward.

10.3.4. Safety Analyses

All safety data will be summarized overall and by prior therapy received using the safety population.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the first dose of study treatment. The number of TEAEs as well as the number and percentage of patients who experienced at least 1 TEAE will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) for each system organ class (or a body system) and each preferred term. Serious adverse events and AEs that lead to discontinuation of investigational product will also be summarized.

Categorical variables, including the incidence of AEs of special interest, together with individual analyses of clinical laboratory results and vital signs are not planned for this Study, but will be included in an integrated database.

~~All clinical laboratory results will be descriptively summarized. Additional summary may be produced by prior treatment received. Individual results that are outside of normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables obtained at the baseline to postbaseline visits will be summarized as changes from baseline. Categorical variables, including the incidence of abnormal values and incidence of AEs of special interest, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures.~~

~~Observed values and changes from baseline (predose or screening if missing) for vital signs and physical characteristics will be summarized by visit. Change from baseline to postbaseline in vital signs, and body weight will be summarized using mean, standard deviation, median, minimum, and maximum. The incidence and average duration of investigational product interruptions will be summarized. Various techniques may be used to estimate the effects of investigational product interruptions on safety measures.~~ Further summaries may be performed and will be planned in the SAP.

Data collected after initiation of rescue therapy will be summarized as appropriate.

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