Protocol I4V-MC-JAIP(c)

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Outpatient Study Evaluating the Pharmacokinetics, Efficacy, and Safety of Baricitinib in Pediatric Patients with Moderate-to-Severe Atopic Dermatitis

NCT03952559

Approval Date: 14-Feb-2023

Protocol I4V-MC-JAIP(c)
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Outpatient Study Evaluating the Pharmacokinetics, Efficacy, and Safety of Baricitinib in Pediatric Patients with Moderate-to-Severe Atopic Dermatitis

BREEZE-AD-PEDS

EUDRA CTA 2018-000349-38

Confidential Information

Baricitinib (LY3009104)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

EU trial number: 2023-503898-38-00

Approval Date: Protocol Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-074361

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	*06-Aug-2020*
Amendment (a)	*12-Jun-2019*
Original Protocol	*06-Sep-2018*

Amendment [c]

The amendment is considered to be substantial because it is likely to have a significant impact on the safety of the study participants

Overall Rationale for the Amendment:

The rationale of this amendment is to align with new EU Clinical Trial Regulation requirements and extend the study duration.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis	Included Regulatory Agency Identifier Number(s)	For harmonization of the protocol
	Updated the section to align with the changes in the main body of the protocol	For consistency
2. Schedule of Activities 4. Objectives and Endpoints 5.1. Overall Design 5.1.3. Period 3: Double-blind Placebo-Controlled Treatment Period 5.1.4. Period 4: Long-term Extension Treatment Period 5.1.5. Period 5: Post-Treatment Follow-up 10.3.3.3. Tertiary/Exploratory Analyses	Extended Study Period 4 by up to an additional 1 year for patients for whom a systemic JAK or biologic treatment is not available	This extension of treatment will allow for continued efficacy and safety data collection and will allow patients to continue to receive baricitinib treatment for up to an additional 1 year until baricitinib is commercially available for the population or not approved.
2. Schedule of Activities 7.7.2. Use of Topical Corticosteroids	Defined that sponsor will provide low- and moderate-potency TCS through study Visit 27. At Visit 28 and beyond, sponsor will not provide TCS.	This will allow use of TCS products that are preferred by the patient and are locally available to the patient upon study completion.
2. Schedule of Activities	Defined that the collection of imaging (x-ray, MRI) is not required after the patient reaches 18 years of age	Most patients will have completed growing by 18 years of age. Discontinuing the collection of imaging when growth is not expected will eliminate the risks associated with unnecessary x-ray exposure.

Section # and Name	Description of Change	Brief Rationale
	Revised footnote “a” and added footnote “s”	To align with the additional visits
4. Objectives and Endpoints 10.3.3.3. Tertiary/Exploratory Analyses	Added “Proportion of patients achieving SCORAD75 at 2, 3, 4, and 5 years during long-term extension.” as exploratory objective	To align SCORAD analysis timepoints with IGA and EASI 75 exploratory objectives
9.4.3 Laboratory Tests	Added a statement to refer Appendix 13 as incorporated Protocol Addendum (4) as a new Appendix 13	To avoid country and region-specific protocol versions in the EU
Appendix 11. Additional Procedures for Countries Participating in the PK Lead-in Period (Study Period 2)	Added this new appendix and included the content from PK Addendum (5). Also, updated the SoA as per current protocol amendment	To avoid country and region-specific protocol versions in the EU
Appendix 12. EU-specific Requirements	Added a new appendix applicable to EU only sites by including the content from Protocol Addenda 6, 7, 8.4, and 12. Also, updated the SoA as per current protocol amendment. • 12.1. CCI • 12.2. • 12.3.	For harmonization of the protocol and to avoid country and region-specific protocol versions in the EU
Appendix 13. Guidance for Blood Sampling When Volume Restrictions May apply	Incorporated Protocol Addendum (4) as a new Appendix 13 to protocol and added a statement to refer this appendix in Section 9.4.3	To avoid country and region-specific protocol versions in the EU
Revised Protocol Sections	Removed this sections	Updated according to internal Lilly guidance
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Synopsis

Title of Study:
A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Outpatient Study Evaluating the Pharmacokinetics, Efficacy, and Safety of Baricitinib in Pediatric Patients with Moderate to Severe Atopic Dermatitis

Regulatory Agency Identifier Number(s):

EU trial number: 2023-503898-38-00

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 2008). In addition to AD resulting from T cell activation, there is also evidence that a defective epidermal barrier contributes to the AD process. Patients with filaggrin mutations are at increased risk for developing AD, as filaggrin contributes to abnormal barrier function (Palmer et al. 2006). Presentation is varied, but includes skin manifestations including pruritus, associated sleep disturbances, and subsequent skin infections. The course of disease includes relapses of varying duration and severity. Atopic dermatitis is one of the most common chronic diseases in childhood. The prevalence of AD is higher in children than in adults, and pediatric patients with AD are afflicted with a heavy disease burden. The prevalence of AD ranges from approximately 9% in teenagers to 14% in children 0 to 4 years of age (Shaw et al. 2011). In addition, the distribution of severity tends to shift to higher severities at older ages with older children being more likely to have moderate to severe disease (Silverberg and Simpson 2014).

Atopic dermatitis has traditionally been treated with emollients and topical corticosteroids to address barrier dysfunction and immune abnormalities: low-potency corticosteroids for mild cases, medium- and high-potency for moderate cases. The standard of care remains medium- to high-potency topical corticosteroids in both adult and pediatric patients. Although topical corticosteroids are used broadly in AD, patients with moderate to severe disease may not achieve good disease control with these treatments. In addition, continuous long-term use of topical corticosteroids, particularly those with higher potency, is not recommended because of side effects. Similar to adults, a need exists for new treatments that demonstrate safety and efficacy in pediatric patients who have responded inadequately to or who are intolerant to topical treatments.

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 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 (RA) (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. 2018); was effective in improving signs and symptoms of active systemic lupus erythematosus (Wallace et al. 2018); and in a recently completed Phase 2 study (I4V-MC-JAHG [JAHG]) was effective at reducing disease severity in adult patients with moderate-to-severe AD (Guttman-Yassky et al. 2018). In addition, baricitinib is being used to treat pediatric patients participating in an expanded access program (protocol I4V-MC-JAGA [JAGA]: *Compassionate Use Protocol for the Treatment of Autoinflammatory Syndromes*) which has been ongoing since 2011 (Kim et al. 2018; Sanchez et al. 2018). Safety information from the expanded access program has not identified any new safety signals for baricitinib beyond those identified in the Phase 3 studies in adult patients with RA.

The mechanism of action, combined with demonstration of clinical benefit in inflammatory diseases involving joints, kidneys, and skin, and additional experience in pediatric patients with rare autoinflammatory diseases provides the rationale for evaluating baricitinib in pediatric patients with moderate-to-severe AD.

Physicians with experience treating pediatric AD patients will participate as investigators in this clinical trial.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary for Double-blind Treatment Period • To demonstrate the superiority of each dose of baricitinib versus placebo in the treatment of patients with moderate-to-severe AD.	• Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16
Primary for PK Lead-in Period • To assess whether baricitinib exposure in pediatric patients receiving baricitinib high dose once daily is comparable to the exposure in adults receiving baricitinib 4-mg once daily.	• Comparability will be assessed using non-compartmental methods (e.g., AUC and C_{max})
Key Secondary *These are prespecified objectives that will be adjusted for multiplicity* • To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week double-blind placebo-controlled treatment period as measured by improvement in signs and symptoms of AD.	• Proportion of patients achieving EASI75 at 16 weeks • Proportion of patients achieving EASI90 at 16 weeks • Mean change from baseline in EASI score at 16 weeks

Objectives	Endpoints
	• Proportion of patients achieving SCORAD75 at 16 weeks
• To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week double-blind placebo-controlled treatment period as assessed by patient-reported outcome measures.	• Proportions of patients achieving a 4-point improvement in Itch NRS at 1 week, 2 weeks, 4 weeks, and 16 weeks for patients ≥10 years old
Other Secondary *These are prespecified objectives that will not be adjusted for multiplicity.*	
• To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week double-blind placebo-controlled period as measured by physician-assessed signs and symptoms of AD.	• Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 4 • Proportion of patients achieving EASI50 at 16 weeks • Proportion of patients achieving IGA of 0 at 16 weeks • Mean change from baseline in SCORAD at 16 weeks • Mean percent change from baseline in SCORAD at 16 weeks • Proportion of patients achieving SCORAD90 at 16 weeks • Mean percent change from baseline in EASI score at 16 weeks • Mean change from baseline in BSA affected at 16 weeks • Proportion of patients developing skin infections requiring antibiotic treatment by Week 16
• To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week, double-blind, placebo-controlled treatment period as assessed by patient-reported outcome/QoL measures.	• Mean number of days without use of TCS over 16 weeks • Mean gram quantity of TCS used over 16 weeks (tube weights) • Mean change from baseline in Itch NRS at 1 week, 4 weeks and 16 weeks for patients ≥10 years old • Mean percent change from baseline in Itch NRS at 1 week, 4 weeks and 16 weeks for patients ≥10 years old • Mean change in the PRISM at 1 week, 2 weeks, 4 weeks, and 16 weeks for patients <10 years old • Mean change from baseline in the total score of the POEM at 16 weeks • Mean change in PGI-S-AD scores at 16 weeks • Mean change from baseline in the PROMIS-pediatric depression at 16 weeks

Objectives	Endpoints
	• Mean change from baseline in the PROMIS-pediatric anxiety at 16 weeks • Mean change from baseline in DFI at 16 weeks • Mean change in CDLQI/IDQOL scores at 16 weeks • Mean change in WPAI-AD-CG scores at 16 weeks • Mean change in EQ-5D-Y scores at 16 weeks. • Mean change from baseline in the score of Item 2 of the ADSS at 1 week and 16 weeks for patients ≥10 years old. • Mean change from baseline in Skin Pain NRS at 16 weeks for patients ≥10 years old
• To assess the patient acceptability and palatability of baricitinib tablets and oral suspension.	• Assessment of tablet or oral suspension product acceptability and palatability during the Open-label PK Lead-in period
• To characterize the pharmacokinetic profile of the baricitinib in pediatric patients with AD.	• Population PK Analysis based on sparse sampling over 16 weeks (Study Period 3) with secondary endpoints including C_{max}, AUC, and t1/2
• To evaluate the potential effects of baricitinib on the cellular and humoral immune system.	• Change of IgG titers from pre-vaccination to 4 weeks and 12 weeks post vaccination in patients eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local guidelines
• To assess efficacy of baricitinib during longer-term treatment.	• Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at 1 year. • Proportion of patients achieving EASI75 at 1 year. • Proportion of patients achieving SCORAD75 at 1 year
• To assess growth and bone safety of baricitinib during longer-term treatment.	• Mean changes in growth (height and weight), growth velocity, and bone age over the course of treatment during the long-term extension treatment period

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; AUC = area under the concentration curve; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; C_{max} = maximum concentration; DFI = Dermatology Family Impact; EASI = Eczema Area and Severity Index; EQ-5D-Y = the European Quality of Life–5 Dimensions–Youth; IDQOL = Infant's Dermatitis Quality of Life Index; IgG = immunoglobulin G; IGA = Investigator's Global Assessment; NRS = numeric rating scale; PK = pharmacokinetic; QoL = quality of life; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PRISM = Parent-Reported Itch Severity Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; t1/2 = half-life; TCS = topical corticosteroids; SCORAD = SCORing Atopic Dermatitis; WPAI-AD-CG = Work Productivity and Activity Impairment: Atopic Dermatitis – Caregiver

Summary of Study Design:

Study I4V-MC-JAIP (JAIP) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib in pediatric patients with moderate-to-severe AD who have responded inadequately to or who are intolerant to topical treatments.

Treatment Arms and Duration:

The study is divided into 5 periods, a 5-week Screening period, a 2-week Open-label pharmacokinetic (PK) Lead-in period, a 16-week Double-Blind Treatment period, an up to 5-year Long-term Extension period, and a 4-week Post-treatment Follow-up period.

The Open-label PK Lead-in period will evaluate if exposure to baricitinib high dose in pediatric patients is comparable with baricitinib exposure in adults. Patients will receive oral baricitinib at a fixed high dose by age group once daily (QD) for approximately 2 weeks. Enrollment will be staggered by age group (10 to <18 years, 6 to <10 years, and 2 to <6 years), with older groups enrolling before younger groups. Enrollment of an age group into the Double-blind Treatment period will begin only after analysis of the PK data for that age group from the PK lead-in has been completed.

Number of Patients:

Approximately 465 will be enrolled into this study.

Approximately 25 patients will be enrolled into the PK lead-in (at least 15 patients aged 10 to <18 years old and at least 10 patients aged 2 to <10 years old).

Approximately 440 patients will be enrolled into the Double-blind Treatment period (with at least 320 patients aged 10 to <18 years old and at least 120 patients aged 2 to <10 years old.

Statistical Analysis:

Approximately 25 patients will be enrolled into the Open-label PK Lead-in (Study Period 2) and may continue on open-label treatment during the long-term extension (Study Period 4). Data from patients participating in the PK lead-in will be analyzed separately from patients randomized into the Double-blind Treatment (Study Period 3).

Approximately 440 patients 2 to <18 years of age will participate in the Double-blind Treatment period (Study Period 3) and will be randomized at a 1:1:1:1 ratio to receive placebo QD, baricitinib low dose QD, baricitinib medium dose QD, or baricitinib high dose QD (110 patients in each treatment group). Patients will be stratified at randomization according to disease severity (Investigator's Global Assessment [IGA] 3 vs. 4) and geographic region if the planned country allocation justifies.

The study will be carried out using an intent-to-treat population defined as all randomized patients for the efficacy analyses. The primary efficacy measure is the binary outcome of response defined as an IGA score of 0 or 1 (clear or almost clear) with a ≥2-point improvement at Week 16. Given the sample size and a non-responder imputation (NRI) method for missing data, the current sample size (N=440 with 1:1:1:1 randomization) will ensure a >95% power to detect any difference between the baricitinib high dose and placebo treatment groups or the baricitinib medium dose and placebo treatment groups, each using a 2-sided alpha of 0.05, assuming a 10% placebo, 25% medium dose, and 30% high dose response rate for the primary endpoint. Patients who are rescued or discontinue treatment will be considered non-responders. Treatment group comparisons for binary efficacy response measures will be analyzed using a logistic regression. The primary analysis will be conducted using a logistic regression analysis with region, disease severity (IGA), age, treatment group, and treatment group-by-age interaction in the model. Other secondary measures of efficacy that are continuous will be analyzed using mixed-model repeated measures (MMRM) methodology. Placebo multiple imputation and last observation carried forward methods will also be used for analysis of continuous endpoints. Population PK and PK/PD analyses based on data from the Double-blind Treatment period will be used to characterize the PK of baricitinib and to explore relationships between baricitinib exposure and efficacy and/or safety endpoints. In the case of slower enrollment for the younger pediatric subgroup (i.e., the older pediatric subgroup completes the double-blind treatment period more than 6 months earlier than the anticipated completion date for the younger subgroup of pediatric patients), the older pediatric subgroup may be analyzed first according to a pre-planned analytical approach to support timely regulatory submission.

Safety analyses will be conducted using the safety population defined as all randomized patients who received at least 1 dose of investigational product (IP) and who did not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit.

2. Schedule of Activities

The Schedule of Activities described below should be followed for all participants enrolled in Study JAIP. In the event participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Appendix 10 and consult with the sponsor's representative for additional guidance.

Table JAIP.1. Schedule of Activities for Patients Participating in the Open-label PK Lead-in

	Screening	Open-label PK Lead-in				Long-term Extension Treatment										
	Period 1	Period 2				Period 4										
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Procedures																
Inclusion and exclusion criteria review	X	X														
Informed consent/Assent	X															
Clinical assessments and general study procedures																
Demographics	X															
Medical History	X															
Substance Use (alcohol, tobacco use for patients ≥10 years)	X															
Previous and current AD treatments	X															
Weight	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Height[b]		X						X	X	X	X	X	X	X	X	X
Vital signs (BP and Pulse)[b]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Occipital frontal circumference measurement in patients <3 years old		X				X	X	X	X	X	X	X	X	X	X	X
Physical examination	X															

Approved on 14 Feb 2023 GMT

	Screening	Open-label PK Lead-in				Long-term Extension Treatment										
	Period 1	Period 2				Period 4										
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Procedures																
Tanner Staging in patients ≥8 years old (see Section 9.4.4.1.)		X														
Symptom-directed physical exam[c]		X	X	X		X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (single)	X															
TB test[d]	X															
Read PPD if applicable (48–72 hours post PPD)[e]	X															
Pre-existing Conditions	X															
Adverse Events		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ePRO (patient diary) dispensed	X	X	X	X		X	X									
ePRO (patient diary) returned		X	X	X		X	X	X								
Begin treatment with open-label baricitinib		X														
IWRS	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
IP tablets dispensed (patients ≥10 years old)		X	X	X		X	X	X	X	X	X	X	X	X	X	X
IP suspension dispensed (patients <10 years old)		X				X		X	X	X	X	X	X	X	X	X

	Screening	Open-label PK Lead-in				Long-term Extension Treatment										
	Period 1	Period 2				Period 4										
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Procedures																
IP returned and compliance assessed			X	X		X	X	X	X	X	X	X	X	X	X	X
Dispense and weigh (tube with cap) TCS[f]			X	X		X	X	X	X	X	X	X	X	X	X	X
Weigh (tube with cap) and record returned TCS[f]				X		X	X	X	X	X	X	X	X	X	X	X
Scales																
vIGA-AD	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
SCORAD	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Health Outcomes Measures and Other Questionnaires																
POEM[g]	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
CDLQI /IDQOL[g]	X	X	X	X		X		X	X	X	X	X	X	X	X	X
DFI[g]		X	X	X		X		X	X	X	X	X	X	X	X	X
PROMIS-Depression[g]	X	X		X		X		X	X	X	X	X	X	X	X	X
PROMIS-Anxiety[g]	X	X		X		X		X	X	X	X	X	X	X	X	X
EQ-5D-Y[g]		X	X	X		X	X	X	X	X	X	X	X	X	X	X
WPAI-AD-CG[g]		X	X	X		X		X	X	X	X	X	X	X	X	X
Missed School Days for school age children[g]	X	X	X	X		X	X	X								
PRISM[g]	X	X	X	X		X	X	X								
Itch NRS[g]	X	X	X	X		X	X	X								

	Screening	Open-label PK Lead-in				Long-term Extension Treatment										
	Period 1	Period 2				Period 4										
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Procedures																
Skin Pain NRS[g]	X	X	X	X		X	X	X								
ADSS[g]	X	X	X	X		X	X	X								
PGI-S-AD[g]	X	X	X	X		X	X	X								
TCS Use[g]			X	X		X	X	X								
Palatability and Acceptability		X		X[g]												
C-SSRS and Self-Harm Supplement[h]	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
Laboratory Assessments																
Clinical chemistry[j, q]	X	X				X	X	X	X	X	X	X	X	X	X	X
Hematology[q]	X	X				X	X	X	X	X	X	X	X	X	X	X
Lipids (fasting)[k, q]		X					X		X		X		X		X	X
IGF-1 and IGFBP-3[q]		X						X		X		X		X		X
Left hand x-ray[l] (see Section 9.4.9.3 for ongoing patients)		X							X		X		X		X	
X-ray of the knee[l] (see Section 9.4.9.3 for ongoing patients)		X							X		X		X		X	
Gonadal hormones (patients 8 to <18 years old)[m, q]		X						X		X		X		X		X
Serum Pregnancy[n]	X															

	Screening	Open-label PK Lead-in				Long-term Extension Treatment										
	Period 1	Period 2				Period 4										
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Procedures																
TSH	X															
HIV	X															
HCV antibody[o]	X															
HBV testing	X															
HBV DNA[p]	X							X	X	X	X	X	X	X	X	X
Urinalysis[q]	X	X				X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy[n, q]		X		X		X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics: blood[q]		X														
Serum IgE[q]		X				X		X	X	X	X	X	X	X	X	X
Exploratory storage samples (serum and plasma)[q]		X				X		X	X	X	X	X	X	X	X	X
RNA and biomarkers: blood[q]		X				X		X	X	X	X	X	X	X	X	X
Baricitinib plasma concentration (PK sample)[r]		X	X	X												
Antipneumococcal IgG multianalyte Ab assay*		At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient. *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.														

	Screening	Open-label PK Lead-in				Long-term Extension Treatment										
	Period 1	Period 2				Period 4										
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Procedures																
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay*			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient. *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.														

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (PK Lead-in Patients)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ ET[a]**	**801**
Weeks from initiation of baricitinib treatment	**124**	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ± 4 after last dose
Clinical assessments and general study procedures													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[b]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (BP and Pulse)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Occipital frontal circumference measurement in patients <3 years old	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam[c]	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

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (PK Lead-in Patients)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ ET[a]**	**801**
Weeks from initiation of baricitinib treatment	**124**	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ± 4 after last dose
Clinical assessments and general study procedures													
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X
IP tablets dispensed (patients ≥10 years old)	X	X	X	X	X	X	X	X	X	X	X		
IP suspension dispensed (patients <10 years old)	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	
Dispense and weigh (tube with cap) TCS[f]	X	X	X	X	X	X	X	X					
Weigh (tube with cap) and record returned TCS[f]	X	X	X	X	X	X	X	X	X			X	X
Scales													
vIGA-AD	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
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Outcomes Measures and Other Questionnaires													
POEM[g]	X	X	X	X	X	X	X	X				X	X
CDLQI /IDQOL[g]	X	X	X	X	X	X	X	X				X	X
DFI[g]	X	X	X	X	X	X	X	X				X	X
PROMIS-Depression[g]	X	X	X	X	X	X	X	X				X	
PROMIS-Anxiety[g]	X	X	X	X	X	X	X	X				X	
EQ-5D-Y[g]	X	X	X	X	X	X	X	X				X	X
WPAI-AD-CG[g]	X	X	X	X	X	X	X	X				X	X
C-SSRS and Self-Harm Supplement[h]	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

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (PK Lead-in Patients)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ ET[a]**	**801**
Weeks from initiation of baricitinib treatment	**124**	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ± 4 after last dose
Clinical assessments and general study procedures													
Laboratory Assessments													
Clinical chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids (fasting)[k]		X		X		X		X		X		X	
IGF-1 and IGFBP-3		X		X		X		X					
Left hand x-ray[l] (see Section 9.4.9.3 for ongoing patients)	X		X		X		X		X		X		
X-ray of the knee[l] (see Section 9.4.9.3 for ongoing patients)	X		X		X		X		X		X		
Gonadal hormones (patients 8 to <18 years old)[m]		X		X		X		X					
HBV DNA[p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X				X	X
Urine Pregnancy[n]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum IgE	X		X		X		X						
Antipneumococcal IgG multianalyte Ab assay*	At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient. *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.												

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (PK Lead-in Patients)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ ET[a]**	**801**
Weeks from initiation of baricitinib treatment	**124**	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ± 4 after last dose
Clinical assessments and general study procedures													
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay*	At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient. *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.												

Abbreviations: Ab = antibody; AD = Atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale 11 categories suicidal ideation/suicidal behavior; CDLQI = Children's Dermatology Life Quality Index; DFI = Dermatitis Family Impact; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-Y = The European Quality of Life-5 Dimensions Youth; ET = early termination; ePRO = electronic patient reported outcomes (device); HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; IDQOL = Infant's Dermatitis Quality of Life Index; IgE = Immunoglobulin E; IGFBP-3 = insulin-like growth factor binding protein-3; IgG = Immunoglobulin G; IP = investigational product; IWRS = interactive web-response system; NRS = numeric rating scale; PGI-S-AD = Patient Global Impression of Severity – Atopic Dermatitis; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; PPD = purified protein derivative; PRISM = Parent-Reported Itch Severity Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; PTF/U = post-treatment follow-up; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TCS = topical corticosteroids; TSH = thyroid stimulating hormone; vIGA-AD = validated investigator's global assessment for atopic dermatitis; WPAI-AD-CG = Work Productivity and Activity Impairment-Atopic Dermatitis-Caregiver.

[a] An early termination visit should be conducted if a patient discontinues from the study before Visit 31. Visit 801 is the post-treatment follow-up visit, which occurs after the patient has been off 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 31/ET; Visit 801 (follow-up visit) is not required. Patient health outcomes assessments (POEM, CDLQI/IDQOL, DFI, PROMIS-Depression, PROMIS-Anxiety, EQ-5D-Y, WPAI-AD-CG) are collected for the early termination visit but are not collected at Visit 31.

[b] Height will be measured using a stadiometer and Sponsor-provided instructions. Blood pressure readings will be collected using the appropriate size pediatric blood pressure cuffs.

[c] The symptom-directed physical examination may be repeated at the investigator's discretion any time a patient presents with physical complaints.

[d] TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally.

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

[f] Only required for patients who have been prescribed sponsor-provided TCS. At Visit 28 and beyond, TCS will no longer be provided by the sponsor.

[g] The following measures (POEM, CDLQI/IDQOL, DFI, PROMIS-Depression and Anxiety, EQ-5D-Y, WPAI-AD-CG, and palatability/acceptability as noted) should be completed prior to any clinical assessments being performed on days when study visits occur. The following measures are collected via daily diary and should be completed at the end of the patient's day: PGI-S-AD, Itch NRS, Skin Pain NRS, ADSS, PRISM, missed school days and TCS use.

[h] Suicidal ideation and behavior subscales excerpt – Adapted for the assessment of 11 preferred ideation and behavior categories. The C-SSRS will only be collected in patients ≥7 years old.

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

[j] Clinical chemistry will include estimated glomerular filtration rate (eGFR, calculated using Bedside Schwartz 2009 formula) calculated by the central laboratory from serum creatinine.

[k] Fasting lipid profile: Patients should not eat or drink anything except water for 4 to 12 hours (depending on age and weight as specified in Section 9.4.3) prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered to be a protocol violation.

[l] Left hand and knee x-rays at an early termination visit is not required if previously taken within 6 months of the early termination visit. The collection of x-rays and other imaging procedures should be discontinued after the patient reaches 18 years of age.

[m] Estradiol (for females) or testosterone (for males) will be collected for the assessment of maturation in patients aged 8 to <18 years.

[n] Pregnancy tests prior to first dose of investigational product for females ≥10 years old of age (<10 years at investigator discretion) if menarche reached or if there is reason to believe the patient is sexually active. Pregnancy test results from Visit 2 must be known prior to first dose of investigational product. A serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and at all subsequent study visits after Visit 3. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

[o] For patients who are positive for HCV antibody, a follow-up test for HCV RNA will be performed automatically. Patients who are positive for HCV antibody and negative for HCV RNA may be enrolled.

[p] Patients who are positive for hBcAb and negative for HBV DNA may be enrolled. Any enrolled patient who is HBcAb positive, regardless of hBsAb status or level, must undergo HBV DNA testing per the schedule (see Section 9.4.8).

[q] At Visit 2 all laboratory samples, with the exception of PK samples, will be obtained prior to the first dose of IP.

[r] PK samples will be collected as described in Section 9.5.

[s] At Visit 27, patients should be discontinued from study treatment and begin study discontinuation procedures unless sponsor's written approval is obtained to allow the patient to continue on study treatment. Refer to Section 5.1.4.

Table JAIP.2. Schedule of Activities for Patients Randomized to Double-blind Treatment in Study Period 3

	Screening	Double-blinded Treatment							Long-term Extension Treatment										
	Period 1	Period 3							Period 4										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Procedures																			
Inclusion and exclusion criteria review	X	X																	
Informed consent/Assent	X																		
Clinical assessments and general study procedures																			
Demographics	X																		
Medical History	X																		
Substance Use (alcohol, tobacco use for patients ≥10 years old)	X																		
Previous and current AD treatments	X																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[b]		X						X			X	X	X	X	X	X	X	X	X
Vital signs (BP and Pulse)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Occipital frontal circumference measurement in patients <3 years old		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X																		

	Screening	Double-blinded Treatment							Long-term Extension Treatment										
	Period 1	Period 3							Period 4										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Tanner Staging in patients ≥8 years old (see Section 9.4.4.1.)		X																	
Symptom-directed physical exam[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (single)	X																		
TB test[d]	X																		
Read PPD if applicable (48–72 hours post PPD)[e]	X																		
Pre-existing Conditions	X																		
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	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	X	X	X	X												
ePRO (patient diary) returned		X	X	X	X	X	X	X											
Randomization		X																	
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP tablets dispensed (patients ≥10 years old)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP suspension dispensed (patients <10 years old)		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	X

	Screening	Double-blinded Treatment							Long-term Extension Treatment										
	Period 1	Period 3							Period 4										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Dispense and weigh (tube with cap) TCS[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weigh (tube with cap) and record returned TCS[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Scales																			
vIGA-AD	X	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	X
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Outcomes Measures and Other Questionnaires																			
POEM[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDLQI /IDQOL[g]	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	X
DFI[g]		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X
PROMIS-Depression[g]	X	X		X	X	X		X		X		X	X	X	X	X	X	X	X
PROMIS-Anxiety[g]	X	X		X	X	X		X		X		X	X	X	X	X	X	X	X
EQ-5D-Y[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-AD-CG[g]		X	X	X	X	X		X		X		X	X	X	X	X	X	X	X
Missed School Days for school age children[g]	X	X	X	X	X	X	X	X											
PRISM[g]	X	X	X	X	X	X	X	X											
Itch NRS[g]	X	X	X	X	X	X	X	X											
Skin Pain NRS[g]	X	X	X	X	X	X	X	X											
ADSS[g]	X	X	X	X	X	X	X	X											
PGI-S-AD[g]	X	X	X	X	X	X	X	X											
TCS Use[g]	X	X	X	X	X	X	X	X											

	Screening	Double-blinded Treatment							Long-term Extension Treatment										
	Period 1	Period 3							Period 4										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
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	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	X
Laboratory Assessments																			
Clinical chemistry[j, q]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[q]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids (fasting)[k, q]		X					X				X		X		X		X		X
IGF-1 and IGFBP-3[q]		X						X				X		X		X		X	
Left hand x-ray[l] (see Section 9.4.9.3 for ongoing patients)		X						X					X		X		X		X
X-ray of the knee[l] (see Section 9.4.9.3 for ongoing patients)		X								X			X		X		X		X
Gonadal hormones (patients 8 to <18 years old)[m, q]		X						X				X		X		X		X	
Serum Pregnancy[n]	X																		
TSH	X																		
HIV	X																		
HCV antibody[o]	X																		
HBV testing	X																		
HBV DNA[p]	X							X			X	X	X	X	X	X	X	X	X
Urinalysis[q]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy[n, q]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Double-blinded Treatment							Long-term Extension Treatment										
	Period 1	Period 3							Period 4										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Pharmacogenetics: blood[q]		X																	
Serum IgE[q]		X			X			X			X	X	X	X	X	X	X	X	X
Exploratory storage samples (serum and plasma)[q]		X			X			X			X	X	X	X	X	X	X	X	X
RNA and biomarkers: blood[q]		X			X			X			X	X	X	X	X	X	X	X	X
Baricitinib plasma concentration (PK sample)[r]		X			X	X	X	X											
Antipneumococcal IgG multianalyte Ab assay*			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient. *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.																
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay*			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.																

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (Patients Randomized to Double-Blind Treatment at Visit 2)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ ET[a]**	**801**
Weeks from randomization	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	**268**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ±4 after last dose
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[b]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (BP and Pulse)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Occipital frontal circumference measurement in patients <3 years old	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-directed physical exam[c]	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
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X
IP tablets dispensed (patients ≥10 years old)	X	X	X	X	X	X	X	X	X	X	X		
IP suspension dispensed (patients <10 years old)	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	
Dispense and weigh (tube with cap) TCS[f]	X	X	X	X	X	X	X	X					
Weigh (tube with cap) and record returned TCS[f]	X	X	X	X	X	X	X	X	X			X	X
Scales													
vIGA-AD	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
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (Patients Randomized to Double-Blind Treatment at Visit 2)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ ET[a]**	**801**
Weeks from randomization	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	**268**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ±4 after last dose
Health Outcomes Measures and Other Questionnaires													
POEM[g]	X	X	X	X	X	X	X	X				X	X
CDLQI /IDQOL[g]	X	X	X	X	X	X	X	X				X	X
DFI[g]	X	X	X	X	X	X	X	X				X	X
PROMIS-Depression[g]	X	X	X	X	X	X	X	X				X	
PROMIS-Anxiety[g]	X	X	X	X	X	X	X	X				X	
EQ-5D-Y[g]	X	X	X	X	X	X	X	X				X	X
WPAI-AD-CG[g]	X	X	X	X	X	X	X	X				X	X
C-SSRS and Self-Harm Supplement[h]	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
Laboratory Assessments													
Clinical chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipids (fasting)[k]		X		X		X		X		X		X	
IGF-1 and IGFBP-3	X		X		X		X						
Left hand x-ray[l] (see Section 9.4.9.3 for ongoing patients)		X		X		X		X		X		X	
X-ray of the knee[l] (see Section 9.4.9.3 for ongoing patients)		X		X		X		X		X		X	
Gonadal hormones (patients 8 to <18 years old)[m]	X		X		X		X						
HBV DNA[p]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X				X	X

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (Patients Randomized to Double-Blind Treatment at Visit 2)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ ET[a]**	**801**
Weeks from randomization	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	**268**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ±4 after last dose
Urine Pregnancy[n]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum IgE		X		X		X		X					
Baricitinib plasma concentration (PK sample)[r]												X	
Antipneumococcal IgG multianalyte Ab assay*	At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient. *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.												
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay*	At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient. *If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination.												

Abbreviations: Ab = antibody; AD = Atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale 11 categories suicidal ideation/suicidal behavior; CDLQI = Children's Dermatology Life Quality Index; DFI = Dermatitis Family Impact; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-Y = The European Quality of Life-5 Dimensions Youth; ET = early termination; ePRO = electronic patient reported outcomes (device); HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; IDQOL = Infant's Dermatitis Quality of Life Index; IgE = immunoglobulin E; IGFBP-3 = insulin-like growth factor binding protein-3; IgG = immunoglobulin G; IP = investigational product; IWRS = interactive web-response system; NRS = numeric rating scale; PGI-S-AD = Patient Global Impression of Severity – Atopic Dermatitis; PK = pharmacokinetics; POEM = Patient Oriented Eczema Measure; PPD = purified protein derivative; PRISM = Parent-Reported Itch Severity Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; PTF/U = post-treatment follow-up; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TCS = topical corticosteroids; TSH = thyroid stimulating hormone; vIGA-AD = validated investigator's global assessment for atopic dermatitis; WPAI-AD-CG = Work Productivity and Activity Impairment-Atopic Dermatitis-Caregiver.

[a] An early termination visit should be conducted if patient discontinues from the study before Visit 31. Visit 801 is the post-treatment follow-up visit, which occurs after the patient has been off 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 31/ET; Visit 801 (follow-up visit) is not required. Patient health outcomes assessments (POEM, CDLQI/IDQOL, DFI, PROMIS-Depression, PROMIS-Anxiety, EQ-5D-Y, WPAI-AD-CG) are collected for the early termination visit but are not collected at Visit 31.

[b] Height will be measured using a stadiometer and Sponsor-provided instructions. Blood pressure readings will be collected using the appropriate size pediatric blood pressure cuffs.

[c] The symptom-directed physical examination may be repeated at the investigator's discretion any time a patient presents with physical complaints.

[d] TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally.

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

[f] For patients prescribed sponsor-provided TCS as background treatment. At Visit 28 and beyond, TCS will no longer be provided by the sponsor.

[g] The following measures (POEM, CDLQI/IDQOL, DFI, PROMIS-Depression and Anxiety, EQ-5D-Y, and WPAI-AD-CG) should be completed prior to any clinical assessments being performed on days when study visits occur. The following measures are collected via daily diary and should be completed at the end of the patient's day: PGI-S-AD, Itch NRS, Skin Pain NRS, ADSS, PRISM, missed school days, and TCS use.

[h] Suicidal ideation and behavior subscales excerpt – Adapted for the assessment of 11 preferred ideation and behavior categories. The C-SSRS will only be collected in patients ≥7 years old.

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

[j] Clinical chemistry will include estimated glomerular filtration rate (eGFR, calculated using Bedside Schwartz 2009 formula) calculated by the central laboratory from serum creatinine.

[k] Fasting lipid profile: Patients should not eat or drink anything except water for 4 to 12 hours (depending on age and weight as specified in Section 9.4.3) prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered to be a protocol violation.

[l] Left hand and knee x-rays at an early termination visit is not required if previously taken within 6 months of the early termination visit. The collection of x-rays and other imaging procedures should be discontinued after the patient reaches 18 years of age.

[m] Estradiol (for females) or testosterone (for males) will be collected for the assessment of maturation in patients aged 8 to <18 years.

[n] Pregnancy tests prior to first dose of investigational product for females ≥10 years old of age (<10 years at investigator discretion) if menarche reached or if there is reason to believe the patient is sexually active. Pregnancy test results from Visit 2 must be known prior to first dose of investigational product. A serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and at all subsequent study visits after Visit 3. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

[o] For patients who are positive for HCV antibody, a follow-up test for HCV RNA will be performed automatically. Patients who are positive for HCV antibody and negative for HCV RNA may be enrolled.

[p] Patients who are positive for hBcAb and negative for HBV DNA may be enrolled. Any enrolled patient who is hBcAb positive, regardless of hBsAb status or level, must undergo HBV DNA testing per the schedule (see Section 9.4.8).

q At Visit 2 all laboratory samples, with the exception of PK samples, will be obtained prior to the first dose of IP.

r PK samples will be collected as described in Section 9.5.

s At Visit 27, patients should be discontinued from study treatment and begin study discontinuation procedures unless sponsor's written approval is obtained to allow the patient to continue on study treatment. Refer to Section 5.1.4.

3. Introduction

3.1. Study 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 2008). In addition to AD resulting from T cell activation, there is also evidence that a defective epidermal barrier contributes to the AD process. Patients with filaggrin mutations are at increased risk for developing AD, as filaggrin contributes to abnormal barrier function (Palmer et al. 2006). Presentation is varied, but includes skin manifestations, including pruritus, associated sleep disturbances, and subsequent skin infections. The course of disease includes relapses of varying duration and severity. Atopic dermatitis is one of the most common chronic diseases in childhood. The prevalence of AD is higher in children than in adults, and pediatric patients with AD are afflicted with a heavy disease burden. The prevalence of AD ranges from approximately 9% in teenagers to 14% in children 0 to 4 years of age (Shaw et al. 2011). In addition, the distribution of severity tends to shift to higher severities at older ages with older children being more likely to have moderate to severe disease (Silverberg and Simpson 2014).

Atopic dermatitis has traditionally been treated with emollients and topical corticosteroids (TCS) to address barrier dysfunction and immune abnormalities: low-potency TCS for mild cases, medium- and high-potency TCS for moderate cases. The standard of care remains medium to high-potency TCS in both adult and pediatric patients. Although TCS are used broadly in AD, patients with moderate to severe disease may not achieve good disease control with these treatments. In a recently published study of dupilumab with concomitant TCS in adult patients with moderate-to-severe AD (Blauvelt et al. 2017), only 12% of patients randomized to placebo with TCS achieved clear or almost clear skin after 16 weeks of treatment. It is generally accepted that TCS response and intolerance in pediatric patients is similar to adults (Lan et al. 2003; Tan and Langley 2004; Lubbe et al. 2006); however, given their larger body surface area to weight ratio, children are at greater risk for systemic effects from TCS use (Eichenfield et al. 2014a). Topical calcineurin inhibitors are approved for the treatment of AD in pediatric patients from the age of 2 with inadequate response or intolerance to TCS (tacrolimus) or where treatment with TCS is either inadvisable or not possible (pimecrolimus). In a recent meta-analysis of clinical trial data of almost 7,000 patients treated over the last 15 years, either with TCS or topical calcineurin inhibitors (TCNIs), efficacy was considered similar between the 2 drug categories (Broeders et al. 2016). Although treatment guidelines have recommended the use of TCNIs in the pediatric population, this recommendation is limited to use based on individual clinical assessment in specific clinical situations (NICE 2007; Eichenfield et al. 2014a; Werfel et al. 2016b). Ciclosporin is the only approved systemic treatment for AD (only approved in some countries) for pediatric patients and is restricted to the treatment of patients ≥16 years old with severe AD when systemic therapy is required. Ciclosporin may be associated with toxicity and side effects, and use is time-limited due to end-organ toxicity, including hypertension and renal toxicity. While no specific data on off-label use in younger children are available, use is considered very rare given that this treatment regimen is already rarely used in

AD adults (Schmitt et al. 2009). Similar to adults, a need exists for new treatments that demonstrate safety and efficacy in pediatric patients who have responded inadequately to or who are intolerant to topical treatments.

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 cytokines involved in AD pathogenesis. The JAK-STAT signaling pathway is functional from infancy, and aberrations in JAK-STAT signaling are implicated in other rare autoinflammatory diseases with onset within the first year of life (Liu et al. 2012; Liu et al. 2014), supporting the assumption that a JAK inhibitor such as baricitinib will be efficacious in the treatment of AD in both adult and pediatric patients.

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 (RA) (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. 2018); was effective in improving signs and symptoms of active systemic lupus erythematosus (Wallace et al. 2018); and in a recently completed Phase 2 study (I4V-MC-JAHG [JAHG]) was effective at reducing disease severity in adult patients with moderate-to-severe AD (Guttman-Yassky et al. 2018). In addition, baricitinib is being used to treat pediatric patients participating in an expanded access program (protocol I4V-MC-JAGA [JAGA]: *Compassionate Use Protocol for the Treatment of Autoinflammatory Syndromes*) which has been ongoing since 2011 (Kim et al. 2018; Sanchez et al. 2018). More than 30 patients ages 2 months to <18 years have been enrolled in the program as of June 2018. Safety information from the expanded access program has not identified any new safety signals for baricitinib beyond those identified in the Phase 3 studies in adult patients with RA.

The current study will investigate a range of baricitinib doses that produce comparable exposures between pediatric patients and adults. The assumption that similar exposures of baricitinib in adults and pediatric patients will result in similar response relies on the similarities in AD disease manifestation, aetiology, pathophysiology, response to existing therapies, and the similarity in the target populations to be enrolled in the adult and pediatric baricitinib studies. This assumption has recently been supported by a consensus committee formed in partnership with the Pediatric Dermatology Research Alliance (PeDRA, a predominantly North American network with some European involvement); the US National Eczema Association (NEA), and the International Eczema Council (IEC 2017) (Siegfried et al. 2018).

Given the prevalence of AD and the need for new AD treatments with demonstrated efficacy and safety in the pediatric population, the mechanism of action, combined with demonstration of

clinical benefit in inflammatory diseases involving joints, kidneys, and skin, and additional experience in pediatric patients with rare autoinflammatory diseases provides the rationale for evaluating baricitinib in pediatric patients with moderate-to-severe AD.

Physicians with a specialty in dermatology and experience treating pediatric patients will participate as investigators in this clinical trial.

3.2. Background

Atopic dermatitis, also known as atopic eczema, is a common chronic relapsing highly symptomatic inflammatory skin disease. Patients with AD may present with skin lesions that can be acute in presentation, with oozing, crusted, eroded vesicles, or papules on erythematous plaques. Patients may also present with lesions that have a sub-acute appearance, with thick and excoriated plaques, or chronic appearance, with lichenified, slightly pigmented, excoriated plaques (Bieber 2010). While clinical manifestations are overall similar in adults and pediatric patients, the localization and type of skin lesions differs slightly. In infants, the first signs of AD usually emerge with eczematous, papulo-vesicular and patchy lesions localized to the cheeks. In childhood, eczematous lesions typically involve flexural areas (ante-cubital fossae, neck, wrists, and ankles) and the nape of the neck, dorsum of the feet, and hands. In adolescence and adulthood, flexural areas as well as head and neck will be typically involved with mostly lichenified plaques (Bieber 2010). Atopic dermatitis causes pruritus attacks throughout the day and worsening at night, which is the primary source of morbidity in this disorder. Pruritus often leads to an "itch-scratch" cycle (36% of patients report that they often or always scratch until their skin bleeds [Langenbruch et al. 2014]) that can further compromise the epidermal barrier and result in dry skin, microbial colonization, and secondary infections (Krakowski et al. 2008; Simpson 2012).

In clinical practice, AD is classified based on a variety of clinical features, including severity of skin lesions and pruritus, and extent of disease (body surface area [BSA] involved). Formal AD severity assessments used in clinical trials (e.g., Investigator's Global Assessment [IGA], a severity scale commonly used in clinical trials to define mild, moderate, and severe disease that assigns a score of "2" for mild disease, "3" for moderate, and "4" for severe) are rarely used in clinical practice, which makes comparison of disease severity across different demographic groups difficult (Futamura et al. 2016). In a population-based survey, approximately two-thirds of individuals with an empirical diagnosis of AD reported having moderate to severe symptoms (Hanifin et al. 2007). Atopic dermatitis severity has been reported to be correlated with age in children, with older children being slightly more likely to have moderate to severe disease (Silverberg and Simpson 2014).

Patients with AD (including children) experience higher rates of bacterial skin infection, with methicillin-resistant *Staphylococcus aureus* colonization occurring in approximately 90% of patients with severe AD versus 1% to 3% in the general population (Ong and Leung 2016). Viral skin infections can also occur in patients with AD. Eczema herpeticum is one of the most frequent viral skin infections in patients with AD and occurs in approximately 3% of these patients (Ong and Leung 2016).

Patients with moderate-to-severe AD carry a heavy disease burden with medical and psychosocial abnormalities. Atopic dermatitis can cause sleep disturbances in both adult and pediatric patients as a result of itching. Sleep disturbances in AD are thought to be associated with nocturnal itch and scratching behavior (Mostaghimi 2008). Similar to adults, health related quality of life (QoL) worsens in children with the severity of skin disease (Ben-Gashir et al. 2004) and may reach or even exceed that experienced with many other chronic diseases of childhood, including asthma, epilepsy, diabetes, and chronic renal disease (Beattie and Lewis-Jones 2006; Blome et al. 2016). Children who experience irregular sleep are more likely to show problematic behaviors including anxiety and depression, social problems, attention problems, and delinquent or aggressive behaviors (Ben-Gashir et al. 2004; Yokomaku et al. 2008; Blome et al. 2016). Another critical aspect of QoL in children with AD is difficulties with their peers. Lawson et al. (1998) showed that as much as 60% experienced bullying, 100% were teased, 30% had poor school attendance, and 54% experienced behavioral disturbances such as irritability, bad-temperedness, boredom, and being hurtful to other family members.

Family QoL can also be severely impaired because of sleep deprivation by the affected child as well as disruption of school and social interactions (Su et al. 1997; Lawson et al. 1998; Leung 2000; Ben-Gashir et al. 2004). Lawson et al. (1998) suggests that 74% of parents experienced a general burden of extra care and that 71% expressed feelings of guilt, exhaustion, frustration, resentment, and helplessness.

There are no known differences in the aetiology of AD between adults and children, as the vast majority of patients (85%) with adult AD are diagnosed before the age of 5 years (Bieber 2010). The underlying cause of AD is not yet completely understood. The importance of genetic factors must be taken into account because a positive parental history is the strongest risk factor for AD in children. The incidence rate of AD in children is doubled if one parent has the disease and is tripled if both parents have the disease (Bieber 2010). Loss of function mutations in filaggrin (filament aggregation protein) gene, 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 (Irvine et al. 2011).

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). In addition to directly inducing itch by activating sensory neurons in the skin (Wilson et al. 2013), 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; Zhong et al. 2014; Divekar and Kita 2015). While the fundamental pathophysiology with excessive T-cell activation is similar in adults and children, recent literature suggests that in early pediatric AD, the Th2 imbalance may be confined to skin-homing (cutaneous lymphocyte antigen–positive) T-cell subsets, while in adults T-cell activation extends into systemic/cutaneous lymphocyte antigen–negative and CD8+ T cells, as well as into IL-22–producing T-cells (Czarnowicki et al. 2015, Werfel et al. 2016a). Thymic stromal lymphopoietin and other key cytokines involved in AD pathogenesis, such as

IL-13, IL-5, IL-4, IL-22, and IL-31, signal through receptors associated with intracellular JAK signal transducers and activators of transcription activation and are anticipated to be modulated by baricitinib treatment (Clark et al. 2014). In addition, several cytokines (e.g., TSLP, IL-33) can directly activate pruritogenic neurons to mediate itch, and these pruritogenic cytokines utilize receptors that can be attenuated by JAK1 and JAK2 inhibitors (Oetjen et al. 2017).

The overall prevalence of AD among children and adolescents is approximately 10% to 13% (Augustin et al. 2015; Shaw et al. 2011; Silverberg and Simpson 2014). A recent analysis of data from 293,181 children up to 18 years of age from a German health insurance database showed a prevalence of 10% for a diagnosis of atopic eczema (Augustin et al. 2015). Epidemiological data from a children's health national survey in the US based on study of a nationally representative sample of 91,642 children age 0 to 17 years showed that the overall prevalence of childhood eczema was 13%, with 67% having mild disease, 26% having moderate disease, and 7% having severe disease (Silverberg and Simpson 2014). These data suggest that AD severity is correlated with age in children, with older children being slightly more likely to have moderate to severe disease. It has been estimated that 2% of pediatric patients with atopic eczema/dermatitis have severe disease that does not respond to topical anti-inflammatory drugs or UV light treatment (McAleer et al. 2012).

3.3. Benefit/Risk Assessment

In the baricitinib Phase 2 study in moderate-to-severe AD, Study JAHG, baricitinib doses of 2- and 4-mg showed early improvement in both physician- and patient-reported signs and symptoms of AD, including improvement in skin inflammation, itch, sleep disruption, and quality of life. For a summary of the Phase 2 Study (JAHG) efficacy data, see Section 5.5 (Justification for Dose).

Serious infections, venous thromboembolic events, hepatotoxicity, and fetal malformations were identified as important potential risks with baricitinib in RA studies. Although infections were seen in about half of the study population exposed to baricitinib in the RA program, only 3.6% of patients reported a serious treatment-emergent infection, and rates were similar in both baricitinib- and placebo-treated patients. In the Phase 2 AD study, approximately 25% of patients treated with the 4-mg dose experienced a treatment-emergent adverse event (TEAE) of infection and infestation, compared to 20% of patients treated with placebo. There were no venous thromboembolic events (VTEs), serious infections, opportunistic infections, or herpes zoster infections reported during the treatment period in the AD Phase 2 study. The nonserious infections for baricitinib noted in the RA program (upper respiratory tract infections, herpes zoster, and herpes simplex) are readily diagnosed, manageable, and typically resolve without long-term sequelae. It is recommended that where indicated, herpes zoster vaccination will be offered to patients prior to receiving baricitinib, and infections have generally been mild to moderate, localized, and without long-term problems. It is important to consider that in AD, patients are at an increased risk for skin infections due to disruption of the skin barrier, which is worsened by occurrence of eczematous skin lesions and scratching (Krakowski et al. 2008). In the Phase 2 study of baricitinib, there was no increase in the occurrence of skin infections with

baricitinib, likely due to improvements observed in skin lesions and itch. Exclusion criteria have been added to the protocol to limit enrollment of patients who are at increased risk of infection.

Cases of hepatotoxicity have not been identified with baricitinib use, but increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin have been seen in RA patients. Most of these increases improved with continued use or temporary discontinuation of baricitinib with no long term effects. Exclusion criteria to not enroll patients with liver failure or increased liver analytes, appropriate monitoring of hepatic analytes and discontinuation criteria have been included in the protocol. Fetal malformations were reported in toxicology studies at higher doses than what is used in human patients. Only a small number of patients have become pregnant in baricitinib clinical trials, and there have been no reports of fetal malformations in these pregnancies. In current study protocols, pregnant patients are excluded from entry, contraceptive use is defined in the inclusion criteria, and patients who become pregnant are discontinued from the trial.

Venous thromboembolic events (VTEs) have been determined to be an important potential risk for baricitinib. There was a numerical imbalance in reports of VTEs in the 24-week placebo-controlled period of the Phase 3 trials of patients with RA. Available evidence does not establish a causal association. The exposure-adjusted incidence rate of VTE for baricitinib-treated RA patients over long-term exposures was similar to the background rates published in the literature for the target population. There was no pattern of increased or decreased risk during long-term exposures, and cases observed with baricitinib were confounded by one or more recognized risk factors for VTE. Venous thromboembolic event risk can be managed through risk mitigation strategies. Exclusion and discontinuation criteria have been added to the protocol to limit participation of patients who are at increased risk of VTE. Therefore, in the context of the cumulative knowledge, the benefit/risk balance for baricitinib for the treatment of adult patients with moderate-to-severe AD is assessed to be favorable. The overall safety profile in the pediatric patients with rare auto-inflammatory conditions participating in the JAGA expanded access program did not identify any new safety signals beyond those identified in the Phase 3 studies in adult patients with RA for the range of doses tested: from 1- to 12-mg/day. Children generally carry less medical disease burden than adults (i.e., children are generally more healthy than adults and they do not have other medical conditions that occur with aging such as diabetes, heart disease, arthritis, etc.); therefore, they will be at a lower risk for some of the adverse events (AEs) related to comorbidities observed in RA studies, and are not anticipated to be at any higher risk of AE potentially associated with baricitinib. Thus it is expected that the benefit/risk balance for baricitinib for the treatment of pediatric patients with moderate-to-severe AD would be similar to adults.

Phase 3 studies of adult patients with AD have been completed; please refer to the Investigator's Brochure (IB) for more information on efficacy and safety in adult patients with AD. In summary, the primary objective (IGA score for AD of clear or almost clear [IGA 0,1]) as well as most other secondary measures were met for the 4-mg dose in completed studies. The 2-mg dose met the primary endpoint in 2 of 3 completed studies and demonstrated clinically relevant efficacy across a range of secondary endpoints across the various studies. The 1-mg dose

demonstrated efficacy on some endpoints but did not show consistent efficacy across the completed studies where it was included. Safety observations in adult patients with AD from long-term extensions up to 2 years in duration have not revealed any new safety signals, and the safety profile for baricitinib in adult patients with AD remains generally consistent with the known safety profile in RA. Acne and increased creatine phosphokinase were reported with greater frequency in adult AD patients than RA patients.

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

4. Objectives and Endpoints

Table JAIP.3 shows the objectives and endpoints of the study.

Table JAIP.3. Objectives and Endpoints

Objectives	Endpoints
Primary Objective for Double-blind Treatment Period • To demonstrate the superiority of each dose of baricitinib versus placebo in the treatment of patients with moderate-to-severe AD.	• Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 16
Primary Objective for PK lead-in Period • To assess whether baricitinib exposure in pediatric patients receiving baricitinib high dose once daily is comparable to the exposure in adults receiving baricitinib 4-mg once daily.	• Comparability will be assessed using non-compartmental methods (e.g., AUC and C_{max})
Key Secondary Objectives *These are prespecified objectives that will be adjusted for multiplicity* • To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week double-blind placebo-controlled treatment period as measured by improvement in signs and symptoms of AD.	• Proportion of patients achieving EASI75 at 16 weeks • Proportion of patients achieving EASI90 at 16 weeks • Mean change from baseline in EASI score at 16 weeks • Proportion of patients achieving SCORAD75 at 16 weeks
• To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week double-blind placebo-controlled treatment period as assessed by patient-reported outcome measures.	• Proportions of patients achieving a 4-point improvement in Itch NRS at 1 week, 2 weeks, 4 weeks, and 16 weeks for patients ≥10 years old
Other Secondary Objectives *These are prespecified objectives that will not be adjusted for multiplicity.*	
• To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week double-blind placebo-controlled period as measured by physician-assessed signs and symptoms of AD.	• Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at Week 4 • Proportion of patients achieving EASI50 at 16 weeks • Proportion of patients achieving IGA of 0 at 16 weeks • Mean change from baseline in SCORAD at 16 weeks • Mean percent change from baseline in SCORAD at 16 weeks • Proportion of patients achieving SCORAD90 at 16 weeks

Objectives	Endpoints
	• Mean percent change from baseline in EASI score at 16 weeks • Mean change from baseline in BSA affected at 16 weeks • Proportion of patients developing skin infections requiring antibiotic treatment by Week 16
• To compare the efficacy of baricitinib high, medium, or low dose to placebo in AD during the 16-week, double-blind, placebo-controlled treatment period as assessed by patient-reported outcome/QoL measures.	• Mean number of days without use of background TCS over 16 weeks • Mean gram quantity of TCS used over 16 weeks (tube weights) • Mean change from baseline in Itch NRS at 1 week, 4 weeks and 16 weeks for patients ≥10 years old • Mean percent change from baseline in Itch NRS at 1 week, 4 weeks and 16 weeks for patients ≥10 years old • Mean change in the PRISM at 1 week, 2 weeks, 4 weeks, and 16 weeks for patients <10 years old • Mean change from baseline in the total score of the POEM at 16 weeks • Mean change in PGI-S-AD scores at 16 weeks • Mean change from baseline in the PROMIS-pediatric depression at 16 weeks • Mean change from baseline in the PROMIS-pediatric anxiety at 16 weeks • Mean change from baseline in DFI at 16 weeks • Mean change in CDLQI/IDQOL scores at 16 weeks • Mean change in WPAI-AD-CG scores at 16 weeks • Mean change in EQ-5D-Y scores at 16 weeks • Mean change from baseline in the score of Item 2 of the ADSS at 1 week and 16 weeks for patients ≥10 years old • Mean change from baseline in Skin Pain NRS at 16 weeks for patients ≥10 years old
• To assess the patient acceptability and palatability of baricitinib tablets and oral suspension.	• Assessment of tablet or oral suspension product acceptability and palatability during the Open-label PK Lead-in period
• To characterize the pharmacokinetic profile of the baricitinib in pediatric patients with AD.	• Population PK Analysis based on sparse sampling over 16 weeks (Study Period 3) with secondary endpoints including C_{max}, AUC, and t1/2

Objectives	Endpoints
• To evaluate the potential effects of baricitinib on the cellular and humoral immune system.	• Change of IgG titers from pre-vaccination to 4 weeks and 12 weeks post vaccination in patients eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local guidelines
• To assess efficacy of baricitinib during longer-term treatment.	• Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at 1 year • Proportion of patients achieving EASI75 at 1 year • Proportion of patients achieving SCORAD75 at 1 year
• To assess growth and bone safety of baricitinib during longer-term treatment.	• Mean changes in growth (height and weight), growth velocity, and bone age over the course of treatment during the long-term extension treatment period
Tertiary/Exploratory Objectives	
• Frequency of patient-reported "no itch" (Itch NRS score = 0) days from daily diaries from Week 12 to Week 16 • Frequency of patient-reported "no pain" (Skin Pain NRS score = 0) days from daily diaries from Week 12 to Week 16 • Time to achieve a 4-point improvement in Itch NRS • Mean change from baseline in the score of Item 1 of the ADSS at 1 week and 16 weeks • Mean change from baseline in the score of Item 3 of the ADSS at 1 week and 16 weeks • To evaluate changes from baseline in IgE levels during the study • To evaluate changes from baseline in eosinophil levels during the study • To characterize baricitinib pharmacokinetics in the AD population and explore relationships between baricitinib exposure and study endpoints • Assessment of efficacy outcomes in patients who choose to take a voluntary drug interruption (drug holiday) during Study Period 4 • Number of patients able to maintain control of AD signs and symptoms without use of TCS • Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at 2, 3, 4, and 5 years during long-term extension • Proportion of patients achieving EASI75 at 2, 3, 4, and 5 years during long-term extension • Proportion of patients achieving SCORAD75 at 2, 3, 4, and 5 years during long-term extension	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; AUC = area under the concentration curve; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; C_{max} = maximum concentration; DFI = Dermatology Family Impact; EASI = Eczema Area and Severity Index; EQ-5D-Y = the European Quality of Life–5 Dimensions–Youth; IDQOL = Infant's Dermatitis Quality of Life Index; IGA = Investigator's Global Assessment; IgE = immunoglobulin E; IgG = immunoglobulin G; NRS = numeric rating scale; PK = pharmacokinetic; QoL = quality of life; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PRISM = Parent-Reported Itch Severity Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; t1/2 = half-life; TCS = topical corticosteroids; SCORAD = SCORing Atopic Dermatitis; WPAI-AD-CG = Work Productivity and Activity Impairment: Atopic Dermatitis – Caregiver.

5. Study Design

5.1. Overall Design

Study I4V-MC-JAIP (JAIP) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, outpatient study evaluating the pharmacokinetics, efficacy, and safety of baricitinib compared with placebo in pediatric patients with moderate-to-severe AD. The study is divided into 5 periods, a 5-week Screening period, a 2-week Open-label PK lead-in period, a 16-week Double-Blind Treatment period, an up to 5-year Long-term Extension period, and a 4-week Post-treatment Follow-up period. While the primary objective of this study is to investigate whether baricitinib is superior to placebo in the treatment of the signs and symptoms of AD in pediatric patients, an important secondary objective of the study is to assess the ability of baricitinib to reduce or eliminate the need for use of topical antiflammatory agents, the use of which is frequently a concern among parents and caregivers of pediatric AD patients.

Approximately 465 patients 2 to <18 years of age who have responded inadequately to or who are intolerant to topical therapy will be enrolled into the study, of which, approximately 25 patients will be enrolled into the Open-label PK Lead-in period (Study Period 2). The remaining patients (at least 440 patients) will be randomized at a 1:1:1:1 ratio to receive placebo QD, baricitinib low dose QD, baricitinib medium dose QD, or baricitinib high dose QD (110 patients in each treatment group with at least 320 patients 10 to <18 years old and at least 120 patients 2 to <10 years old).

The original protocol was written as a monotherapy study (including TCS washout), and the open-label PK Lead-in period (Study Period 2) will be conducted as such. Protocol amendment JAIP(a) permits the use of background low- and medium-potency TCS, and all patients participating in Study Period 3 (Double-blind treatment) will follow this for subsequent amendments including the amendment, JAIP(b).

Patients will be stratified at randomization according to disease severity (IGA 3 vs. 4) and geographic region (if the planned country allocation justifies). Definitions of geographic regions and plan for analysis by region will be described in the statistical analysis plan (SAP).

Study governance considerations are described in detail in Appendix 3.

5.1.1. Period 1: Screening

The duration of the Screening period is between 8 and 35 days prior to Visit 2 (Week 0). At Visit 1, the patient or parent/legal guardian will sign the informed consent form (ICF) prior to any study assessments, examinations, or procedures being performed. All screening procedures will be performed according to the Schedule of Activities (Section 2). Patients who receive a purified protein derivative (PPD) skin test at Visit 1 will need to return within 48 to 72 hours later to have the skin test read.

Patients Participating in Study Period 2 (PK Lead-in)

Patients who will participate in the open-label PK lead-in (Study Period 2) will be required to wash out of prior AD treatments as described in Section 6.1 (Study Population) and Section 7.7.

Patients Participating in Study Period 3 (Double-blind treatment)

Prior to randomization (Study Period 3), systemic treatments for AD will be washed out for 4 weeks. Certain topical treatments (not including emollients) will be discontinued prior to Visit 2 as described in Section 6.1 (Inclusion Criteria [6 c]) and Section 7.7. Sponsor-provided low- and medium-potency TCS will be given to patients at Visit 1, and patients will discontinue use of other TCS medications and begin use of the Sponsor-provided TCS medications as prescribed by the investigator (as clinically indicated). During the screening period, TCNIs (e.g., tacrolimus and pimecrolimus) or topical PDE-4 inhibitor (i.e., crisaborole, where approved) are permitted in place of TCS as on areas where application of TCS is considered inappropriate by the investigator; use should be limited to problem areas (e.g., face, neck, skin folds, genital areas, etc.).

All Patients

Patients will be required to use emollients daily during the 14 days preceding Visit 2 and throughout the study. If patients have been using emollients daily at the time of screening, then those cumulative days can be utilized to meet inclusion criterion [7]. Patients will receive a daily reminder via the daily diary to apply emollient. Additionally, collection of data through daily diaries will be required throughout the Screening period. The baseline for the daily patient-reported outcome (PRO) will be the average score of the 7 days prior to Visit 2; thus the minimum screening window was set at 8 days.

Investigators should review the vaccination status of their patients to assess that patients are up to date with immunizations following the local guidelines for vaccination of pediatric patients <18 years of age with vaccines intended to prevent infectious disease prior to entering patients into the study. Typhoid and Bacillus Calmette-Guérin (BCG) live vaccines are not permitted within 12 weeks of Visit 2. If a patient received a live vaccine within 28 days prior to Visit 2 or intends to receive a live vaccine during Study Period 2 or 3, the patient is not eligible for the study. If patients become eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine during the study according to local recommended schedules of vaccination, antibody titers to the vaccine will be evaluated pre-immunization and at 4 and 12 weeks post-immunization. A primary immune response will be assessed in patients who have never received TDaP or pneumococcal conjugate vaccines previously, and secondary/booster responses will be assessed if the patients have previously received the vaccines.

Patients who meet all of the inclusion and none of the exclusion criteria (Sections 6.1 and 6.2) will continue to Visit 2.

5.1.2. Period 2: Open-label PK lead-in

The Open-label PK Lead-in period will evaluate if exposure to baricitinib high dose in pediatric patients is comparable with baricitinib exposure in adults. Patients will receive oral baricitinib at a fixed high dose by age group QD for approximately 2 weeks. The 2-week, open-label PK lead-in will include serial PK sampling so that baricitinib exposure can be evaluated in this

population. Enrollment will be staggered by age group (10 to <18 years, 6 to <10 years, and 2 to <6 years), with older groups enrolling before younger groups.

Approximately 25 patients will be enrolled into the PK lead-in with at least:

- Oldest age group: 15 patients 10 to <18 years old including at least 5 patients in each of the following age groups:
    - 10 to <12 years
    - 12 to <15 years
    - 15 to <18 years
- Middle age group: at least 5 patients 6 to <10 years old, and
- Youngest age group: at least 5 patients 2 to <6 years old

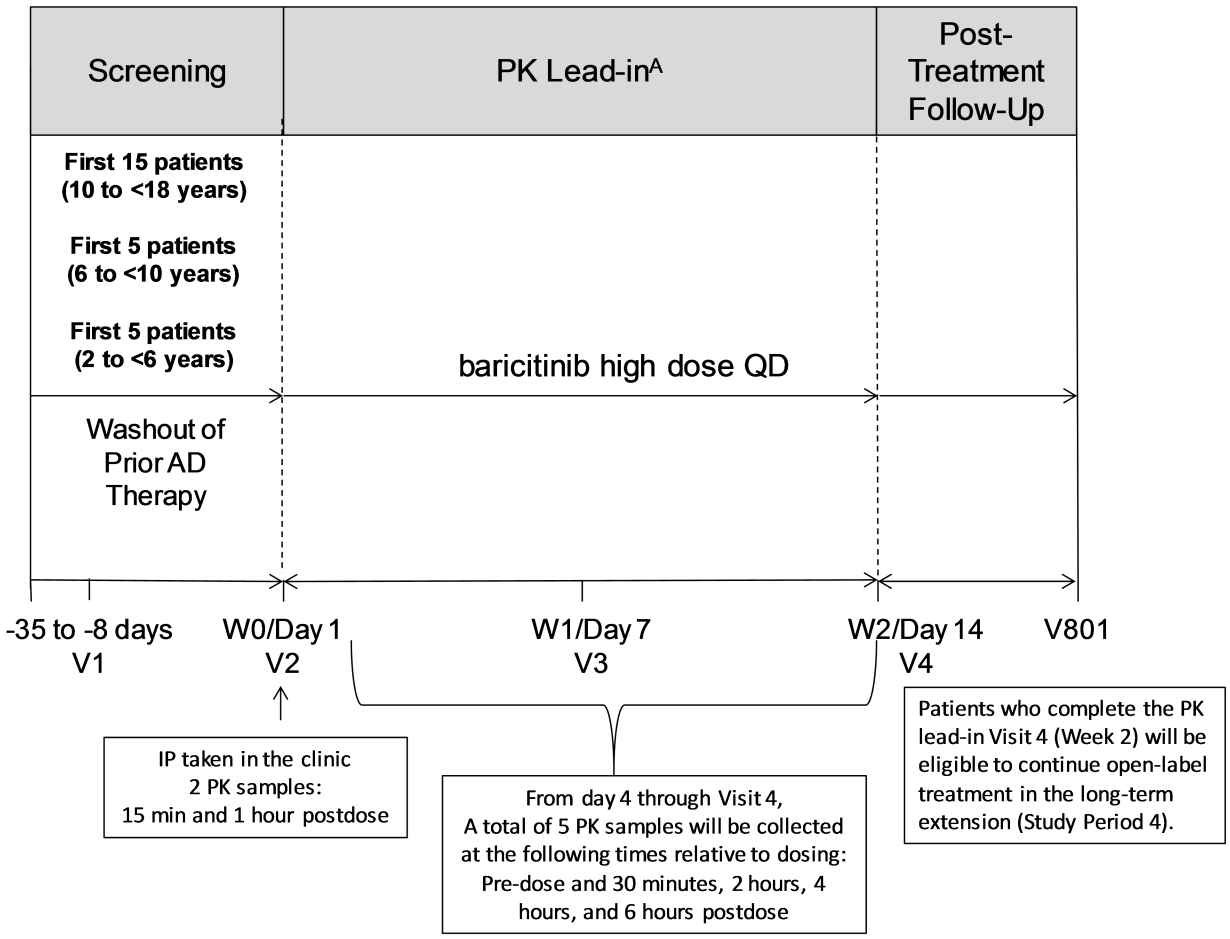
At Visit 2 (Week 0, baseline), study eligibility for each patient will be reviewed, based on all inclusion and exclusion criteria (Sections 6.1 and 6.2) and laboratory test results. Patients who meet all criteria will proceed in the study and begin open-label treatment in the PK lead-in period (Visits 2, 3, and 4).

After patients in the oldest age group (10 to <18 years old) have completed the 2-week, open-label PK lead-in, an analysis will be conducted to evaluate the PK and safety profiles and confirm baricitinib exposure and dosing prior to any enrollment of patients in this age group into the Double-blind Treatment period.

After the analysis of the PK data for the patients in the oldest age group (10 to <18 years old) has completed, the middle age group (6 to <10 years old) will begin enrollment into the PK lead-in period. After analysis of the PK lead-in data for the patients in the middle age group (6 to <10 years old) has completed, the youngest age group (2 to <6 years old) will begin enrollment into the PK Lead-in period. Enrollment of patients in the middle and youngest age groups directly into the Double-blind Treatment period will begin only after analysis of the PK lead-in data for the specific age group has been completed.

After completing the PK lead-in (Visit 4), patients may proceed to the Long-term Extension period (Visit 9) 2 weeks after completing Visit 4 and continue to receive open-label baricitinib at the same dose they received in the PK lead-in.

The study design for the Open-label PK Lead-in period is illustrated in Figure JAIP.1. A Schedule of Activities showing required procedures for the open-label PK lead-in is included in Section 2. The PK sampling schedule is described in Section 9.5. Patients participating in the PK lead-in will follow the procedures shown in the Schedule of Activities (Section 2) for Visits 2, 3, and 4 with serial PK samples collected as described in Section 9.5. A total of 7 PK samples will be collected during the PK lead-in period (2 PK samples will be collected at Visit 2, and 5 PK samples will be collected during the 2 weeks following Visit 2).



Abbreviations: AD = atopic dermatitis; PBPK = Physiologically Based Pharmacokinetic; PK = pharmacokinetic; QD = once daily; V = visit; W = week.

[A] Based on PBPK modelling results, the high dose for patients 10 to <18 years old is 4 mg, and the high dose for patients 2 to <10 years is 2 mg.

Figure JAIP.1. Illustration of study design for Clinical Protocol I4V-MC-JAIP (PK Lead-in, Study Period 2).

5.1.3. Period 3: Double-blind Placebo-Controlled Treatment Period

General enrollment into Study Period 3 will begin for an age group only after analysis of the PK lead-in data for the specific age group confirms appropriate dose selection. Patients who participated in the PK lead-in will not participate in Study Period 3.

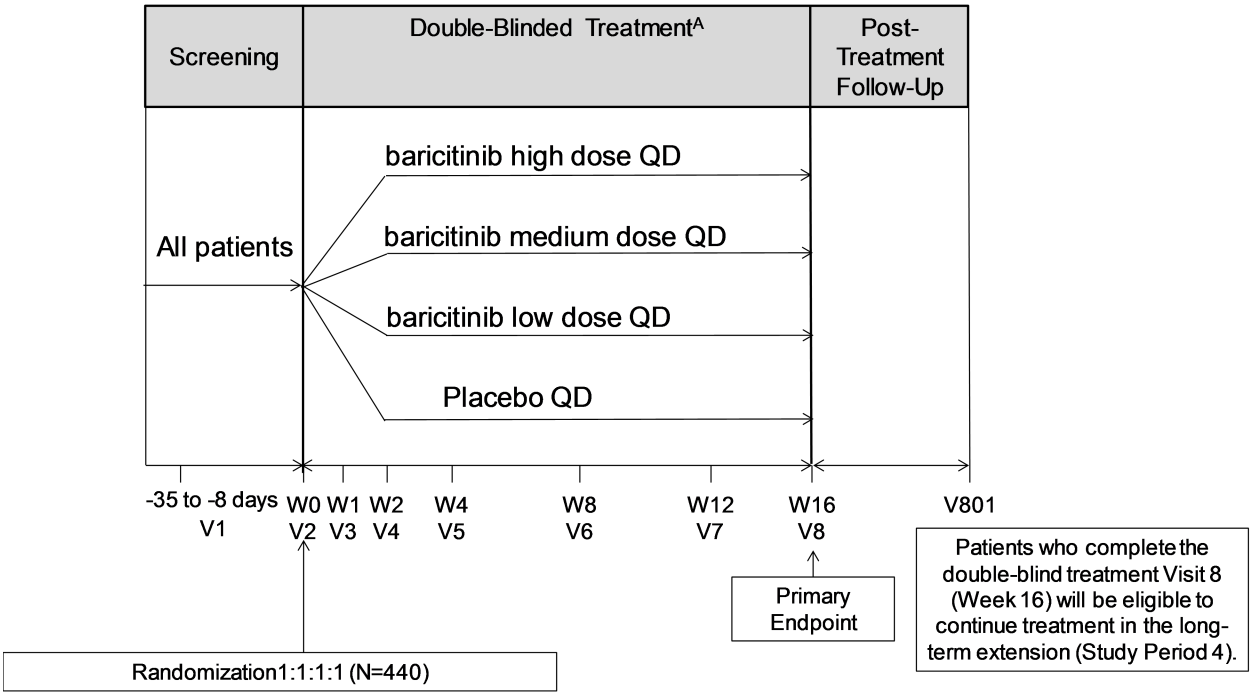
Patients who will participate in the double-blind treatment period (Study Period 3) will continue using Sponsor-provided low- and medium-potency TCS as clinically indicated and determined by the investigator. At Visit 2 (Week 0, baseline), study eligibility for each patient will be reviewed, based on all inclusion and exclusion criteria (Sections 6.1 and 6.2, respectively) and laboratory test results. Patients who meet all of the inclusion criteria and none of the exclusion criteria will proceed to randomization and begin the 16-week double-blind, placebo-controlled treatment period (Figure JAIP.2).

At Visit 2, after laboratory samples are collected and all assessments are completed, patients will take the first dose of investigational product (IP) at the clinic and PK samples will be drawn 15 minutes and 1 hour postdose. Pharmacokinetic sampling and the related timing of dosing for IP for each visit are detailed in Section 9.5.

Patients will be randomized at a 1:1:1:1 ratio into 1 of the 4 treatment groups (placebo QD, baricitinib low dose QD, baricitinib medium dose QD, or baricitinib high dose QD). Investigational product will be administered daily for 16 weeks (treatment period Visits 2 through 8). All patients will be required to use emollients daily. Daily diaries will continue to be utilized throughout the treatment period. The use of low- and medium-potency TCS, TCNIs, and phosphodiesterase type 4 (PDE-4) inhibitor for the treatment of AD is allowed as background treatment as described in Section 7.7.1. High- and ultra-high-potency TCS and systemic therapies may be used as rescue treatment during Study Period 3 (details of rescue therapy and criteria are included in Section 7.7.5). Assessments of disease severity will be performed by the investigator at all study visits including unscheduled and early termination visits (ETVs).

The primary efficacy endpoint and final visit in the treatment period will be at Week 16 (Visit 8). Patients who complete through the Week 16 study visit will be eligible to continue in the Long-term Extension period for up to 5 additional years of treatment.

If a patient discontinues IP for any reason, the patient should remain in the study through Week 16 (Visit 8). If the patient refuses and wishes to withdraw consent, an ETV should be performed as soon as logistically possible.



Abbreviations: PK = pharmacokinetic; QD = once daily; V = visit; W = week.

[A] Dosing for the Double-blind Treatment period will be confirmed through the PK lead-in. The anticipated daily baricitinib doses for patients 10 to <18 years old are 4 mg, 2 mg, and 1 mg. The anticipated daily baricitinib doses for patients 2 to <10 years old are 2 mg, 1 mg, and 0.5 mg.

Figure JAIP.2. Illustration of study design for Clinical Protocol I4V-MC-JAIP (Double-Blinded Treatment, Study Period 3).

5.1.4. Period 4: Long-term Extension Treatment Period

PK Lead-in Patients:

Patients participating in the PK lead-in period (Study Period 2) may proceed to the Long-term Extension period (Visit 9) 2 weeks after completing Visit 4 and continue to receive open-label baricitinib at the same dose they received in the PK lead-in. Patients may continue in the long-term extension for up to an additional 5 years (Figure JAIP.3).

Non-PK Lead-in Patients:

Patients who participate in the Double-blind Treatment period (Study Period 3) and complete through Week 16 (Visit 8) will be eligible to continue in the Long-term Extension period for up to 5 additional years of treatment (Figure JAIP.3). At Visit 8 (primary endpoint and end of the double-blind period), patients will be transitioned into the long-term extension treatment period as follows:

- Patients randomized to Double-blind Treatment who have achieved a response of IGA 0, 1, or 2 at Visit 8 (Week 16) without requiring rescue with topical treatments or systemic treatments during Study Period 3 will continue on the Double-blind Treatment to which they were randomized at Visit 2 (Week 0).

- Patients randomized to Double-blind Treatment who have not achieved a response (i.e., IGA of ≥3) or who have required rescue with topical treatments (i.e., high-/ultra-high-potency TCS) or systemic treatments during Study Period 3 will be transitioned to open-label baricitinib at the high dose for their age group.

All Patients:

During Study Period 4, patients are allowed to use TCS (all potencies), TCNI, and/or a PDE-4 inhibitor (e.g., crisaborole) as background treatments with IP if they experience worsening or lack of control of their AD.

During the first year of the extension treatment, use of background TCS, TCNI, and PDE-4 inhibitors is allowed as described in Section 7.7.2. During Study Period 4, for patients on double-blind treatment whose IGA worsens to 3 or 4 and who are unable to recapture an IGA response of 0, 1, or 2, despite the use of emollients and TCS, the patient may be transitioned at the discretion of the investigator to open-label baricitinib at the high dose for their age group.

After the first year of the extension treatment period, treatment and transition to open-label baricitinib will continue as in the first year; however, patients will be allowed to voluntarily interrupt IP treatment after Visit 15 provided they continue to complete all other study visit procedures per protocol. In addition to investigator discretion and patient/parent agreement, at least 1 of the response criteria described below must be met in order to initiate a voluntary interruption of the IP:

- IGA ≤2
- EASI75 or better (≥75% reduction in Eczema Area and Severity Index [EASI] from Visit 2)
- <3% BSA involvement

Voluntary interruption of treatment (drug holiday) is an approach to long-term treatment that may be more representative of actual treatment practice, where patients may use baricitinib intermittently (i.e., "treat when needed") rather than on a continuous basis. The IP may be resumed (at the same dose) after a voluntary interruption if symptoms worsen based on investigator assessment of benefit/risk and patient/parent agreement. The symptoms leading to resumption of the IP will be captured on the case report form (CRF).

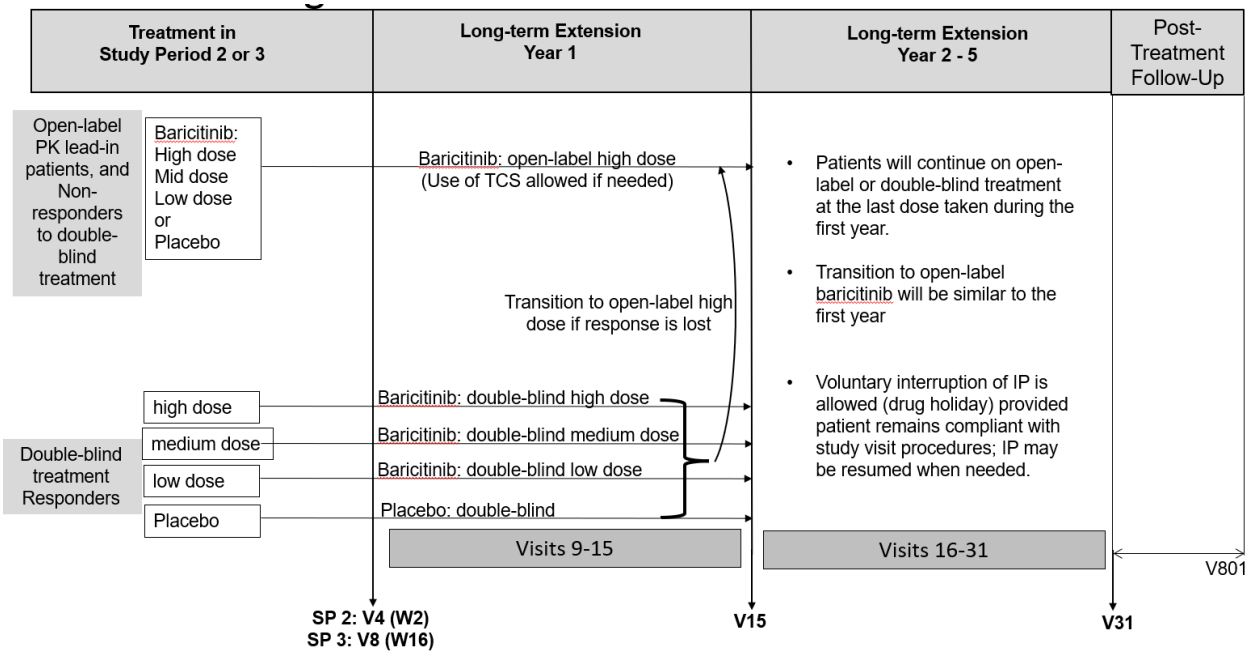
During the long-term extension live vaccines (e.g., booster immunization with attenuated vaccine measles, mumps, and rubella [MMR] or varicella zoster virus [VZV]) may be considered if they are essential based on the local guideline and/or in the opinion of the investigator and with appropriate interruption of baricitinib treatment prior to and after the live vaccine (see Section 7.7.4).

The benefit/risk profile will be reassessed throughout the study and patients may be discontinued at any time. In particular, during the long-term extension period, the investigators should continue to assess the benefit/risk profile of patients to remain in the trial after Week 16. For a patient having safety and tolerability issues, or one who is not achieving adequate treatment

response, investigators should use clinical judgment on whether to continue or discontinue patient participation in the study.

The total duration of this study is expected to last until the anticipated approval of baricitinib in this indication; however, given that the benefit risk in AD had not been demonstrated in pivotal Phase 3 adult studies at the time of the original protocol approval, the study duration had been initially set at 2 years. Data from the Phase 3 AD studies in adults and initial data from the current study (JAIP) have now indicated a favorable benefit/risk; therefore, this protocol has been amended to further extend the duration of Study JAIP for a total treatment period of up to 5 years or until the anticipated approval and availability of baricitinib for the treatment of AD.

At Visit 27, patients eligible for treatment with a commercially available, approved, systemic JAK or biologic therapy should be discontinued from study treatment; this will be considered the final visit of Study Period 4. For patients 12 years of age and older at the time of Visit 27, Visit 27 will be the final treatment visit unless prior documented written sponsor's approval has been obtained to allow the patient to continue on study treatment. Patients younger than 12 years of age at the time of Visit 27 who are not eligible for commercially available, approved, systemic JAK or biologic therapies may be eligible to continue in Study Period 4 beyond Visit 27. The investigator must provide documentation supporting the need for continued treatment under the study protocol and obtain sponsor's written approval prior to patient completing Visit 27. Patients <12 years of age should be discontinued from study treatment at the first study visit after meeting eligibility for an approved systemic JAK or biologic alternative. The investigator should discuss post-study treatment options with the patient prior to Visit 27 to ensure continuity of patient care.



Abbreviations: IP = investigational product; PK = pharmacokinetic; SP = study period; TCS = topical corticosteroid; V = visit; W = week.

Figure JAIP.3. Illustration of study design for Clinical Protocol I4V-MC-JAIP (Long-term Extension, Study Period 4).

5.1.5. Period 5: Post-Treatment Follow-Up

Patients who complete Study Period 2 through Visit 4 (Week 2) and patients who complete Study Period 3 through Visit 8 (Week 16) and do not enter the long-term extension study will have a post-treatment follow-up visit (Visit 801) approximately 28 days after the last dose of IP. Patients who complete Study Period 4 through Visit 31 will have a post-treatment follow-up visit (Visit 801) approximately 28 days after the last dose of IP.

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

Patients who have discontinued IP but remain in the study for more than 28 days without IP will have an ETV if they chose 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, patients should complete an unscheduled visit prior to the first dose of the new therapy.

5.2. Number of Participants

Approximately 465 patients will be enrolled into this study.

Approximately 25 patients will be enrolled into the open-label PK lead-in (at least 15 patients aged 10 to <18 years old and at least 10 patients aged 2 to <10 years old).

Approximately 440 patients will be enrolled/randomized into the Double-blind Treatment period (with at least 320 patients aged 10 to <18 years old and at least 120 patients aged 2 to <10 years old.

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 study will enroll pediatric patients with moderate to severe AD who have a history of inadequate response or intolerance to existing topical therapies and for whom a systemic treatment such as baricitinib may, therefore, be appropriate.

During the Screening period (Period 1), a washout of systemic and certain topical treatments for AD will be incorporated prior to randomization to minimize confounding effects due to background treatment. The PK lead-in (Period 2) will confirm that the baricitinib exposure at the high dose for each pediatric AD age group is comparable to the 4-mg dose exposure in adults with AD. The double-blind, placebo-controlled treatment period (Period 3) is designed to minimize bias in the evaluation of the efficacy and safety of 3 baricitinib doses, relative to placebo, through 16 weeks of treatment. Patients who will participate in the double-blind treatment period (Study Period 3) will be allowed to continue treatment with TCS. Sponsor-provided low- and medium-potency TCS will be given to patients at Visit 1, and patients will use the TCS medications as prescribed by the investigator (as clinically indicated).

Topical corticosteroids are the first-line anti-inflammatory treatment in adult and pediatric patients with AD, even for patients treated with systemic treatments. For this reason, this study will assess the efficacy of baricitinib in combination with background low- to medium-potency TCS including a TCS run-in during the screening period from Visit 1 to Visit 2. In consideration of the disease severity, all patients in Study Period 3 (double-blind treatment) are eligible for rescue to higher potency TCS. Investigators are allowed to rescue patients who are experiencing unacceptable or worsening symptoms of AD. Once rescue medication is used, the patient will be determined to be a nonresponder for the 16-week primary analysis (see Section 10.3.1).

Investigator's Global Assessments are commonly used in clinical trials, both for qualifying patients for enrollment and for evaluating treatment efficacy (Langley et al. 2015; Futamura et al. 2016). There is no single "gold standard" disease severity scale for AD; however, IGA scales provide clinically meaningful measures to patients and investigators that are easily described and that correspond to disease severity categories (e.g., moderate to severe). The scale that will be used in this trial, the validated Investigator's Global Assessment of Atopic Dermatitis (vIGA-AD, referred to throughout the protocol as IGA), has been developed internally and assesses AD severity using a 5-point scale.

The 16-week efficacy endpoint was chosen because it is likely that a robust clinical effect will be observed with baricitinib within this timeframe based on the Phase 2 study results in AD and from previous studies in another inflammatory skin condition.

The long-term extension (Period 4) should offer additional opportunity for patients to receive benefit from treatment and provide additional long-term safety and tolerability information.

After the first year of the extension treatment period, patients will be allowed to voluntarily interrupt IP treatment provided they continue to complete all other study visit procedures per protocol. This voluntary interruption (drug holiday) based on response, investigator discretion, and patient/parent agreement is an approach to long-term treatment that may be more representative of actual treatment practice, where patients may use baricitinib intermittently (i.e., "treat when needed") rather than on a continuous basis. Investigational product may be resumed after a voluntary interruption if symptoms worsen.

The Post-treatment Follow-up period (Period 5) is for safety monitoring after the patient has been off IP for approximately 28 days.

5.5. Justification for Dose

The PK of baricitinib have been characterized in adults and are linear and time-independent across a wide dose range. Renal elimination is the principal mechanism for baricitinib's clearance through glomerular filtration and active secretion via OAT3, Pgp, BCRP, and MATE2-K. Baricitinib is expected to behave similarly between pediatrics and adults, based on the ADME of baricitinib and Physiologically Based Pharmacokinetic (PBPK) modelling (PBPK program Simcyp®). Physiologically Based Pharmacokinetic modelling was used to predict exposures and set the high dose for pediatric age cohorts within the age range to be studied (2 years to <18 years). Considering safety and tolerability, the high dose in each pediatric age group will be set to the dose that produces comparable exposure to the highest effective baricitinib dose tested in the adult Phase 2 AD study (4-mg). Lower doses at ½ and ¼ the high dose will be studied to cover the dose range where clinical response can be anticipated (similar ratios of the high dose as being studied in the adult Phase 3 AD studies, [i.e., 4, 2 and 1 mg]).

Older pediatric population (10 to <18 years)
Based on PBPK modelling, it is anticipated that a 4-mg dose will produce comparable exposure in pediatric patients (10 years to <18 years old) and adults with AD. Based on a 4-mg dose, the model-predicted area under the concentration curve (AUC) and the maximum concentration (C_{max}) in 10 to <18 year old patients with AD is within the 5th and 95th percentiles of the AUC and C_{max} in adult patients with AD. Therefore the maximum dose in older pediatric patients 10 to <18 years old is proposed to be 4-mg with medium and low doses of 2-mg and 1-mg, respectively (same doses being tested in the ongoing adults Phase 3 AD studies).

In the baricitinib Phase 2 AD Study in adults (JAHG), both the 2-mg and 4-mg doses showed benefit on the primary and major secondary endpoints (EASI, IGA, SCORing Atopic Dermatitis [SCORAD], Patient Oriented Eczema Measure [POEM] and Dermatology Life Quality Index [DLQI]) as compared to placebo, and both doses had an acceptable safety profile at Week 16.

However, the 4-mg dose appeared to demonstrate a more rapid benefit (at 4 weeks) on the more stringent endpoints (EASI75, EASI90, and IGA 0 or 1) compared to the 2-mg dose, particularly in the subgroup of patients with baseline EASI scores ≥16. Although in Study JAHG the 4-mg dose seemed to perform better than the 2-mg dose on more stringent endpoints, on other endpoints, including EASI-50, and EASI change from baseline, 2-mg and 4-mg doses showed similar efficacy compared to placebo. Given that the 4-mg and 2-mg doses demonstrated similar efficacy for a number of endpoints, it is possible that the 1-mg dose could also be beneficial, and thus the efficacy profile of the 1-mg dose will be evaluated. Based on the Phase 2 study (JAHG), 3 doses are being tested in Phase 3 adult AD studies (1, 2, and 4-mg) to cover the range of exposures where clinical responses could be anticipated.

Provided that the PK lead-in confirms that exposure in older pediatric patients is comparable to adults, the same range of doses will be used in older pediatric patients (1, 2, and 4 mg). If the PK lead-in indicates that exposures in adults and older pediatric patients are not comparable, the doses to be tested in JAIP will be chosen such that the expected exposure will be comparable to that in the adult AD studies.

Younger pediatric population (2 to <10 years)
In children 2 years to <10 years with AD, PBPK modelling suggests that a dose of 2-mg produces comparable exposure to the 4-mg dose in adults with AD. The model-predicted AUC and C_{max} of 2-mg in 2 to <10 year old AD patients is within the 5^{th} and 95^{th} percentiles of the AUC and C_{max} of the 4-mg dose in adult patients with AD. Therefore the maximum dose in children 2 to <10 years old is proposed to be 2 mg with proposed medium and low doses of 1 mg and 0.5 mg, respectively. If the PK lead-in indicates that exposures in adults and children 2 years to <10 years are not comparable, the doses to be tested in JAIP will be chosen such that the expected exposure will be comparable to that in the adult AD studies.

6. Study Population

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

6.1. Inclusion Criteria

Study investigator(s) will review patient history and screening test results at Visit 1 and Visit 2 to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for randomization in the study. All screening activities must be completed and reviewed before the patient is randomized.

Type of Patient and Disease Characteristics

[1] Are 2 to <18 years of age and are at or above the 5th percentile of weight for age (e.g., ≥10.6 kg for a 2 year old) at the time of informed consent. Full date of birth will be recorded except in countries where it is not allowed.

[2] Have a diagnosis of AD at least 12 months (if ≥6 years old) and at least 6 months (if 2 to <6 years old) prior to screening as defined by the American Academy of Dermatology: Guidelines of care for the management of AD; Section 1. Diagnosis and assessment of atopic dermatitis (Appendix 8).

[3] Have moderate-to-severe AD, including all of the following:

a. EASI score ≥16 at screening (Visit 1) and at Visit 2

b. IGA score of ≥3 at screening (Visit 1) and at Visit 2

c. ≥10% of BSA involvement at screening (Visit 1) and at Visit 2.

[4] Have a documented history by a physician and/or investigator of inadequate response to topical corticosteroids (TCS) AND inadequate response OR history of intolerance to topical calcineurin inhibitors (TCNI). Patients participating in Study Period 3 should be able to tolerate low- or medium-potency TCS.

NOTE: In regions where TCNI are not available or not recommended by treatment guidelines, only a documented history of inadequate response to TCS is required.

Inadequate response is defined as failure to achieve stable long-term disease control (for example, IGA ≤2) based on the following criteria:

- TCS: after use of at least a moderate-potency TCS for at least 4 weeks or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter, within 6 months of screening.

- TCNI: after use for at least 4 weeks of treatment or for the maximum duration recommended by the product prescribing information, whichever is shorter.

- TCS and TCNI: Patients who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, systemic corticosteroids, or mycophenolate mofetil will also be considered as a surrogate for having inadequate response to topical therapy.

Intolerance to TCNI is defined as:

- a documented history of clinically significant adverse reactions that in the opinion of the investigator outweigh the benefits of retreatment (e.g., skin burning).

NOTE: if intolerant to TCNI, then the inadequate response criteria above does not need to be met for TCNI but must still be met for TCS.

[5] Agree to discontinue use of the following excluded medications/treatments for at least 4 weeks prior to Visit 2 and throughout the study unless otherwise specified below:

a. oral systemic corticosteroids

b. systemic immunomodulators, including, but not limited to, cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine

c. any other systemic therapy used to treat AD or symptoms of AD (approved or off-label use)

d. phototherapy, includes therapeutic phototherapy (psoralen plus ultraviolet-A, ultraviolet-B), excimer laser as well as self-treatment with tanning beds (see Section 7.7.5 regarding use as recue therapy).

[6] Agree to discontinue use of the following excluded medications for at least 7 days prior to Visit 2 and throughout the study unless otherwise specified (see Section 7.7):

Patients participating in Study Period 2

a. TCS or topical immune modulators (e.g., tacrolimus or pimecrolimus)

b. Topical PDE-4 inhibitor (crisaborole)

Patients participating in Study Period 2 or Study Period 3

c. Topical JAK inhibitor (e.g., tofacitinib or ruxolitinib) and/or any other investigative topical treatments.

[7] Have applied emollients daily for at least 14 days prior to Visit 2 and agree to use emollient daily throughout the study.

Patient Characteristics

[8] Are male or nonpregnant, nonbreastfeeding female patients

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 the opposite sex.

Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 4 weeks following the last dose of IP. Periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

Otherwise, patients and their partners of childbearing potential must agree to use 2 effective methods of contraception, where at least 1 form is highly effective for the entirety of the study and for at least 4 weeks following the last dose of IP.

The following contraception methods are considered acceptable (the patient and their partner should choose 2, and 1 must be highly effective [defined as less than 1% failure rate per year when used consistently and correctly]):

- Highly effective birth control methods:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, intravaginal or implantable
    - Intrauterine device (IUD)/ intrauterine hormone-releasing system (IUS)
    - Vasectomized partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Effective birth control methods:
    - Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
    - Diaphragm with spermicide
    - Cervical sponge
    - Cervical cap with spermicide
    - Oral contraceptives that do not inhibit ovulation

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

Adolescent females who have started menses (even one cycle and any amount of spotting) are considered to be of childbearing potential.

Females of nonchildbearing potential are not required to use birth control and they are defined as:

- Females who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis, or have not started menses (and are not sexually active)

Informed Consent

[9] A parent or legal guardian must be able to read, understand, and give documented (electronic or paper signature) informed consent for a child to participate in this study. In addition to informed consent given by the parent or legal guardian, the pediatric patient, if capable, may be required to give documented assent as specified by ethics board(s).

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if any of the following criteria are met:

Medical Conditions

[10] Are currently experiencing or have a history of other concomitant skin conditions (e.g., psoriasis or lupus erythematosus) that would interfere with evaluations of the effect of study medication on AD.

[11] Are patients who, in the opinion of the investigator, are currently experiencing or have a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or intravenous (IV) treatment for skin infections that may interfere with participation in the study.

[12] Have a history of eczema herpeticum within 12 months prior to screening.

[13] Have a history of 2 or more episodes of eczema herpeticum in the past.

[14] Are patients who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics.

Note: Patients may not be rescreened until at least 4 weeks after the date of their previous screen failure and at least 2 weeks after resolution of the infection.

[15] Have any serious concomitant illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (e.g., unstable chronic asthma).

[16] Have been treated with the following therapies:

a. monoclonal antibody (e.g., ustekinumab, omalizumab, dupilumab) for less than 5 half-lives prior to Visit 2.

b. prior treatment with any oral JAK inhibitor (e.g., tofacitinib, ruxolitinib) less than 4 weeks prior to Visit 2

c. any parenteral corticosteroid administered by intramuscular or IV injection within 2 weeks prior to study entry (Visit 1) or within 6 weeks prior to planned randomization (Visit 2) or are anticipated to require parenteral injection of corticosteroids during the study.

d. an intra-articular corticosteroid injection within 2 weeks prior to study entry (Visit 1) or within 6 weeks prior to planned randomization (Visit 2).

   Note: Intranasal or inhaled steroid use is allowed during the trial.

e. probenecid at the time of Visit 2 that cannot be discontinued for the duration of the study

Medical Conditions in General

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

[18] Have uncontrolled arterial hypertension as determined by the investigator and characterized by a repeated systolic or diastolic blood pressure >95th percentile based on age, sex and height.

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

[20] Are immunocompromised and, in the opinion of the investigator, at an unacceptable risk for participating in the study.

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

[22] Have a history of VTE or are considered at high risk of VTE as deemed by the investigator.

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

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

[25] Have a current or recent clinically serious viral, bacterial, fungal, or parasitic infection, including but not limited to the following:

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

a. typhoid infection within 12 weeks prior to screening.

b. a history of herpes zoster (shingles).

c. symptomatic herpes simplex at Visit 2.

d. active or chronic viral infection from hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).

e. household contact with a person with active tuberculosis (TB).

f. history of TB or evidence of active TB

g. clinically serious infection or received IV antibiotics for an infection, within the past 4 weeks of Visit 2.

h. any other active or recent infection within 4 weeks of Visit 2 (including chicken pox) that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

[26] Have received a typhoid or BCG live vaccine within 12 weeks of Visit 2 or have received any other live vaccine within 28 days prior to Visit 2 or intend to receive a live vaccine during Study Period 2 or 3.

[27] Have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within the 2 years prior to screening.

[28] Have presence of significant uncontrolled neuropsychiatric disorder, are clinically judged by the investigator to be at risk for suicide, or have a "yes" answer to any of the following on the Columbia Suicide Severity Rating Scale (C-SSRS) collected for patients ≥7 years old at the screening visit:

a. Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS or

b. Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS or

c. 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;

and the ideation or behavior occurred within 2 months prior to Visit 1.

Note: a patient does not necessarily have to be excluded if they have self-injurious behavior that would be classified as nonsuicidal self-injurious behavior. If this situation arises, the patient should be referred to a psychiatrist or appropriately trained professional as indicated.

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

Prior/Concurrent Clinical Trial Experience

[30] Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study.

[31] Have participated, within the last 30 days (3 months for studies conducted in the UK) in a clinical study involving an IP.

If the previous IP has a long half-life (2 weeks or longer), 5 half-lives or 30 days (whichever is longer) should have passed (3 months for studies conducted in the UK).

[32] Have previously been randomized in this study or any other study investigating baricitinib, or who have experienced hypersensitivity to the active substance or to any of the excipients.

Other Exclusions

[33] Patient or parent/caregiver/legal guardian are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures, including use of data collection devices.

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

[35] Are Lilly or Incyte employees or their designee.

Diagnostic Assessments

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

[37] Patients with evidence of active TB or latent TB based on medical history and clinical features are excluded. In addition, if the following criteria are met, the patient will be excluded:

- positive PPD test (i.e., ≥5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), and/or
- QuantiFERON®-TB Gold test or T-SPOT® TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be excluded. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be excluded.

[38] Have a positive test for HBV infection defined as:

a. positive for hepatitis B surface antigen (HBsAg), or

b. positive for hepatitis B core antibody (HBcAb) and positive hepatitis B virus deoxyribonucleic acid (HBV DNA).

Note: Patients who are HBcAb positive and HBV DNA negative may be enrolled in the study. Patients who meet these criteria at screening will be identified by the central laboratory and monitored during the study.

[39] Have HCV infection (positive for anti-hepatitis C antibody with confirmed presence of HCV ribonucleic acid [RNA])

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

[40] Have evidence of HIV infection and/or positive HIV antibodies.

[41] Have screening laboratory test values, including thyroid-stimulating hormone (TSH), outside the reference range for the population or investigative site that, in the opinion of the investigator, pose an unacceptable risk for the patient's participation in the study.

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

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

a. AST or ALT ≥2x upper limit of normal (ULN)

b. alkaline phosphatase (ALP) ≥2x ULN
Note: Patients may be allowed to enroll if there is no other evidence of liver, bone, or other abnormality but cases must be discussed and judged not clinically significant by Lilly Medical prior to enrollment.

c. total bilirubin ≥1.5x ULN
Note: Patients may be allowed to enroll if there is no other evidence of liver or other abnormality but cases must be discussed and judged not clinically significant by Lilly Medical prior to enrollment.

d. hemoglobin <10.0 g/dL (100.0 g/L)

e. total white blood cell count <2500 cells/μL (<2.50x10^3/μL or <2.50 GI/L)

f. neutropenia (absolute neutrophil count [ANC] <1200 cells/μL) (<1.20x10^3/μL or <1.20 GI/L)

g. lymphopenia (lymphocyte count <750 cells/μL) (<0.75x10^3/μL or <0.75 GI/L)

h. thrombocytopenia (platelets <100,000/µL) (<100x10^3/µL or <100 GI/L)

i. estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (eGFR, calculated using Bedside Schwartz 2009 formula).

Note: For cases with any of the aforementioned laboratory abnormalities (Exclusion Criteria [41] and [42]), the tests may be repeated during screening, and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Patients who are entered into the study but do not meet the enrollment criteria for participation in this study (screen failure) may be rescreened a maximum of 2 times. The interval between screen failure and rescreenings should be at least 4 weeks. At the time of rescreening, the individual (patient or parent/legal guardian) must sign a new ICF, repeat all necessary screening procedures, and will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of baricitinib (high, medium, and low) doses to placebo. The IP will be administered by mouth once daily. The high doses to be used in the Study Periods 3 and 4 will be confirmed during the PK lead-in period. Table JAIP.4 shows the proposed treatment regimens.

Table JAIP.4. Treatment Regimens

Regimen for Patients 10 to <18 years old	Open-label Investigational Product Supplied (Study Periods 2 and 4)	Dose
Baricitinib High Dose (4–mg QD)	Baricitinib 4-mg tablets	1 tablet per day
Regimen for Patients 2 to <10 years old	**Open-label Investigational Product Supplied (Study Periods 2 and 4)**	**Dose**
Baricitinib High Dose (2–mg QD)	Oral suspension formulation[a]	1 mL per day
Regimen for Patients 10 to <18 years old	**Double-blind Investigational Product Supplied (Study Periods 3 and 4)**	**Dose**
Baricitinib High Dose (4–mg QD)	Baricitinib 4-mg tablets Placebo to match 2-mg tablets Placebo to match 1-mg tablets	3 tablets per day
Baricitinib Medium Dose (2–mg QD)	Baricitinib 2-mg tablets Placebo to match 4-mg tablets Placebo to match 1-mg tablets	3 tablets per day
Baricitinib Low Dose (1–mg QD)	Baricitinib 1-mg tablets Placebo to match 4-mg tablets Placebo to match 2-mg tablets	3 tablets per day
Placebo QD	Placebo to match 4-mg tablets Placebo to match 2-mg tablets Placebo to match 1-mg tablets	3 tablets per day
Regimen for Patients 2 to <10 years old	**Double-blind Investigational Product Supplied (Study Periods 3 and 4)**	**Dose**
Baricitinib High Dose (2-mg QD)	Oral suspension formulation[a]	1 mL per day
Baricitinib Medium Dose (1-mg QD)	Oral suspension formulation[a]	0.5 mL per day
Baricitinib Low Dose (0.5-mg QD)	Oral suspension formulation[a]	0.25 mL per day
Placebo QD	Placebo oral suspension formulation to match[a]	1 mL per day or 0.5 mL per day or 0.25 mL per day

Abbreviation: QD = once daily.

[a] The oral suspension formulation has a stability of 100 days after opening (breaking the seal). The oral suspension should be dispensed as shown in the Study Schedule (Section 2).

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

- explaining the correct use of the investigational agent(s) to the patient and parent/caregiver and site personnel
    - Ensuring that patients ≥10 years old are able to swallow whole tablets
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the Sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

The Sponsor (or its designee) will provide the following IP:

- tablets containing 4-mg of baricitinib
- tablets containing 2-mg of baricitinib
- tablets containing 1-mg of baricitinib
- placebo tablets to match baricitinib 4-mg tablets, 2-mg tablets, and 1-mg tablets.
- liquid suspension containing baricitinib at 2 mg/mL strength
- liquid suspension containing placebo to match baricitinib 2 mg/mL strength

For older patients (10 to <18 years old), packaging of the double-blind IP for each dose will include 3 tablets per day provided in blister packs (Study Periods 3 and 4). Each tablet has a distinctive shape and color, 4-mg versus 2-mg versus 1-mg, and each strength tablet has a matching placebo. Each active dose package will contain the appropriate active strength tablet, and corresponding placebo tablets for the other strengths, as noted in Table JAIP.4. Open-label IP tablets will be provided in bottles (Study Periods 2 and 4).

For younger patients (2 to <10 years old), baricitinib oral suspension (containing 2-mg/mL baricitinib) or matching placebo will be supplied as a ready-to-use oral suspension. Baricitinib oral suspension will be provided in a bottle and doses will be delivered to the patient using an oral syringe as described in Table JAIP.4. The Sponsor will provide an instructions for use (IFU) document that describes the process for administration of the oral suspension. The investigator or appropriate site personnel should review the instructions for use with the patient and parent/caregiver to ensure understanding of the correct administration procedure for the oral suspension.

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

7.1.2. Medical Devices

N/A

7.2. Method of Treatment Assignment

Patients participating in the PK lead-in who meet all criteria for enrollment will receive open label baricitinib at the high dose for their age group beginning at Visit 2.

Patients not participating in the PK lead-in who meet all criteria for enrollment will be randomized in a 1:1:1:1 ratio (placebo, baricitinib low dose; baricitinib medium dose; baricitinib high dose) to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign blister packs or bottles containing double-blind IP to each patient according to the Study Schedule (Section 2). Site personnel will confirm that they have located the correct blister packs or bottles by entering a confirmation number found on the blister packs or bottles into the IWRS.

Randomization will be stratified by disease severity at baseline (IGA 3 versus 4) and geographic region if the planned country allocation justifies. Definitions of geographic regions and plan for analysis by region will described in the SAP.

7.2.1. Selection and Timing of Doses

The IP 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.

At a visit where a PK sample is collected, the actual time of doses administered will be recorded in the patient's electronic case report form (eCRF) according to Section 9.5.

7.3. Blinding

The PK-lead-in (Period 2) is open-label. Patients who participate in the PK lead-in and transition to the long-term extension (Period 4) will continue on open-label IP.

Study Period 3 is double-blind. Patients who are responders after completion of Period 3 will remain on double-blind treatment during the long-term extension (Period 4). Patients who are non-responders to double-blind treatment in Study Period 3 will transition to open-label treatment in the long-term extension (Period 4). In addition, patients on double-blind treatment in Study Period 4 may be transitioned to open-label treatment if response is lost.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. All study assessments will be performed by study personnel who are blinded to the patient's treatment group. Except in clinical circumstances where unblinding is required, the patients, investigators, Lilly study team, and any personnel interacting directly with patients or investigative sites will remain blinded to baricitinib and placebo assignment until after completion of the Double-blind Treatment periods. It is expected that the need for unblinding a patient's treatment prior to completion of the Double-blind Treatment periods will be extremely rare. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the medical care of the patient. Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the patient's well-being

requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. Patient safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a subject's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately that an unblinding has occurred, and effort should be made to keep the number of individuals at the clinical site with knowledge of the unblinded treatment arm to a minimum. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible. Unblinding should only occur when decisions regarding patient care will be made based on whether or not the patient was on active drug.

Processes to maintain blinding during the analysis conducted by the Data Monitoring Committee (DMC) are described in Section 10.3.8.1.

7.4. Dosage Modification

The baricitinib dose for an individual patient will not change during the PK lead-in period (Study Period 2). However, the baricitinib dose for an age-based cohort to be randomized into Study Period 3 may change based on the data from the PK lead-in period. If the data from the PK lead-in show that the exposure for a high dose in an age group is significantly greater than expected and not comparable to the 4 mg dose in adults, then the dose range for that age group will be adjusted (i.e., the medium and low doses will be studied) for the Double-blind Treatment period (Study Period 3). Patients will not be enrolled into the Double-blind Treatment period (Study Period 3) until the doses for an age cohort have been confirmed from the PK lead-in; therefore no changes in doses for an individual patient are anticipated during Study Period 3. Patients who complete the PK lead-in (Study Period 2) will be eligible to enter the long-term extension (Period 4) on the open-label dose they received at the start of the PK lead-in period, and if the dose is modified for an age group after patients have already entered the long-term extension (Period 4), the patient will be transitioned to the modified dose.

7.5. Preparation/Handling/Storage/Accountability

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

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

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

Follow storage and handling instructions on the IP packaging.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit after Visit 2 during Study Periods 2, 3, and 4.

Patients treated with baricitinib or placebo will be considered to be noncompliant if they miss >20% of the prescribed doses during the study (unless the patient's IP was withheld by the investigator for safety reasons).

Similarly, patients will be considered to be noncompliant if they are judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of study medication. Patients found to be noncompliant with the IP should be assessed to determine the reason for noncompliance and educated and/or managed as deemed appropriate by the investigator to improve compliance.

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

Patient 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 appropriate Concomitant Medication 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 7.7.5.

7.7.1. 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. If daily applications are missed, it will not be considered a protocol violation. Emollients will not be supplied by the Sponsor, unless required by local regulations.
    - Patients should not apply emollients on the day of their study visit prior to the procedures to allow for adequate assessment of skin dryness.
- Open-label PK lead-in (Study Period 2): Low- or mid-potency TCS (e.g., hydrocortisone 2.5% ointment and/or triamcinolone 0.1% cream) and high- or ultra-high-potency TCS are only permitted as rescue therapy as described in Section 7.7.5 (Rescue Therapy).
- Double-blind Placebo-controlled Treatment Period (Study Period 3): Background TCS therapy with medium-potency and/or low-potency TCS (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment) is to be used on active lesions as described in Section 7.7.2 (Use of Topical Corticosteroids).
- Long-term Extension Treatment Period (Study Period 4): Protocol-defined background TCS therapy (all potencies) will be allowed as concomitant treatment as described in Section 5.1.4.
- TCNIs (e.g., tacrolimus and pimecrolimus) or topical PDE-4 inhibitor (i.e., crisaborole, where approved) are permitted in place of TCS as rescue therapy during Study Period 2 or background therapy during Study Periods 3 and 4, on areas where application of TCS is considered inappropriate by the investigator; use should be limited to problem areas (e.g., face, neck, skin folds, genital areas, etc.) as described in Section 7.7.2 (Use of Topical Corticosteroids) and Section 7.7.5 (Rescue Therapy).
- Phototherapy, including therapeutic phototherapy (psoralen and ultraviolet A, ultraviolet B, excimer laser), is permitted as rescue therapy in Period 4 at the discretion of the investigator (see Section 7.7.5, Rescue Therapy); however, it requires a temporary interruption of IP (see Section 8.1.1).
- Bleach baths are permitted at the discretion of the investigator.

In addition, the following therapies are permitted during the study:

- intranasal or inhaled steroids
- leukotriene inhibitors (e.g., montelukast [Singulair], zafirlukast [Accolate], and zileuton [Zyflo])
- topical anesthetics and topical and systemic anti-infective medications
- cyclosporine ophthalmic emulsion (e.g., Restasis)
- nonlive vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations.

It is recommended that patients using medications for sleep (including antihistamines) be on a stable dose for 2 weeks prior to Visit 1. For those patients on stable dosing of medications for

sleep at entry, downward dose adjustments or discontinuation of treatment may occur during the study.

No more than 1 intra-articular or soft tissue (bursa, tendons, and ligaments) corticosteroid injection is allowed up until the 16-week primary endpoint. After 16 weeks, such injections are permitted.

Any changes to these concomitant medications must be recorded on the appropriate Concomitant Therapy eCRF.

Treatment with concomitant therapies for other medical conditions (not excluded per protocol) is permitted during the study.

7.7.2. Use of Topical Corticosteroids

Open-label PK Lead-in Period (Study Period 2)

A washout period of 7 days is required for all TCS prior to Visit 2.

TCS medications are not permitted during Study Period 2 except as rescue treatment (see Section 7.7.5 [Rescue Therapy]).

Investigators should attempt to manage patients with emollients; however, investigators are allowed to rescue patients who are experiencing unacceptable or worsening symptoms of AD at any time. Prior to rescue, it is recommended that increased frequency of emollient use is attempted to at least twice a day or more in an effort to control symptoms. The rationale for rescue will be documented.

Double-blind Placebo-controlled Treatment Period (Study Period 3)

At Visit 1, patients will receive Sponsor-provided TCS (triamcinolone 0.1% cream or equivalent-potency TCS, and hydrocortisone 2.5% ointment or equivalent-potency TCS). Patients will use the Sponsor-provided TCS medications as prescribed by the investigator (as clinically indicated).

After Visit 2, medium-potency TCS (e.g., triamcinolone 0.1% cream) should continue to be applied to affected areas as clinically indicated until lesions are under control (clear or almost clear). The medium-potency TCS should be tapered and stopped as clinically indicated (e.g., transition to hydrocortisone 2.5% ointment for an additional 7 days, then stop). Low-potency TCS (e.g., hydrocortisone 2.5% ointment), a TCNI, or a topical PDE-4 inhibitor (e.g., crisaborole) may also be used to replace the medium-potency TCS on areas of thin skin (face, neck, folds, and genital areas) and areas with skin atrophy. Low potency TCS and TCNIs may be used until the lesions are under control (clear or almost clear) and then be tapered and stopped as clinically indicated.

If lesions reappear during the course of the study, the patients should resume the application of medium-potency TCS (e.g., triamcinolone 0.1% cream) or low-potency TCS (e.g., hydrocortisone 2.5% ointment), TCNI, or PDE-4 inhibitor as described above.

Patients whose lesions persist or worsen despite the use of emollients and low- and/or medium-potency TCS may be considered for topical rescue with high- or ultra-high-potency TCS.

On the days of study visits, topical therapy including TCS should not be applied before the patient has undergone all study procedures and clinical evaluations in order to allow adequate assessment of skin dryness. Inability to follow this guidance for use of TCS will not be considered a protocol violation.

Long-term Extension Treatment Period (Study Period 4):

Background TCS therapy with medium-potency and/or low-potency TCS (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment), TCNI, or PDE-4 inhibitor (e.g., crisaborole) is allowed. For patients whose lesions persist or worsen despite the use of emollients and low- and/or medium-potency TCS, high- or ultra-high-potency TCS may be used as concomitant treatment.

Medium-, high-, or ultra-high-potency TCS should be tapered and stopped as clinically indicated (e.g., transition to hydrocortisone 2.5% ointment for an additional 7 days, then stop).

If lesions reappear during the course of the study, the patients should resume the applications of medium-potency TCS (e.g., triamcinolone 0.1% cream) or low-potency TCS (e.g., hydrocortisone 2.5% ointment), high- or ultra-high-potency TCS, TCNI, or PDE-4 inhibitor as described above.

Sponsor-provided low- and medium-potency TCS is available for dispensing through Visit 27. At Visit 28 and beyond, TCS use is allowed; however, sponsor will no longer provide the TCS products.

7.7.3. Use of Antihistamines

Use of antihistamines is allowed throughout the study. It is recommended that patients using antihistamines be on a stable dose for 2 weeks prior to Visit 1. For those patients on stable dosing of antihistamines at entry, downward dose adjustments or discontinuation of treatment may occur during the study.

7.7.4. Prohibited Medications and Procedures

Prohibited Medications and Procedures Not Requiring Urgent 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, the prohibited therapy must be discontinued. If the patient is not able to discontinue use of the following then IP will be permanently discontinued.

- allergen immunotherapy

- self-treatment with tanning booth

Prohibited Medications and Procedures 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 IP is required. If the protocol guidance below is followed, use of these medications will not be considered a protocol violation.

- Live vaccines may be considered during Study Period 4 if they are essential based on the local guideline and/or in the opinion of the investigator. The IP should be temporarily interrupted for at least 12 weeks for live typhoid and BCG vaccines and for at least 28 days for all other live vaccines including MMR or VZV booster vaccinations.
- systemic corticosteroids for the treatment of an AE (if used for AD see below). 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 IP is required.
- any systemic therapy, investigational or commercial (approved or off-label use), used as rescue for the treatment of AD (including systemic corticosteroids, see Section 7.7.5, Rescue Therapy).
- Probenecid: if a patient is inadvertently started on probenecid, IP should be temporarily interrupted and can be resumed after the patient has discontinued probenecid. If a patient is not able to discontinue probenecid, then IP should be permanently discontinued.

Prohibited Medications Requiring Permanent Discontinuation (during Study Period 4) of Investigational Product

- systemic immunosuppressive/immunomodulatory substances, including, but not limited to, cyclosporine, methotrexate, mycophenolate mofetil, interferon-γ, azathioprine, biologic agents, or other JAK inhibitors (e.g., tofacitinib and ruxolitinib).

7.7.5. Rescue Therapy

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit should be used for this purpose if necessary.

7.7.5.1. Rescue during Periods 2 and 3

Choice of rescue therapy treatment (Study Period 2)

- Triamcinolone cream 0.1% and/or hydrocortisone 2.5% ointment. The use should be recorded via weight of the dispensed and returned tube and cap as indicated in the Schedule of Activities (Section 2). In countries where these topical formulations are not available or are not considered suitable for an individual patient, an equivalent-potency TCS cream and/or ointment that is in line with local practices can be used. Refer to Appendix 9 for guidance on potency equivalence.

- Investigators may also select to use TCNIs and/or crisaborole where approved, although it will not be provided. If TCNIs are prescribed, use should be limited to problem areas only (e.g., face, neck, skin folds, genital areas, etc.).
- On the days of study visits, topical therapy (including emollients) should not be applied before the patient has undergone all study procedures and clinical evaluations to allow adequate assessment of skin dryness.
- Patients rescued to topical therapy will continue to take IP and use of rescue therapy will be documented in the eCRF.

For patients who do not improve sufficiently with rescue topical therapy after 7 days, a higher potency TCS may be used (see Appendix 9), and IP may continue. High- or ultra-high-potency TCS may be used once daily for up to 14 consecutive days or less based on the maximum duration recommended in the prescribing information. It is recommended that if a patient reaches "clear" to "almost clear" skin after topical rescue, then medium- and/or high-potency TCS and TCNI should be stopped, and low-potency TCS (for example, hydrocortisone 2.5% ointment) should be used QD for an additional 7 days, then stopped. If lesions return, patients can be retreated with TCS with or without TCNIs and/or crisaborole as before, at the discretion of the investigator.

Choice of rescue therapy treatment (Study Period 3)

Patients whose lesions persist or worsen despite the use of emollients and low- and/or medium-potency background TCS may be considered for topical rescue with high- or ultra-high-potency TCS.

Rescue with Systemic Therapies

Patients whose disease cannot be controlled by the measures described above may be rescued to systemic therapies (conventional systemics or biologics) during Study Period 3. These patients will be required to discontinue IP before initiating systemic treatment. Patients rescued to systemic therapies during Study Period 3 prior to the primary endpoint (Visit 8) should be encouraged to continue with study visits and assessments through Visit 8. After appropriate discontinuation of the oral systemic treatment, patients may transition to open-label baricitinib at the high dose for their age group in Study Period 4. Patient who require use of biologic treatments will not be allowed to enter Study Period 4.

7.7.5.2. Rescue during Period 4

During Period 4, patients who participated in the PK lead-in will continue on open-label treatment at the dose they received in the PK lead-in (high dose for age group); patients who were non-responders (IGA ≥3) to randomized treatment in Period 3 or who have required rescue with topical or systemic treatments during Study Period 3 will transition to open-label treatment at the high dose allowed for their age group. Patients who were responders (IGA 0, 1, or 2) to randomized treatment in Period 3 without requiring rescue with topical or systemic treatments during Study Period 3 will continue on double-blind treatment at the same dose as initially randomized in Period 3.

During Study Period 4, for patients on double-blind treatment whose IGA worsens to 3 or 4 and who are unable to recapture an IGA response of 0, 1, or 2, despite the use of emollients and TCS (as described in Section 7.7.2), the patient may be transitioned at the discretion of the investigator to open-label baricitinib at the high dose for their age group.

After the first year of the extension treatment period, treatment and transition to open-label baricitinib will continue as described above; however, patients will be allowed to voluntarily interrupt baricitinib treatment (drug holiday) as described in Section 5.1.4, provided they continue to complete all other study visit procedures per protocol. The IP may be resumed at the same dose after a voluntary interruption if symptoms worsen.

Patients may be rescued with phototherapy at the discretion of the investigator during Study Period 4. Patients rescued with phototherapy will remain in the study and be required to temporarily interrupt use of IP until completion of the phototherapy (see Section 8.1.1 for Temporary Interruption of Investigational Product).

Patients who require rescue with systemic therapies (conventional systemics or biologics) during Period 4 will be considered to be nonresponders and will be discontinued from the study.

7.8. Treatment after the End of the Study

After the conclusion of the study, continued access to baricitinib will not be provided. 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 Discontinuation from Study Treatment

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 IP. For example, IP should be temporarily interrupted if the patient experiences a cardiovascular adverse event 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 JAIP.5.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table JAIP.5, specific guidance is provided for temporarily interrupting treatment and 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 JAIP.5 may be restarted at the discretion of the investigator.

Table JAIP.5. 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 >5x ULN	ALT and AST return to <2x 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 (shingles or chicken pox)	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection
Clinical features of VTE (such as deep vein thrombosis or pulmonary embolism) are present[a]	After ruling out event of VTE

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

[a] Evaluate promptly and institute appropriate treatment. If upon evaluation VTE is ruled out and no other temporary or permanent discontinuation criteria are met, then IP may be resumed.

Although temporary interruption of IP is not a requirement at times of increased potential risk of VTE (e.g., surgery, significant air travel, or other situations involving prolonged immobilization), following appropriate VTE prophylaxis guidelines is recommended to help manage the VTE risk under these circumstances.

If rescue with phototherapy is required during Study Period 4, then the IP must be temporarily interrupted until the phototherapy treatments have been completed (see Section 7.7.5, Rescue Therapy).

During the long-term extension the patient will be allowed to receive live vaccines with appropriate interruption of baricitinib treatment prior to and after the live vaccine (see Section 7.7.4).

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

8.1.2. Permanent Discontinuation from Study Treatment

Investigational product should be permanently discontinued if the patient or the patient’s designee (parent/legal guardian/caregiver) requests to discontinue IP.

Discontinuation due to a hepatic event or liver test abnormality.
Patients who are discontinued from IP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via case report form (CRF) or other designated data transmission methods.

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

- ALT or AST >8× ULN
- ALT or AST >5× ULN for more than 2 weeks
- ALT or AST >3× ULN and total bilirubin level (TBL) >2× ULN or international normalized ratio (INR) >1.5
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and/or rash
- ALP >3× ULN (unless allowed after discussion with Sponsor)
- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, and/or rash

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

- white blood cell count <1000 cells/µL ($1.00x10^3$/µL or 1.00 GI/L)
- ANC <500 cells/µL ($0.50x10^3$/µL or 0.50 GI/L)
- lymphocyte count <200 cells/µL ($0.20x10^3$/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, IP 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 JAIP.5) following the resolution of the intercurrent illness or other identified factor may the investigator restart IP, after consultation with the Lilly-designated medical monitor.

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

- pregnancy
- malignancy
- hepatitis B virus DNA is detected with a value above the limit of quantitation or 2 sequential tests return a value of below the limit of quantitation (see Section 9.4.8).
- develop a VTE event

If a patient who is participating in the Double-blind Treatment period (Study Period 3) discontinues IP for any reason, the patient is encouraged to remain in the study through Week 16 (Visit 8) and follow the regular visit schedule to provide the primary efficacy and safety data. Patients discontinuing from the IP 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 CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with IP. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

In some instances, it will be clear that the inadvertently enrolled patient needs to be withdrawn from the study drug. This is the case for important protocol deviations, where it is clear that the protocol deviation(s) may significantly impact the completeness, accuracy, and/or reliability of the study data or may significantly affect a subject's rights, safety, or well-being (ICH 2012). In other instances, where the protocol deviation is considered non-important since it will not significantly impact patient safety or interpretation of the study data, the Investigator and the Sponsor may agree it is medically appropriate to allow the patient to continue in the study with appropriate documentation of the rationale. Preplanned per-protocol analyses will be described in the statistical analysis plan for the study and will include analyses of key efficacy endpoints with and without data from patients with protocol deviations.

8.2. Discontinuation from the Study

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

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- 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 systemic therapeutic agent (not allowed as part of rescue therapy [Section 7.7.5]) 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.
      Note: Patients rescued to systemic therapies prior to the primary endpoint (Week 16) will be encouraged to continue with study visits and assessments through Visit 8.
- subject decision
    - the patient requests to be withdrawn from the study.

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

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

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

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

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

9.1. Efficacy Assessments

Please refer to the Schedule of Activities (Section 2) and Appendix 6 for details on frequency of collection, method of data collection, method of administration, and age range of administration for all efficacy and health outcomes and quality-of-life measures.

9.1.1. Primary Efficacy Assessments

Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD): The IGA used in this study is the vIGA-AD (referred to as the IGA throughout the protocol) and measures the investigator's global assessment 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) (information available at WWW.eczemacouncil.org). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification.

The IGA is a commonly used scale in clinical trials in adult and pediatric patients (Langely et al. 2015; Futamura et al. 2016).

9.1.2. Secondary Efficacy Assessments

9.1.2.1. Eczema Area and Severity Index scores

The investigator-rated 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). Body surface area affected by AD will be derived from data collected as part of the EASI assessment.

The EASI is a validated scale in patients down to 2 months of age (Barbier et al. 2004).

9.1.2.2. SCORing Atopic Dermatitis

The SCORing Atopic Dermatitis (SCORAD) index is an investigator-rated assessment that 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 (via patient-rated visual analog scale). These 3 aspects: extent of disease,

disease severity, and subjective symptoms combine to give a maximum possible score of 103 (Stalder and Taieb 1993; Oranje et al. 2007).

9.1.3. Immunological Measurements

Patients will be immunized with appropriate vaccinations as part of or in the course of their usual care according to the local requirement throughout the study period. When the patients become eligible for a TDaP and/or a pneumococcal conjugate vaccine during the study, they are immunized with the vaccines and their antibody titers to the antigens will be evaluated pre-immunization and at 4 and 12 weeks post-immunization. A primary immune response will be assessed in patients who have never received TDaP or pneumococcal conjugate vaccines previously and secondary/booster responses will be assessed if the patients have previously received the vaccines.

9.1.4. 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 and in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

9.1.4.1. Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (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 to 28 with higher total scores indicating greater disease severity (Charman et al. 2004).

The POEM is a validated scale in patients down to 1 year of age (Charman et al. 2004).

9.1.4.2. Itch Numeric Rating Scale

The Itch Numeric Rating Scale (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).

9.1.4.3. 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 past 24 hours.

9.1.4.4. 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 last 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 last 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.

9.1.4.5. 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."

9.1.4.6. PROMIS Depression Short Form

Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children (information available at WWW.healthmeasures.net; PROMIS - Depression). It can be used with the general population and with individuals living with chronic conditions. The PROMIS Depression item bank assesses self-reported negative mood (sadness, guilt), views on self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The PROMIS Depression Short Form (8a v2.0 and 6a v2.0) is available in a pediatric self-report (ages 8 to <18 years) and for parents/caregivers serving as proxy reporters for their children (youth ages ≥5 years). Children aged <5 years will not complete this assessment. Both pediatric self-report and proxy-report versions assess depression "in the past seven days." Response options range from 1 = Never; 2 = Rarely; 3 = Sometimes; 4 = Often; to 5 = Almost always. Total raw scores are converted to T-Scores with higher scores representing greater depression.

9.1.4.7. PROMIS Anxiety Short Form

Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children (information available at WWW.healthmeasures.net; PROMIS - Anxiety). It can be used with the general population and with individuals living with chronic conditions. The PROMIS Anxiety item bank assesses self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). The PROMIS Anxiety Short Form (8 questions, 8a v2.0) is available in a pediatric self-report (ages 8 to <18 years) and for parents/caregivers serving as proxy reporters for their children (youth ages ≥5years). Children aged <5 years will not complete this assessment. Both pediatric self-report and proxy-report versions assess anxiety "in the past seven days." Response options range from 1= Never; 2 = Rarely; 3 = Sometimes; 4 = Often; to 5 = Almost always. Total raw scores are converted to T-Scores with higher scores representing greater anxiety.

9.1.4.8. Infants' Dermatitis Quality of Life Index

The Infant's Dermatitis Quality of Life Index (IDQOL) is a simple, caregiver-administered, 11-question, validated, quality-of-life questionnaire that is designed for use in pediatric patients <4 years old with AD (Lewis-Jones et al. 2001; Basra et al. 2013). It is completed by the child's

parent or regular caregiver. It covers 2 domains including Dermatitis Severity and Life Quality Index. The recall period is over the "last week." Response categories for the Dermatitis Severity domain include "None," "Fairly good," "Average," "Severe," and "Extremely severe" with corresponding scores of 0, 1, 2, 3, and 4, respectively. The Life Quality Index domain response categories vary for individual questions; however, each question has 4 response options with corresponding scores ranging from 0-3. Total scores of the Life Quality Index range from 0-30 with higher scores indicating greater impairment of quality of life. The Dermatitis Severity is scored separately and can be correlated with the IDQOL. An IDQOL total score of 0 to 1 is considered as having no effect on a child's life.

9.1.4.9. Children's Dermatology Life Quality Index

The Children's Dermatology Life Quality Index (CDLQI) is a simple, patient-administered, 10-question, validated, quality-of-life questionnaire that is designed for use in children ≥4 years old that covers 6 domains including symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment (Lewis-Jones and Finlay 1995). The recall period is over the "last week." Response categories include "not at all," "only a little," "quite a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, with unanswered ("not relevant") responses scored as 0 and "Prevented School" scored as 3. Scores range from 0 to 30 with higher scores indicating greater impairment of quality of life. A CDLQI total score of 0 to 1 is considered as having no effect on a child's life (Waters et al. 2010).

9.1.4.10. Dermatitis Family Impact Questionnaire

The Dermatitis Family Impact (DFI) questionnaire is a simple, caregiver-administered, 10-question, validated, quality-of-life questionnaire that is designed to assess the impact of AD on the quality of life of the parents and family members of children with AD (Lawson et al. 1998; Dodington et al. 2013). The recall period is over the "last week." Response options include "Not at all," "A little," "A lot," and "Very much," with corresponding scores of 0, 1, 2, and 3, respectively. Scores range from 0 to 30 with higher scores indicating greater impairment of quality of life.

9.1.4.11. European Quality of Life–5 Dimensions–Youth

The European Quality of Life-5 Dimensions-Youth version (EQ-5D-Y) is a widely used, generic questionnaire that assesses health status "today" (The EuroQol Group 2014). The EQ-5D-Y is self-completed for pediatric patients ≥8 years old and is completed by parents/caregivers (proxy) for children 4 to <8 years old. This assessment will not be completed for children <4 years old per developer recommendation. The questionnaire consists of 2 parts: the first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 3 possible levels of response (no problems, some problems, or a lot of problems). This part of the EQ-5D-Y can be used to generate a health state index score, which is often used to compute QALY for utilization in health economic analyses. The health state index score is calculated based on the responses to the 3 dimensions, providing a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility.

The second part of the questionnaire consists of a visual analog scale on which the patient rates their perceived health state from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Published studies by EuroQol Group members showed preliminary evidence of the instrument's feasibility, reliability, and validity (Ravens-Sieberer et al. 2010).

9.1.4.12. Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis - Caregiver

The Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis Caregiver (WPAI-AD-CG) assesses the effect of a child's AD on the parent/caregiver's work productivity during the past 7 days. The WPAI-AD-CG 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, 1996), with higher scores indicating greater impairment and less productivity.

9.1.4.13. Parent-Reported Itch Severity Measure

The Parent-Reported Itch Severity Measure (PRISM) is a single-item, parent/caregiver-administered scale that reports the overall severity of their child's itching. Parent/Caregiver's report the overall severity of their child's itching based on observed actions of the child in the past 24 hours. Response options range include "No Itch," "Mild," "Moderate," "Severe," and "Very Severe." The PRISM will be completed for patients <10 years old by the parent/caregiver.

9.1.4.14. Additional Assessments (TCS Use, Missed School Days)

Topical corticosteroids use will be collected using a daily diary. This is a single question used to record if a patient has applied a TCS to the skin in the last 24 hours. Either the patient or parent/caregiver can provide the response.

The number of missed school days for school age children will be reported via daily diary by the parent/caregiver or patient.

9.1.5. Product Acceptability and Palatability Assessments

The assessment of acceptability and palatability of the baricitinib formulations (tablet and oral suspension) will only be collected for patients participating in the Open-label PK Lead-in period (Study Period 2).

The patient and/or parent/caregiver will be asked to provide responses to questions designed to assess the acceptability and palatability of the formulations, either tablet or oral suspension. The questionnaire for tablet acceptability will assess the patient's ability to swallow the tablet. The questionnaire for suspension acceptability and palatability will assess the patient's experience relating to the taste and smell of the suspension and ease of administering and taking the suspension (Davies and Tuleu 2008; Kozarewicz 2014).

The appropriate questionnaire will be administered at baseline (Visit 2, after dosing) and Visit 4 (after approximately 2 weeks of use). The questionnaire will be responded to by

parents/caregivers (proxy) for children aged 2 to <10 years (suspension formulation). For children aged 10 years and older, the questionnaire will be self-completed (tablets).

9.1.6. Appropriateness of Assessments

All assessments utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant except the Skin Pain NRS, ADSS, PGI-S-AD, PRISM, missed school days, and acceptability/palatability 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 IP or the study, or that caused the patient to discontinue the IP before completing the study. The patient should be followed until the event resolves or stabilizes with appropriate diagnostic evaluation; for events that are not anticipated to resolve or stabilize, the patient should be followed until the treating physician (in consultation with the Sponsor) determines that appropriate follow-up has been completed. 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 protocol procedure and IP, via eCRF.

Investigators should record the following via eCRF for each AE: date of onset, date of termination, severity, and their assessment of the potential relatedness of each AE to IP.

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. 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 IP. However, if an SAE occurs after signing the ICF, but prior to receiving IP, the SAE should be reported to the Sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via initiation of SAE eCRF. Once the SAE eCRF form is initiated, an email is automatically triggered to the Sponsor's global patient safety department. Investigators can contact the Sponsor via telephone at any time using the qualified medical personnel or Lilly affiliate medical contact details which are provided in the site study file. If alerts are issued via telephone, they are to be immediately followed with official notification via completion of the SAE eCRF. If the eCRF is unavailable (for example, for system maintenance) for a period of time that would compromise the sites' ability to report an event within 24 hours of awareness, a paper version of the form should be downloaded from the Investigator Space portal, completed by the investigator, and submitted via fax to the Sponsor's global patient safety department. This form includes a fax cover page that is pre-populated with the appropriate fax number. Serious adverse events submitted via the paper method are entered into the eCRF once the database is available. The 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic adverse event should have additional data collected using the eCRF.

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

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition 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/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 IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

Adverse events of special interest will include the following:

- infections (including tuberculosis [TB], herpes zoster, or opportunistic infections)
- malignancies (except for successfully treated basal or squamous cell skin carcinoma)
- hepatic events (see Section 9.4.9.1)
- major adverse cardiovascular events (MACE) (see Section 9.4.9)
- thrombotic events (such as deep vein thrombosis and pulmonary embolism)

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 IPs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

Baricitinib single doses up to 40-mg and multiple doses of up to 20-mg daily for 10 days have been administered in clinical studies without dose-limiting toxicity. Pharmacokinetic data of a single dose of 40-mg in healthy volunteers indicate that >90% of the administered dose is

expected to be eliminated within 24 hours. In case of an overdose, the patient should be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

9.4. Safety

Any clinically significant findings from electrocardiogram (ECG) testing, 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. Electrocardiograms

A single 12-lead standard ECG will be obtained locally at Visit 1 and read by a qualified physician (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

9.4.2. Vital Signs

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

Blood pressure readings will be collected using the appropriate size pediatric blood pressure cuffs.

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

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). Flexibility in blood sample collection is allowed where blood sample volume restrictions may apply; refer to protocol Appendix 13.

Use of local anesthetics (e.g., EMLA cream) consistent with local prescribing information are permitted during the study visit to ease discomfort associated with venipunctures. Home visits to collect blood and urine samples may be allowed upon written approval from the sponsor and if consistent with local regulations.

Alkaline phosphatase laboratory results may be out of the normal range in pediatric patients because of normal bone growth processes, and collection of a blood sample for bone alkaline phosphatase may be requested by the Sponsor as a reflex test if the alkaline phosphatase result is high.

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of IP should be reported to Lilly or its designee as an AE via CRF/electronic data entry / designated data transmission methods.

Fasting Laboratory Tests:

Recommended fasting times by age and weight are as follows:

- Adolescents ≥12 years: fast for 12 hours prior to laboratory test
- Children 8 to <12 years and weighing >50 kg: fast for 12 hours prior to laboratory test
- Children 8 to <12 years and weighing ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 25 to ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 10 to ≤25 kg: fast for 6 hours prior to laboratory test
- Children <8 years and weighing <10 kg: fast for 4 hours prior to laboratory test

Urinalysis:

If an urinalysis sample is unable to be collected in younger children, particularly those who have not been toilet trained, this will not be considered to be a protocol violation provided that the site maintains appropriate documentation of why the sample is missing.

9.4.4. Physical Exam

For each patient, a complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1 (Screening). A symptom-directed physical examination will be performed at other visits as specified in the Schedule of Activities (Section 2). A complete physical examination may be repeated at the investigator's discretion at any time a patient presents with physical complaints.

9.4.4.1. Tanner Stage Scale

The Tanner Stage Scales are a series of line drawings that are designed to assess sexual maturity of the patient, and will be included as a baseline assessment. The line drawings are intended for patient self-assessment; however, this assessment may be also conducted by an appropriate health care professional if the patient and legal guardian agree (Marshall and Tanner 1969, 1970; Tanner and Davies 1985; Chavarro et al. 2017). Assessment by the health care professional will not be completed if the patient and parent do not provide appropriate consent and assent. The self-assessment will only be collected if the appropriate translation of the scale is available for use at the time of the baseline assessment.

9.4.5. Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The C-SSRS will only be collected in patients ≥7 years old. A children's version of the C-SSRS will be completed for patients 7 to <12 years old, and an adolescent/adult version of the C-SSRS will be completed

for patients 12 to <18 years old. 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 qualified site personnel. 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 where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

9.4.6. 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.

9.4.7. Tuberculosis Testing

Patients will be tested at screening (Visit 1) for evidence of active or latent TB as described in the exclusion criteria (Section 6.2). Investigators should follow local guidelines for monitoring.

9.4.8. Hepatitis B Virus DNA Monitoring

Patients who are HBcAb positive and HBV DNA negative (undetectable) at Visit 1 will require measurement of HBV DNA per the Schedule of Activities, 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,” HBV DNA monitoring will be performed per study schedule (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 IP (see Section 8.1.2) and should be referred to a hepatology specialist.

9.4.9. Safety Monitoring

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

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring committee (an advisory group for this study formed to protect the integrity of data; refer to Interim Analyses section [Section 10.3.8]) can conduct additional analyses of the safety data.

The Lilly CRP 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 in a blinded manner by Lilly during the clinical trial. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or a clinical AE is deemed serious, unexpected, and possibly related to IP, only Lilly Global Patient Safety will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

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

- regular monitoring of lipid levels
- potential MACE (cardiovascular death, 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), venous and arterial thrombotic events, and noncardiovascular deaths will be identified by the investigative site or through medical review and will be sent to a blinded Clinical Event Committee for adjudication at regular intervals.

9.4.9.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2X ULN (for patients with baseline <2x ULN), or elevated TBL ≥2X 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 and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the case report form (CRF) or other designated data transmission methods if 1 or more of the following conditions occur:

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

9.4.9.2. Venous Thromboembolic Event Assessment

If a patient develops the clinical features of a deep vein thrombosis or pulmonary embolism, appropriate local laboratory tests and imaging are recommended, as necessary, for diagnosis of the event. For confirmed cases, additional laboratory testing should be performed as outlined in Appendix 5. All suspected VTE events will be independently adjudicated by an external blinded Clinical Event Committee.

9.4.9.3. Growth Monitoring

Height and weight, left hand x-rays, knee x-rays, hormone levels, and occipital frontal circumference will be collected as described below and according to the Schedule of Activities (Section 2) to allow for the identification of potential effects on growth and development:

- Height measurements will be made using a stadiometer. Height measurements must be recorded to 1 decimal place without rounding.
- Weight measurements must be recorded to 1 decimal place without rounding.
- Instruments used for measuring height and weight should be appropriately and regularly calibrated.
- All measurements of height and weight should be made without shoes and after the removal of any heavy personal items (that is, large jewelry, wallets, coats, etc.).
- Height and weight changes in pediatric patients (both at an individual and group level) will be reviewed by the DMC external to Lilly.
- Left hand x-rays will be collected to assess effects on bone age.
    - Ongoing patients will have hand x-rays completed approximately every 6 months per the Schedule of Activities (Section 2) after approval of this protocol amendment and completion of the consent form. A central vendor will be used for reading of the x-ray images.
- Knee x-rays will be collected to monitor bone growth.

- An x-ray of the knee (anteroposterior) will be collected approximately every 6 months as shown in the Schedule of Activities (Section 2). A central vendor will be used for reading of the x-ray images.
- Ongoing patients will have a knee x-ray at the next scheduled visit after approval of this protocol amendment and completion of the consent form. Subsequent knee x-rays will be collected per the Schedule of Activities (Section 2), unless the subsequent visit is within 3 months of the first knee x-ray, in which case the knee x-ray can be skipped at this timepoint to avoid unnecessary radiation exposure.
- If a local addendum is in place that specifies another mode of imaging (e.g., magnetic resonance imaging [MRI] instead of x-ray), the local addendum should be followed. Otherwise, the current protocol amendment should be followed with regard to knee x-rays.

- Any symptomatic areas of bones/joints will be assessed and investigated as appropriate by study investigators. Any diagnoses made based on symptomatic areas of bones/joints or imaging data will be reported as appropriate (e.g., recorded on eCRF).
- Biomarkers that will be collected to provide information on bone health include: ALP and calcium (collected as part of the clinical chemistry panel).
- Insulin-like growth factor (IGF)-1, the principal mediator of growth hormone, and IGF-binding protein (IGF-BP)-3, the principal carrier protein for IGF-1, will be collected for the assessment of growth-related disorders.
- Gonadal hormones (estradiol for females or testosterone for males) will be collected for the assessment of pubertal development in patients 8 to <18 years of age.

9.5. Pharmacokinetics

9.5.1. Open-label PK Lead-in (Study Period 2)

Blood samples will be collected during the Open-label PK Lead-in period using a commercially available microsampling device (see Schedule of Activities in Section 2). These blood samples will be used to determine the concentrations of baricitinib using a validated bioanalytical method. The timing will be as follows:

- At Visit 2 (Week 0/Day 1), patients will take their first dose of IP in the clinic, and PK samples will be collected 15 minutes and 1 hour postdose.
- On Day 2 and thereafter: patients will take their IP once daily at home. Patients should be instructed to take their dose at approximately the same time each day.
- On Day 4, patients will take their IP at home, and PK samples will be collected at 2 hours and 4 hours postdose. If PK samples are not collected on Day 4, they may be collected on the following days up to and including the date of Visit 3 (Week 1).

- On Day 11, a PK sample will be collected BEFORE the IP is taken. Immediately after the PK sample is collected, the patient will take the IP, and PK samples will be collected at 30 minutes and 6 hours postdose. If PK samples are not collected on Day 11, they may be collected on the following days up to and including the date of Visit 4 (Week 2). All PK samples must be completed before the patient leaves the clinical site at Visit 4.

One patient in the older age group may be selected to provide 1 venous blood sample to assess concordance between venous blood samples and microsamples. During Study Period 2, the actual date and 24-hour clock time of the PK sample collection, and the date and time of the last 2 doses of IP will be recorded. For samples drawn on Day 4 and 11, the 2 previous doses should be the dose given on the day of the PK sample collection and the dose given the previous day.

9.5.2. Double-blind Treatment Period (Study Period 3)

A venous blood sample will be drawn at the times indicated in the Schedule of Activities (Section 2) (Weeks 0 [first dose, 2 samples], 4, 8, 12, and 16). These blood samples will be used to determine the plasma concentrations of baricitinib using a validated bioanalytical method. The timing will be as follows:

- At Visit 2 (Week 0), patients will take their IP in the clinic, and PK samples will be drawn 15 minutes and 1 hour postdose. NOTE: At Visit 2, all other laboratory samples (i.e., all non-PK samples) will be obtained prior to the first dose of IP in order to ensure accurate baseline data are collected.
- At Visit 5 (Week 4), patients will be asked to take their IP at home prior to visiting the clinic. The clinic visit should be scheduled so that the blood sample collected during this visit is drawn 2 to 4 hours after the dose is taken at home.
- For Visit 6 (Week 8) and Visit 7 (Week 12) patients will be asked to not take their IP before visiting the clinic, and a blood sample will be collected at any time predose on the day of the clinic visits. If the patient has taken the oral dose prior to the visit, the sample may be drawn anytime postdose, and the inability to collect a predose sample will not be considered a protocol violation.
- At Visit 8 (Week 16), patients will be asked to take their IP at home prior to visiting the clinic. The clinic visit should be scheduled so that the blood sample collected during this visit is drawn 4 to 6 hours after the oral dose is taken at home.
- For the ETV, a sample may be drawn anytime if the last dose of IP was taken within the last 48 hours.

For visits where PK samples will be collected, the actual date and 24-hour clock time of sample collection, and the date and time of the last 2 doses prior to the sample being drawn, should be recorded. At Visit 5 (Week 4) and Visit 8 (Week 16), these 2 doses should be the dose given the morning of the day of sample collection and the dose given the previous day. At Visit 6 (Week 8) and Visit 7 (Week 12), the 2 previous doses should be the dose taken yesterday and the dose taken the day before that.

This sampling schedule should be followed as closely as possible; however, failure to take PK samples at these specified times will not be considered a protocol violation. If the patient fails to follow the directions for a particular visit, the sample should still be collected at that visit, and the date and 24-hour clock time of sample collection and the date and time of the 2 doses prior to the sample being drawn should be recorded.

Only samples from patients receiving baricitinib will be assayed; samples from patients receiving placebo will not be assayed. Pharmacokinetic samples will be kept in storage at a laboratory facility designated by the Sponsor. Pharmacokinetic samples may also be assayed for additional exploratory analyses. Pharmacokinetic results will not be provided to investigative sites until the completion of the study or to the blinded study team until the study has been unblinded.

Bioanalytical samples collected to measure IP concentration will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Refer to Section 10.3.6.

9.6.1. Whole Blood Samples for Pharmacogenetic Research

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

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

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 at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits. 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.

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

9.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics [PD], mechanism of action, variability of patient response

(including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Blood samples for 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 at a facility selected by Lilly or its designee for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. 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.

9.8. Medical Resource Utilization and Health Economics

The EQ-5D-Y is being utilized in this study to collect data for input into economic models. See Section 9.1.4.11 for instrument description.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 25 patients will be enrolled into the Open-label PK Lead-in (Study Period 2) and may continue on open-label treatment during the long-term extension (Study Period 4). Data from patients participating in the PK lead-in will be analyzed separately from patients randomized into the Double-blind treatment (Study Period 3).

Study JAIP will aim to enroll at least 440 patients 2 to <18 years of age into the Double-blind Treatment period (Study Period 3), which includes at least 320 older pediatric patients (10 to <18 years) and at least 120 younger pediatric patients (2 to <10 years). The proposed sample size (N=440) will ensure a >95% power to detect any difference between the baricitinib high dose and placebo treatment groups or the baricitinib medium dose and placebo treatment groups, each using a 2-sided alpha of 0.05, assuming a 10% placebo, 25% medium dose, and 30% high dose response rate for the primary endpoint using a chi-squared test. The assumptions are based on what was observed in the Phase 2 study (JAHG). The proposed end point of IGA 0 or 1 represents patients whose AD is clear or almost clear from a baseline of moderate or severe disease. The anticipated effect size represents 3 times more patients achieving this benefit compared to placebo which, in discussion with therapeutic experts, is of a magnitude that is considered to be clinically relevant.

Furthermore, in older pediatric patients the sample size of 320 is sufficient to detect that the baricitinib high or medium dose is superior to placebo at least 80% of the time. Similarly, in the younger pediatric patients, the planned sample size of 120 patients has > 80% simulated power using the Bayesian approach described in Section 10.3.7.3 and in the Study JAIP SAP to detect any difference between the baricitinib high dose or medium dose and placebo treatment groups with a probability threshold of 0.95.

The primary analysis will be conducted using a logistic regression analysis with region, disease severity (IGA), age, treatment group, and treatment group-by-age interaction in the model. The p-value and 95% confidence interval (CI) for the odds ratio from the logistic regression model are used for primary statistical inference. The primary analysis will include data from the entire study population 2 to <18 years old, and a frequentist approach will be used for the analysis. However, in the event that the older subgroup of patients (10 to <18 years old) completes the Double-blind Treatment period (Study Period 3) more than 6 months earlier than anticipated for the younger subgroup of patients (2 to <10 years old), each age subgroup is adequately powered and can be individually unblinded and analyzed according to a pre-planned analysis approach as described in Section 10.3.8 below. This is to ensure that potential delay in completing the enrollment of the younger patients will not delay analysis and submission of the data from the older patients.

Sample size estimates were calculated using nQuery® Advisor 7.0 for the older subgroup of patients, and power estimates were obtained from R 3.5.0 and JAGS 4.2.0 for the younger subgroup of patients.

10.2. Populations for Analyses

Unless otherwise specified, the efficacy and health outcome analyses will be conducted on the intent-to-treat population, defined as all randomized patients, even if the patient does not receive the correct treatment or otherwise did not follow the protocol. Patients will be analyzed according to the treatment to which they were assigned. Significant protocol violations will be described in the SAP.

Safety analyses will be performed for all randomized patients who received at least 1 dose of IP and who did not discontinue from the study for the reason "Lost to Follow-up" at the first postbaseline visit.

Safety analyses for the Post-treatment Follow-up period will be conducted on the follow-up population, defined as all randomized patients who received at least 1 dose of IP and entered the Post-treatment Follow-up period. Patients will be analyzed according to the dosing regimen to which they were assigned in the Treatment Period.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

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 tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated (e.g., refer to Section 10.3.7.3). Treatment comparisons of discrete efficacy variables between baricitinib and placebo will be made using a logistic regression analysis with region, disease severity, age, treatment group, and treatment group-by-age interaction in the model. The percentages, difference in percentages, and 95% confidence interval (CI) of the difference in percentages will be reported. Treatment-by-age interaction will be added to the logistic regression model of the primary and key secondary variables as a sensitivity analysis. If this interaction is significant at a 2-sided 0.1 level, further inspection will be used to assess whether the interaction is quantitative (i.e., the treatment effect is consistent in direction but not size of effect) or qualitative (the treatment is beneficial for some but not all age groups). The p-value from the Fisher exact test will also be produced.

When evaluating continuous measures over time, a restricted maximum likelihood-based mixed-effects model of repeated measures (MMRM) will be used. The model will include treatment, age cohort, baseline severity, visit, and treatment-by-visit interaction, and treatment-by-age cohort interaction as fixed categorical effects and baseline score and baseline score-by-visit interaction as fixed continuous effects. Region may be included in the model if

applicable. An unstructured (co)variance structure will be used to model the between- and within-patient errors. If this analysis fails to converge, other structures will be tested. The Kenward–Roger method will be used to estimate the degrees of freedom. Type III sums of squares for the least squares means (LSMs) will be used for the statistical comparison; 95% CI will also be reported. Contrasts will be set up within the model to test treatment groups at specific time points of interest. Further details on the use of MMRM will be described in the SAP.

Treatment comparisons of continuous efficacy and health outcome variables may also be made using analysis of covariance (ANCOVA) with region, disease severity, treatment group, and baseline value in the model. Type III tests for LSM will be used for statistical comparison between treatment groups. The LSM difference, standard error, p-value, and 95% CI may also be reported. The method used to handle missing data will be specified in the SAP.

Fisher's exact test will be used for the AEs, discontinuation, and other categorical safety data for between-treatment group comparisons. Continuous vital signs, body weight, and other continuous safety variables including laboratory variables will be analyzed by an ANCOVA with treatment and baseline value in the model. Shift tables for categorical safety analyses (e.g., "high" or "low" laboratory results) will also be produced.

Missing data imputation:

1. Nonresponder imputation (NRI): All patients who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the NRI analysis for categorical variables such as IGA 0/1 or EASI 50/75/90 after discontinuation and onward. Patients who receive rescue therapy will be analyzed as nonresponders after rescue and onward. An additional analysis will be performed that includes all available data whether rescue medication was given or not.
2. Continuous variables such as EASI and SCORAD scores will be assumed to be missing after rescue or discontinuation and then an MMRM analysis will be performed. An additional analysis will be performed that includes all available data whether rescue medication was given or not.
3. Last observed carried forward (LOCF). An additional analysis will be performed that uses the last observed value on or prior to discontinuation or rescue therapy. This will then be analyzed using a logistic model for categorical variables or ANCOVA for continuous variables as described above.

Additional sensitivity analyses for the primary and key secondary endpoints such as a reference based multiple imputation method may be performed and will be specified in the SAP.

Adjustment for Multiple Comparisons:

Multiplicity controlled analyses will be performed on the primary and major secondary endpoints to control the overall family-wise Type I error rate at a 2-sided α level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2011) will be used. The graphical approach

is a closed testing procedure; hence it strongly controls the family-wise error rate across all endpoints (Alosh et al. 2014). Each dose of baricitinib will be tested separately using the graphical approach. Details of the specific graphical testing scheme (including testing for each dose of baricitinib and testing order, interrelationships, Type I error allocation, and the associated propagation) will be prespecified in the SAP.

The following is a list of primary and key secondary endpoints to be tested:

Primary:

- proportion of baricitinib-treated patients (at each dose) achieving IGA of 0 or 1 and ≥2-point improvement from baseline at Week 16.

Key Secondaries Evaluated for Each Baricitinib Dose (high, medium, and low):

- proportion of patients achieving EASI75 at 16 weeks
- proportion of patients achieving EASI90 at 16 weeks
- mean change from baseline in EASI score at 16 weeks
- proportion of patients achieving SCORAD75 at 16 weeks
- proportions of patients achieving a 4-point improvement in Itch NRS at 1 week, 2 weeks, 4 weeks, and 16 weeks

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

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

10.3.2.2. Patient Characteristics

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

10.3.2.3. Concomitant Therapy

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

10.3.2.4. Treatment Compliance

Treatment compliance will be evaluated at every clinic visit. 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 IP 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

10.3.3.1. Primary Analyses

The primary efficacy measure is the binary outcome of response defined as IGA score of 0 or 1 (clear or almost clear skin) and ≥2-point improvement from baseline at Week 16. The primary analysis will be conducted using a logistic regression analysis with region, disease severity (IGA), age, treatment group, and treatment group-by-age interaction in the model. Nonresponder imputation for missing data as described above will be used.

The primary analysis will include data from the entire study population 2 to <18 years old and will use a frequentist analysis approach. However, in the event that the older subgroup of patients (10 to <18 years old) completes the Double-blind Treatment period (Study Period 3) more than 6 months earlier than the anticipated completion for the younger subgroup of patients (2 to <10 years old), each age subgroup will be unblinded and analyzed separately according to a pre-planned analysis approach as described in Section 10.3.8 below. This is to ensure that potential delay in completing the enrollment of the younger patients will not delay analysis and submission of the data from the older patients.

Additional analysis of the primary efficacy outcome will include analyzing the outcome as observed, that is, whether or not rescue medication was used.

10.3.3.2. Secondary Analyses

The following secondary categorical outcomes will be analyzed in a similar manner as the primary, that is, using the same logistic regression model. Nonresponder imputation will be used for these analyses unless otherwise noted.

- EASI75 at Week 16 and 1 year. EASI75 is defined as having an improvement of at least 75% from baseline. Besides NRI, this outcome will also be analyzed using observed cases, that is, whether rescue medication was given or not.
- EASI90 at Week 16. EASI90 is defined as having an improvement of at least 90% from baseline.
- EASI50 at Week 16. EASI50 is defined as having an improvement of at least 50% from baseline.
- SCORAD75 at Week 16 and 1 year. SCORAD75 is defined as having an improvement of at least 75% from baseline.
- SCORAD90 at Week 16. SCORAD90 is defined as having an improvement of at least 90% from baseline.
- IGA score of 0 or 1 (clear or almost clear skin) and ≥2-point improvement from baseline at Week 4 and 1 year.

- IGA of 0 at 16 weeks.
- 4-point improvement in Itch NRS at 1 week, 2 weeks, 4 weeks, and 16 weeks.

The following continuous measures will be analyzed with the MMRM analysis described above unless otherwise noted. Contrasts within the MMRM analysis will be used to assess treatment differences for time points of interest as specified above in the list of objectives.

- Mean change from baseline in the following outcome measures:
    - ADSS Item 2
    - EASI score
    - SCORAD score
    - BSA
    - Itch NRS
    - Skin Pain NRS
    - POEM
    - PGI-S-AD
    - PROMIS-Depression
    - PROMIS-Anxiety
    - DFI
    - CDLQI and IDQOL total score
    - WPAI-AD-CG
    - EQ-5D-Y
    - PRISM

Baricitinib tablet or oral suspension product acceptability and palatability during the PK lead-in period will be summarized categorically (frequency and percentage) by age group, for each visit separately and in aggregate.

The EASI total score and SCORAD total score will also be analyzed as observed, that is, not assuming missing values after rescue medication is given.

The following categorical data will be analyzed using Fisher exact test described above unless otherwise noted.

- Patients requiring rescue with TCS
- Patients requiring rescue with systemic treatments
- School days missed

The following measures will be analyzed by an ANCOVA with treatment and baseline value in the model.

- Mean number of days without use of TCS over 16 weeks
- Mean gram quantity of TCS used over 16 weeks (tube weights)

10.3.3.3. Tertiary/Exploratory Analyses

- Proportion of patients achieving IGA of 0 or 1 with a ≥2-point improvement at 2, 3, 4, and 5 years during long-term extension
- Proportion of patients achieving EASI75 at 2, 3, 4, and 5 years during long-term extension
- Proportion of patients achieving SCORAD75 at 2, 3, 4, and 5 years during long-term extension
- Frequency of patient-reported "no itch" (Itch NRS score = 0) days from daily diaries from Week 12 to Week 16
- Time to achieve a 4-point improvement in Itch NRS
- Frequency of patient-reported "no pain" (Skin Pain NRS score = 0) days from daily diaries from Week 12 to Week 16
- Mean change from baseline in the score of Item 1 of the ADSS at 1 week and 16 weeks
- Mean change from baseline in the score of Item 3 of the ADSS at 1 week and 16 weeks
- Changes from baseline in IgE levels during the study
- Changes from baseline in eosinophil levels during the study
- Characterization of baricitinib pharmacokinetics in the AD population and exploration of relationships between baricitinib exposure and study endpoints
- Assessment of efficacy outcomes in patients who choose to take a voluntary drug interruption (drug holiday) during Study Period 4
- Number of patients able to maintain control of AD signs and symptoms without use of TCS

Details of the tertiary/exploratory analyses will be further described in the SAP.

10.3.4. Safety Analyses

All safety data will be descriptively summarized by treatment group and analyzed 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 and percentage of patients who experienced at least 1 TEAE will be summarized using MedDRA (Medical Dictionary for Regulatory Activities) for each Preferred Term within System Organ Class by treatment group. Serious adverse events and AEs that led to permanent discontinuation from the IP will also be summarized by treatment group. Special safety topics will be summarized and analyzed including the proportion and rate of patients developing skin infections requiring antibiotic treatment. Fisher's exact test will be used to perform comparisons between each baricitinib dose and the placebo group, where applicable.

Clinical laboratory results will be descriptively summarized by treatment group. Individual results that are outside of normal reference ranges will be flagged in data listings. Quantitative clinical laboratory variables obtained at baseline and postbaseline visits will be summarized along with change from baseline by treatment group. Change from baseline to endpoint will be analyzed using ANCOVA with treatment and baseline value in the model. Categorical variables, such as treatment-emergent laboratory abnormalities, will be summarized by frequency and percentage. Shift tables will be presented for selected laboratory measures.

Observed values and changes from baseline for vital signs and physical characteristics will be descriptively summarized by treatment group and time point. Change from baseline to postbaseline in vital signs, height, and body weight will be analyzed using ANCOVA with treatment and baseline value in the model. Treatment-emergent abnormalities in vital signs (pulse and blood pressure) and weight will be evaluated based on pediatric standards.

A summary of temporary interruptions of study drug will be provided, showing the number of patients experiencing at least one temporary interruption and the number of temporary interruptions. Duration of each temporary interruption and the cumulative duration of interruptions using descriptive statistics will be provided.

Analyses of Growth (height, weight, and body mass index [BMI]):

Observed height velocity by sex and age group will be calculated at baseline and approximately every 3 months thereafter throughout the study:

- (Current Height [cm] - Previous Height [cm])/Interval (months) between Measurements × 12

Age-specific z-scores for height velocity by sex and age group will be calculated for each patient with reference to standard height velocity tables (from age- and sex- matched peers) according to the following formula:

- (Observed Height Velocity [cm/y] - Mean Height Velocity for Age and Sex [cm/y])/(standard deviation of reference population)

Similar analyses for weight and BMI velocity and z-scores will be conducted.

Data collected after initiation of rescue therapy will be summarized or listed where applicable.

More details of the safety analysis for this study will be provided in the SAP.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Open-label PK Lead-in (Study Period 2): Serial PK sampling will be conducted to confirm that the high doses in pediatric age cohorts will produce comparable exposure to the 4-mg dose in adults. Comparability will be assessed using non-compartmental methods (e.g., AUC and C_{max}).

Double-blind Treatment (Study Period 3): All plasma baricitinib concentration–time data will be pooled and evaluated using population PK methods. A covariate screen of patient and study-specific factors will be included in the analyses based on factors investigated in previous

and (if any) ongoing PK analyses and on their relevance to the target population. Exploratory and/or model-based analyses examining the relationships between baricitinib exposure and efficacy and response endpoints will be conducted. Other analyses of efficacy and safety outcome measures may also be assessed as scientifically appropriate and warranted by available data. Details about the analyses to be conducted will be contained in the PK/PD analysis plan.

10.3.6. Evaluation of Immunological Measures

Patients who are immunized with TDaP or pneumococcal conjugate vaccines will have their IgG antibody titers to the antigens evaluated preimmunization and at 4 and 12 weeks postimmunization. A primary immune response will be assessed in patients who have never received TDaP or pneumococcal conjugate vaccines previously, and secondary/booster responses will be assessed if the patients have previously received the vaccines. More detailed analytical methods will be described in the SAP.

10.3.7. Other Analyses

10.3.7.1. Health Outcomes

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

10.3.7.2. Acceptability and Palatability

Responses from the tablet and suspension acceptability and palatability questionnaires will be summarized categorically (frequency and percentage) by age group, for each visit separately and in aggregate. In addition, general trends from baseline and Week 2 in acceptability and palatability will be analyzed.

10.3.7.3. Subgroup Analyses

To assess whether the treatment effect is similar across subgroups for the primary efficacy outcome, a logistic model will be used and will include treatment, stratification variables, the subgroup variable (e.g., age) and the subgroup by treatment interaction. If the interaction is statistically significant at α=0.10, the nature of the interaction will be explored, that is, within each subgroup the treatment effect will be estimated. Similarly, for the continuous variable of EASI, the MMRM analysis will include additional variables for subgroup and the subgroup by treatment interaction.

Subgroups to be evaluated will include baseline disease severity, sex, age (<10 years or ≥10 years), race, prior therapy (intolerance or inadequate response to TCS/TCNI), other atopic conditions (e.g., food allergies, asthma, allergic rhinitis/rhinoconjunctivitis). Further definitions for the levels of the subgroup variables, the analysis methodology, and any additional subgroup analyses will be defined in the SAP. Because this study is not powered for subgroup analyses, all subgroup analyses (with the exception of age cohorts, which are adequately powered) will be treated as exploratory.

In the subgroup of older pediatric patients (10 to <18 years old), a frequentist approach will be used.

Younger Pediatric Patients (2 to <10 years old)
In the subgroup of younger pediatric patients (2 to <10 years old), a hierarchical Bayesian analysis will be conducted using a logistic regression analysis as described above. This logistic regression will also include covariate adjustments for disease severity (IGA) and treatment group in the model. The posterior probability and 95% credible interval (CrI) for the difference in proportion from the logistic regression model are used for primary statistical inference. Details of the Bayesian approach are described in the SAP.

The analysis of the younger pediatric patients will leverage results observed in older pediatric patients through a Bayesian approach for the primary efficacy outcome at 16 weeks. In this approach, the posterior distribution of the treatment response of baricitinib high dose in older pediatric patients will be used in the construction of a proper prior distribution for baricitinib high dose in younger pediatric patients which will be further described in the study JAIP SAP. A similar approach will be used for the baricitinib medium and low doses in younger pediatric patients given that these doses are expected to provide exposures that are similar to their corresponding doses in older pediatric patients. The statistical approach taken for the young pediatric patients is therefore grounded in (1) making best possible use of prospective patients' data through efficient analysis procedures and (2) formally evaluating and modelling these data in light of the broader scientific context provided by existing information from older pediatric patients regarding patient outcomes on both the treatment and placebo regimens. This is consistent with the EMA's Reflection paper on the use of extrapolation in the development of medicines for pediatrics. Furthermore, the methodology assures robust conclusions about efficacy of the investigational medicine in younger patients while ensuring the feasibility of the trial.

Additionally, a consistency check will be conducted to determine whether the response for a specific treatment arm in the younger pediatric populations is within the 95% CI observed in older pediatric patients. The planned sample size is 120 patients with 1:1:1:1 randomization. The planned sample size has >80% simulated power to detect any difference between the baricitinib high dose and placebo treatment groups or the baricitinib medium dose and placebo treatment groups with probability of at least 0.95 and that the observed effect is consistent with the effect seen in older pediatric patients. This calculation relies on the assumption that leveraging information from older patients in Study JAIP is warranted. If the consistency check is not satisfied, no information from the older cohort will be used. In the event that the subgroup of younger pediatric patients has slow patient accrual, this will become the primary analysis for the younger patient subgroup.

10.3.8. Interim Analyses

No interim analyses are planned for this study. The analysis of Study Period 3 data is considered to be the primary analysis. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol. Additional analyses in order to support regulatory submission may be required after patients have completed the primary endpoint during Study Period 3, and these additional analyses will be specified in the SAP.

In the event that the older subgroup of patients (10 to <18 years old) completes the Double-blind Treatment period (Study Period 3) more than 6 months earlier than the anticipated completion date for the younger subgroup of patients (2 to <10 years old), each age subgroup is adequately powered and can be individually unblinded and analyzed according to a pre-planned analytical approach. In this pre-planned approach, the older subgroup of patients will be locked and analyzed (using a frequentist approach) after all patients in the subgroup have completed or discontinued from Study Period 3, and this analysis will be considered the primary analysis for the older subgroup. Subsequently, after all patients in the younger subgroup have completed or discontinued from Study Period 3, the data from the younger subgroup will be locked and analyzed (using a Bayesian approach), and this analysis will be considered the primary analysis for the younger age subgroup. The database lock and analysis of the data from the older subgroup of patients will not be considered an interim analysis and no alpha will be spent because the analysis of each age subgroup will be conducted independently and will be considered the primary analysis for the age group. In this situation, the combined analysis of the entire study population (2 to <18 years old) will be considered a secondary analysis. Further details of this pre-planned analytical approach will be included in the study JAIP SAP.

10.3.8.1. Data Monitoring Committee

A DMC will monitor the overall safety of this trial. The DMC will consist of members external to Lilly. This DMC will follow the rules defined in the DMC charter, focusing on potential and identified risks for this molecule and for this class of compounds. Data Monitoring Committee membership will include, at a minimum, specialists with expertise in pediatrics, statistics, and other appropriate specialties.

The DMC will be authorized to review unblinded results of analyses by treatment group prior to database lock, including study discontinuation data, AEs including SAEs, clinical laboratory data, vital sign and growth data, etc. The DMC may recommend continuation of the study as designed; temporary suspension of enrollment; or the discontinuation of a particular age cohort, dose regimen or the entire study. While the DMC may request to review efficacy data to investigate the benefit/risk relationship in the context of safety observations for ongoing patients in the study, no information regarding efficacy will be communicated. Moreover, the study will not be stopped for positive efficacy results nor will it be stopped for futility. Hence, no alpha is spent. Details of the DMC, including its operating characteristics, will be documented in a DMC charter and DMC analysis plan.

Besides DMC members, a limited number of pre-identified individuals may gain access to the limited unblinded data from Study Period 3, as specified in the unblinding plan, prior to the database lock for the primary analysis or final database lock to initiate the final population PK/PD model development processes or for preparation of regulatory documents, respectively. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has completed.

Unblinding details will be specified in a separate unblinding plan document.

10.3.8.2. Adjudication Committee

A blinded external Clinical Event Committee will adjudicate potential MACE (cardiovascular death, myocardial intervention [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), venous and arterial thrombotic events, and noncardiovascular deaths. Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the Charter.

10.3.8.3. Unblinded Study Team for Regulatory Submission

For the purpose of regulatory submission, a limited number of pre-identified individuals will have access to unblinded efficacy data when all the patients complete Week 16 assessments; hence, a portion of the long-term assessments may be unblinded prior to the final database lock. Only the blinded study team will communicate with sites on regular trial conduct issues, and study sites will not receive any efficacy and safety information on an individual patient level from this early analysis for regulatory submission.

Besides DMC members and the Unblinded Study Team for Regulatory Submission, a limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the final database lock for preparation of regulatory documents. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has completed.

Unblinding details will be specified in a separate unblinding plan document to ensure proper firewalls between the unblinded study team and the blinded study team and study sites.

11. References

Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med*. 2014;33(4):693-713.

Augustin M, Radtke MA, Glaeske G, Reich K, Christophers E, Schaefer I, Jacobi A. Epidemiology and Comorbidity in Children with Psoriasis and Atopic Eczema. *Dermatology*. 2015;231(1):35-40.

Barbier N, Paul C, Luger T, Allen R, De Prost Y, Papp K, Eichenfield LF, Cherill R, Hanifin J. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. *Br J Dermatol*. 2004;150(1):96-102.

Basra MK, Gada V, Ungaro S, Finlay AY, Salek SM. Infants' Dermatitis Quality of Life Index: a decade of experience of validation and clinical application. *Br J Dermatol.* 2013;169(4):760-768.

Beattie PE, Lewis-Jones MS. An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families: further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score. *Br J Dermatol*. 2006;155(6):1249-1255.

Blome C, Radtke MA, Eissing L, Augustin M. Quality of life in patients with atopic dermatitis: disease burden, measurement, and treatment benefit. *Am J Clin Dermatol*. 2016;17(2):163-169.

Ben-Gashir MA, Seed PT, Hay RJ. Quality of life and disease severity are correlated in children with atopic dermatitis. *Br J Dermatol*. 2004;150(2):284-290.

Bieber T. Atopic dermatitis. *N Engl J Med.* 2008;358(14):1483-1494.

Bieber T. Atopic dermatitis. *Ann Derm*. 2010;22(2):125-137.

Blauvelt A, Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, Simpson EL, Papp KA, Hong HC, Rubel D, Foley P, Prens E, Griffiths CEM, Etoh T, Pinto PH, Pujol RM, Szepietowski JC, Ettler K, Kemeny L, Zhu X, Akinlade B, Hultsch T, Mastey V, Gadkari A, Eckert L, Amin N, Graham NHM, Pirozzi G, Stahl N, Tancopoulos GD, Shumel B. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year,randomised, double-blinded, placebocontrolled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303.

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J.* 2011;53(6):894-913.

Broeders JA, Ahmed Ali U, Fischer G. Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience. *J Am Acad Dermatol*. 2016;75(2):410-419.e3.

Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients'

perspective [published correction appears in *Arch Dermatol*. 2005;141(3):381]. *Arch Dermatol.* 2004;140(12):1513-1519.

Chavarro JE, Watkins DJ, Afeiche MC, Zhang Z, Sánchez BN, Cantonwine D, Mercado-García A, Blank-Goldenberg C, Meeker JD, Téllez-Rojo MM, Peterson KE. Validity of self-assessed sexual maturation against physician assessments and hormone levels. *J Pediatr.* 2017;186:172-178.e3.

Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J Med Chem*. 2014;57(12):5023-5038.

Czarnowicki T, Esaki H, Gonzalez J, Malajian D, Shemer A, Noda S, Talasila S, Berry A, Gray J, Becker L, Estrada Y, Xu H, Zheng X, Suárez-Fariñas M, Krueger JG, Paller AS, Guttman-Yassky E. Early pediatric atopic dermatitis shows only a cutaneous lymphocyte antigen (CLA)1 TH2/TH1 cell imbalance, whereas adults acquire CLA1 TH22/TC22 cell subsets. *J Allergy Clin Immunol*. 2015;136(4):941-951.e3.

Davies E, Tuleu C. Medicines for children: a matter of taste. *J Pediatrics*. 2008;153(5):599-604, 604.e1-604.e2.

Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, de la Torre I, Gaich C, Rooney T, Schlichting D, de Bono S, Emery P. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95.

Divekar R, Kita H. Recent advances in epithelium-derived cytokines (IL-33, IL-25, and thymic stromal lymphopoietin) and allergic inflammation. *Curr Opin Allergy Clin Immunol*. 2015;15(1):98-103.

Dodington SR, Basra MK, Finlay AY, Salek MS. The Dermatitis Family Impact questionnaire: a review of its measurement properties and clinical application. *Br J Dermatol*. 2013;169(1):31-46.

Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, Bergman JN, Chamlin SL, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Feldman SR, Hanifin JM, Margolis DJ, Silverman RA, Simpson EL, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W, Sidbury R. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014a;71(1):116-132.

Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Silverman RA, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W, Sidbury R. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014b;70(2):338-351.

Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, Gurbuz S, Dickson C, de Bono S, Schlichting D, Beattie S, Kuo WL, Rooney T, Macias W, Takeuchi T. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol*. 2017;69(3):506-517.

Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, Covington MB, Thomas B, Collier P, Favata MF, Wen X, Shi J, McGee R, Haley PJ, Shepard S, Rodgers JD, Yeleswaram S, Hollis G, Newton RC, Metcalf B, Friedman SM, Vaddi K. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol*. 2010;184(9):5298-5307.

Futamura M, Leshem YA, Thomas KS, Nankervis H, Williams HC, Simpson EL. A systematic review of Investigator Global Assessment (IGA) in atopic dermatitis (AD) trials: Many options, no standards. *J Am Acad Dermatol*. 2016;74(2):288-294.

Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, Beattie SD, Koch AE, Cardillo TE, Rooney TP, Macias WL, de Bono S, Schlichting DE, Smolen JS. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243-1252.

Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, de la Peña A, Nunes FP, Janes J, Gamalo M, Donley D, Paik J, DeLozier AM, Nickoloff BJ, Simpson EL. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol*. 2018;80(4):913-921.e9.

Hanifin JM, Reed ML: Eczema Prevalence and Impact Working Group. A population-based survey of eczema prevalence in the United States. *Dermatitis*. 2007;18(2):82-91.

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10(1):11-18.

[ICH] International Conference on Harmonisation. Efficacy Guidelines. Available at: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. Published 2012. Accessed August 2018.

[IEC] International Eczema Council. Investigator Global Assessment Scale. Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) Scale. 2017. Available at: http://www.eczemacouncil.org/research/investigator-global-assessment-scale/. Published 2017. Accessed August 2018.

Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med*. 2011;365(14):1315-1327.

Kim H, Brooks KM, Tang CC, Wakim P, Blake M, Brooks SR, Montealegre Sanchez GA, de Jesus AA, Huang Y, Tsai WL, Gadina M, Prakash A, Janes JM, Zhang X, Macias WL, Kumar P, Goldbach-Mansky R. Pharmacokinetics, pharmacodynamics, and proposed dosing of the oral JAK1 and JAK2 inhibitor baricitinib in pediatric and young adult CANDLE and SAVI patients. *Clin Pharmacol Ther*. 2018;104(2):364-373.

Kimball AB, Naegeli AN, Edson-Heredia E, Lin CY, Gaich C, Nikai E, Yosipovitch G. Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2016;175(1):157-162.

Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. *Int J Pharm*. 2014;469(2):245-248.

Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics*. 2008;122(4):812-824.

Lan CC, Huang CC, Chen YT, Wang LF, Lin CT, Chen GS. Tacrolimus ointment for the treatment of atopic dermatitis: report of first clinical experience in Taiwan. *Kaohsiung J Med Sci*. 2003;19(6):296-304.

Langenbruch A, Radtke M, Franzke N, Ring J, Foelster-Holst R, Augustin M. Quality of health care of atopic eczema in Germany: results of the national health care study AtopicHealth. *J Eur Acad Dermatol Venereol*. 2014;28(6):719-726.

Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat*. 2015;26(1):23-31.

Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens RG. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. *Br J Dermatol*. 1998;138(1):107–113.

Leung DY. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol*. 2000;105(5):860–876.

Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. *Br J Dermatol.* 1995;132(6):942-949.

Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. *Br J Dermatol.* 2001;144(1):104-10.

Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Montealegre Sanchez GAM, Tenbrock K, Wittkowski H, Jones OY, Kuehn HS, Lee CR, DiMattia MA, Cowen EW, Gonzalez B, Palmer I, DiGiovanna JJ, Biancotto A, Kim H, Tsai WL, Trier AM, Huang Y, Stone DL, Hill S, Kim HJ, St. Hilaire C, Gurprasad S, Plass N, Chapelle D, Horkayne-Szakaly I, Foell D, Barysenka A, Candotti F, Holland SM, Hughes JD, Mehmet H, Issekutz AC, Raffeld M, McElwee J, Fontana JR, Minniti CP, Moir S, Kastner DL, Gadina M, Steven AC, Wingfield PT, Brooks SR, Rosenzweig SD, Fleisher TA, Deng Z, Boehm M, Paller AS, Goldbach-Mansky R. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med*. 2014;371(6):507-518.

Liu Y, Ramot Y, Torrelo A, Paller AS, Si N, Babay S, Kim PW, Sheikh A, Lee CC, Chen Y, Vera A, Zhang X, Goldbach-Mansky R, Zlotogorski A. Mutations in proteasome subunit β type 8 cause chronic atypical neutrophillic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum.* 2012;64(3):895-907.

Lubbe J, Friedlander SF, Cribier B, Morren MA, Garcia-Diez A, Gelmetti C, Hofmann H, Houwing RH, Kownacki S, Langley RG, Virtanen M, Wolff K, Wisseh S, McGeown C, Abrams B, Schneider D. Safety, efficacy, and dosage of 1% pimecrolimus cream for the treatment of atopic dermatitis in daily practice. *Am J Clin Dermatol*. 2006;7(2):121-131.

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44(235):291–303.

Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.* 1970;45(239):13–23.

McAleer MA Flohr C, Irvine AD. Management of difficult and severe eczema in childhood. *BMJ*. 2012;345:e4770.

Moniaga CS, Jeong SK, Egawa G, Nakajima S, Hara-Chikuma M, Jeon JE, Lee SH, Hibino T, Miyachi Y, Kabashima K. Protease activity enhances production of thymic stromal lymphopoietin and basophil accumulation in flaky tail mice. *Am J Pathol*. 2013;182(3):841-851.

Mostaghimi L. Prevalence of mood and sleep problems in chronic skin diseases: a pilot study. *Cutis*. 2008;81(5):398–402.

Naegeli AN, Flood E, Tucker J, Devlen J, Edson-Heredia E. The Worst Itch Numeric Rating Scale for patients with moderate to severe plaque psoriasis or psoriatic arthritis. *Int J Dermatol.* 2015;54(6):715-722.

[NICE] National Institute for Health and care Excellence. Atopic eczema in under 12s: diagnosis and management. Clinical guideline [CG57]. Section 1.2. Assessment of severity, psychological and psychosocial wellbeing and quality of life. 2007. Available at: https://www.nice.org.uk/guidance/CG57/chapter/1-Guidance. Accessed August 27, 2018.

Nomura T, Kabashima K. Advances in atopic dermatitis in 2015. *J Allergy Clin Immunol*. 2016;138(6):1548-1555.

Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, Chen S, Trier AM, Xu AZ, Tripathi SV, Luo J, Gao X, Yang L, Hamilton SL, Wang PL, Brestoff JR, Council ML, Brasington R, Schaffer A, Brombacher F, Hsieh CS, Gereau RW 4th, Miller MJ, Chen ZF, Hu H, Davidson S, Liu Q, Kim BS. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch. *Cell*. 2017;171(1):217-228.e13.

Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;51(3):329-337.

Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol*. 2007;157(4):645-648.

Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, Goudie DR, Sandilands A, Campbell LE, Smith FJ, O'Regan GM, Watson RM, Cecil JE, Bale SJ, Compton JG, DiGiovanna JJ, Fleckman P, Lewis-Jones S, Arseculeratne G, Sergeant A, Munro CS, El Houate B, McElreavey K, Halkjaer LB, Bisgaard H, Mukhopadhyay S, McLean WH. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38(4):441-446.

Papp KA, Menter MA, Raman M, Disch D, Schlichting DE, Gaich C, Macias W, Zhang X, Janes JM. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *Br J Dermatol*. 2016;174(6):1266-1276.

[PROMIS] Patient-Reported Outcomes Measurement Information System. Dynamic tools to measure health outcomes from the patient perspective. Anxiety. 2016. Available at:

http://www.healthmeasures.net/administrator/components/com_instruments/uploads/PROMIS%20Anxiety%20Scoring%20Manual%2009202016.pdf. Accessed August 29, 2018.

[PROMIS] Patient-Reported Outcomes Measurement Information System. Dynamic tools to measure health outcomes from the patient perspective. Depression. 2017. Available at: http://www.healthmeasures.net/administrator/components/com_instruments/uploads/PROMIS%20Depression%20Scoring%20Manual%2002222017.pdf. Accessed August 29, 2018.

Ravens-Sieberer U, Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, Egmar AC, Gusi N, Herdman M, Jelsma J, Kind P, Olivares PR, Scalone L, Greiner W. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. *Qual Life Res*. 2010;19(6):887-897.

Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. *Clinical Drug Investigations*. 1996;11(5):278-288.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353-365.

Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, Schalm S, Murias S, Dare JA, Brown D, Stone DL, Gao L, Klausmeier T, Foell D, Jesus AA, Chapelle DC, Kim H, Dill S, Colbert R, Failla L, Kost B, O'Brien M, Reynolds JC, Folio LR, Calvo KR, Paul SM, Weir N, Brofferio A, Soldatos A, Biancotto A, Cowen EW, Digiovanna JG, Gadina M, Lipton AJ, Hadigan C, Holland SM, Fontana J, Alawad AS, Brown RJ, Rother KI, Heller T, Brooks KM, Kumar P, Brooks SR, Waldman M, Singh HK, Nickeleit V, Silk M, Prakash A, Janes JM, Ozen S, Wakim PG, Brogan PA, Macias WL, Goldbach-Mansky R. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest*. 2018;128(7):3041-3052.

Schmitt J, Schmitt NM, Kirch W, Meurer M. Outpatient care and medical treatment of children and adults with atopic eczema. *J Dtsch Dermatol Ges.* 2009;7(4):345-351.

Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol*. 2011;131(1):67-73.

Siegfried EC, Jaworski JC, Eichenfield LF, Paller A, Hebert AA, Simpson EL, Altman E, Arena C, Blauvelt A, Block J, Boguniewicz M, Chen S, Cordoro K, Hanna D, Horii K, Hultsch T, Lee J, Leung DY, Lio P, Milner J, Omachi T, Schneider C, Schneider L, Sidbury R, Smith T, Sugarman J, Taha S, Tofte S, Tollefson M, Tom WL, West DP, Whitney L, Zane L. Developing drugs for treatment of atopic dermatitis in children (≥3 months to <18 years of age): Draft guidance for industry. *Pediatr Dermatol*. 2018 May;35(3):303-322.

Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis*. 2014;25(3):107-114.

Simpson EL. Comorbidity in atopic dermatitis. *Curr Dermatol Rep*. 2012;1(1):29-38.

Stalder J, Taïeb A. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186(1):23-31.

Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child*. 1997;76(2):159-162.

Tadicherla S, Ross K, Shenefelt PD, Fenske NA. Topical Corticosteroids in Dermatology. *J Drugs Dermatol*.append 2009;8(12):1093-1105.

Tan J, Langley R. Safety and efficacy of tacrolimus ointment 0.1 % (Protopic) in atopic dermatitis: a Canadian open-label multicenter study. *J Cutan Med Surg*. 2004;8(4):213-219.

Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr.* 1985;107(3):317-329.

Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, del Carmen Morales L, Gonzaga JR, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich CL, Rooney T, Schlichting D, Macias WL, de Bono S, Tanaka. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med.* 2017;376(7):652-662.

The EuroQol Group. EQ-5D-Y User Guide. Version 1.0. 2014. Available at: https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-Y_User_Guide_v1.0_2014.pdf. Published August 2014. Accessed August 29, 2018.

Tuttle KR, Brosius FC, Adler SG, Kretzler M, Mehta RL, Tumlin JA, Tanaka Y, Haneda M, Liu J, Silk ME, Cardillo TE, Duffin KL, Haas JV, Macias WL, Nunes FP, Janes JM**.** JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: Results from a phase 2 randomized controlled clinical trial. *Nephrol Dial Transplant.* 2018; [epub ahead of print: doi.org/10.1093/ndt/gfx377].

Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, Dörner T, Cardiel MH, Bruce IN, Gomez E, Carmack T, DeLozier AM, Janes JM, Linnik MD, de Bono S, Silk ME, Hoffman RW. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet*. 2018;392(10143):222-231.

Waters A, Sandhu D, Beattie P, Ezughah F, Lewis-Jones S. Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores. *Br J Dermatol.* 2010;163(suppl 1):121.

Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, Hoetzenecker W, Knol E, Simon HU, Wollenberg A, Bieber T, Lauener R, Schmid-Grendelmeier P, Traidl-Hoffmann C, Akdis CA. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2016a;138(2):336-349.

Werfel T, Heratizadeh A, Aberer W, Ahrens F, Augustin M, Biedermann T, Diepgen T, Fölster-Holst R, Gieler U, Kahle J, Kapp A, Nast A, Nemat K, Ott H, Przybilla B, Roecken M, Schlaeger M, Schmid-Grendelmeier P, Schmitt J, Schwennesen T, Staab D, Worm M. S2k guideline on diagnosis and treatment of atopic dermatitis – short version. *Allergo J Int.* 2016b;25:82-95.

[WHO] World Health Organization. Model Prescribing Information: Drugs used in skin diseases. 1997; Geneva.

Wilson SR, Thé L, Batia LM, Beattie K, Katibah GE, McClain SP, Pellegrino M, Estandian DM, Bautista DM. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell*. 2013;155(2):285-295.

Yokomaku A, Misao K, Omoto F, Yamagishi R Tanaka K, Takada K, Kohyama J. A study of the association between sleep habits and problematic behaviors in preschool children. *Chronobiol Int*. 2008;25(4):549-564.

Zhong J, Sharma J, Raju R, Palapetta SM, Prasad TS, Huang TC, Yoda A Tyner JW, van Bodegom D, Weinstock DM, Ziegler SF, Pandey A. TSLP signaling pathway map: a platform for analysis of TSLP-mediated signaling. *Database (Oxford)*. 2014:bau007.

Ziegler SF, Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H. The biology of thymic stromal lymphopoietin (TSLP). *Adv Pharmacol*. 2013;66:129-155.

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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration curve
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.
BMI	body mass index
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
C_{max}	maximum concentration
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
C-SSRS	Columbia Suicide Severity Rating Scale

CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DFI	Dermatitis Family Impact
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
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 outcome
EQ-5D-Y	European Quality of Life-5 Dimensions-Youth version
ERB	ethical review board
ETV	early termination visit
GCP	good clinical practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDQOL	Infant's Dermatitis Quality of Life Index

IEC	International Eczema Council
IGA	Investigator's Global Assessment
IGF-BP-3	Insulin-like Growth Factor Binding Protein-3
IL	interleukin
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.
IV	intravenous
IWRS	interactive web-response system
JAK	Janus kinase
LOCF	last observed carried forward
LSM	least squares mean
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMR	measles, mumps, and rubella
MMRM	mixed-effects model of repeated measures
MRI	magnetic resonance imaging
NEA	National Eczema Association
NRI	nonresponder imputation
NRS	Numeric Rating Scale
PBPK	Physiologically Based Pharmacokinetic
PD	pharmacodynamics
PDE-4 inhibitor	phosphodiesterase type 4 inhibitor
PeDRA	Pediatric Dermatology Research Alliance
PGI-S-AD	Patient Global Impression of Severity–Atopic Dermatitis

PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PPD	purified protein derivative
PRISM	Parent-Reported Itch Severity Measure
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
QD	once daily
QoL	quality of life
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SUSAR	suspected unexpected serious adverse reaction
t1/2	half life
TB	tuberculosis
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.
TSH	thyroid-stimulating hormone
TSLP	thymic stromal lymphopoietin
TYK2	tyrosine kinase 2
ULN	upper limit of normal
vIGA-AD	validated Investigator's Global Assessment for Atopic Dermatitis
VTE	venous thromboembolic event (deep vein thrombosis or pulmonary embolism)

VZV	varicella-zoster virus
WPAI-AD-CG	Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis Caregiver

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Absolute Reticulocyte Count	
Mean cell volume	Total bilirubin
Mean cell hemoglobin	
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
	Bone alkaline phosphatase[l]
Platelets	Alanine aminotransferase (ALT)
Absolute counts of:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Blood urea nitrogen (BUN)
Neutrophils, juvenile (bands)	Creatinine
	Cystatin C
Lymphocytes	Uric acid
Monocytes	Calcium
Eosinophils	Glucose
Basophils	Albumin
	Total protein
	Estimated glomerular filtration rate (eGFR)[e]
	Creatine phosphokinase (CPK)
	Gamma-glutamyl transferase (GGT)
Urinalysis[a,b,d]	
Color	**Other Tests**[a]
Specific gravity	Hepatitis B Surface antigen (HBsAg)[f]
pH	Anti-Hepatitis B Core antibody (HBcAb)[f]
Protein	HBV DNA[k]
Glucose	Anti-Hepatitis B Surface antibody (HBsAb)[f]
Ketones	Human immunodeficiency virus (HIV)[f]
Bilirubin	Hepatitis C antibody[f,g]
Urobilinogen	Thyroid-stimulating hormone (TSH)
Blood	Exploratory storage samples (serum, plasma and mRNA)
Leukocyte esterase	Pregnancy Test[h]
Nitrite	Gonadal hormone (estradiol for females, and testosterone for males[i]
	Serum immunoglobulin (IgG, and IgE)
	IGF-1 and IGFBP-3
Lipids[a,c]	QuantiFERON®-TB Gold or T-SPOT®.TB[j]
Total cholesterol	PPD (local testing)
Low-density lipoprotein	Baricitinib plasma levels
High-density lipoprotein	
Triglycerides	

Abbreviations: HBV = hepatitis B virus; IGFBP-3 = insulin-like growth factor binding protein-3; PPD = purified protein derivative; RBC = red blood cell; TB = tuberculosis; 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] Fasting lipid profile. Patients should not eat or drink anything except water for 4 to 12 hours (depending on age and weight as specified in Section 9.4.3) prior to test. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

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

[e] For patients <18 years old, eGFR calculated by Bedside Schwartz 2009 formula. For patients ≥18 years old, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine 2009 equation.

[f] Test required at Visit 1 only to determine eligibility of patient for the study.

[g] A positive hepatitis C antibody (Hep C antibody) result will be confirmed with an alternate hepatitis C method (HCV RNA).

[h] For all females of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a local urine pregnancy test will be performed at Visit 2 and at all subsequent study visits after Visit 3. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

[i] Gonadal hormones will be collected for patients aged 8 to <18 years.

[j] The QuantiFERON®-TB Gold test is the preferred alternative to the PPD test for the evaluation of TB infection. In countries where the QuantiFERON®-TB Gold test or T-SPOT® is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT® must be performed locally. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

[k] HBV DNA testing will be done in those patients who are HBcAb+ at screening.

[l] Collection of a sample for bone alkaline phosphatase may be requested by the Sponsor as a reflex test if the alkaline phosphatase result is high.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

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

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable as specified by ethics board(s).

Appendix 3.1.2. Recruitment

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

Appendix 3.1.3. Ethical Review

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

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

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

- the protocol and related amendments and addenda, current IB and updates during the course of the study
- informed consent form and Assent Form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable International Conference on Harmonisation (ICH) GCP Guidelines
- applicable laws and regulations

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

Appendix 3.1.5. Investigator Information

Physicians with experience in treating pediatric AD patients will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The clinical study report (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.

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 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 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 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 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 or ECG 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.

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

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I4V-MC-JAIP is described in Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, 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 cells; WBC = white blood cells.

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

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

Appendix 5. Monitoring Tests for Confirmed VTE

Selected tests may be obtained in the event of a confirmed venous thromboembolic event (VTE) and may be required in follow-up with patients in consultation with Eli Lilly and Company, its designee, or the 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; fXa = clotting factor Xa; MTHFR = methylene tetrahydrofolate reductase; PT = prothrombin time; PTT = partial thromboplastin time.

Appendix 6. Administration of Efficacy, Safety, Health Outcomes, and Quality of Life Measures

The PRO assessments collected via eCOA device are shown in the order that they will be presented to the patient/parent. PRO assessments collected via eCOA device at the site should be completed prior to any clinical assessments being performed on days when study visits occur. Patients who turn 18 years old during the study will continue to provide information for the assessments. The version of the assessment initiated at baseline will not change for a patient during the study even if the patient changes age during the study.

Assessment	Collection	Investigator or PRO	Patient Age at Visit 1 (unless otherwise noted)
SCORAD-VAS	eCOA: at site	PRO	8 to <18 years: patient-rated (with help from caregiver as needed) 2 to <8 years: parent/caregiver-rated with patient
POEM	eCOA: at site	PRO	8 to <18 years: Patient-rated (with help from caregiver as needed) 2 to <8 years: Parent/caregiver-rated with patient
CDLQI	eCOA: at site	PRO	8 to <18 years: Patient-rated (with help from caregiver as needed) 4 to <8 years: Parent/caregiver-rated with patient
IDQOL	eCOA: at site	PRO	2 to <4 years: parent/caregiver-rated
PROMIS-Anxiety (collected only in countries where translations are available)	eCOA: at site	PRO	8 to <18 years: patient-rated 5 to <8 years: parent/caregiver-rated as proxy
PROMIS-Depression (collected only in countries where translations are available)	eCOA: at site	PRO	8 to <18 years: patient-rated 5 to <8 years: parent/caregiver-rated as proxy
EQ-5D-Y	eCOA: at site	PRO	8 to <18 years: patient-rated 4 to <8 years: parent/caregiver-rated as proxy
DFI	eCOA: at site	PRO	2 to <18 years: Parent/caregiver-rated
WPAI-AD-CG	eCOA: at site	PRO	2 to <18 years: Parent/caregiver-rated
Palatability and Acceptability (only collected during Study Period 2, PK lead-in)	paper: at site	PRO	10 to <18 years: patient-rated (tablets) 2 to <10 years: parent/caregiver-rated (suspension)
vIGA-AD	paper: at site	Investigator	2 to <18 years

Assessment	Collection	Investigator or PRO	Patient Age at Visit 1 (unless otherwise noted)
EASI	eCOA: at site	Investigator	2 to <18 years
SCORAD	eCOA: at site	Investigator	2 to <18 years
C-SSRS Self-harm Supplement Form Self-harm Follow-up Form	paper: at site	Investigator	7 to <18 years (if patient turns 7 years old during the study, C-SSRS collection will begin after patient turns 7 years old)
PRISM	eCOA: daily diary	PRO	2 to <10 years: parent/caregiver-rated
Itch NRS	eCOA: daily diary	PRO	10 to <18 years: patient-rated
Skin Pain NRS	eCOA: daily diary	PRO	10 to <18 years: patient-rated
ADSS	eCOA: daily diary	PRO	10 to <18 years: patient-rated
PGI-S-AD	eCOA: daily diary	PRO	10 to <18 years: patient-rated
Emollient Reminder	eCOA: daily diary	PRO	2 to <18 years: reminder only
TCS Use	eCOA: daily diary	PRO	10 to <18 years: patient-rated 2 to <10 years: parent-caregiver-rated
Missed School Days	eCOA: daily diary	PRO	10 to <18 years: patient-rated 2 to <10 years: Parent/caregiver-rated

Abbreviations: ADSS = Atopic Dermatitis Sleep Scale; CDLQI = Children's Dermatology Life Quality Index; DFI = Dermatitis Family Impact; EASI = Eczema Area and Severity Index; eCOA = electronic clinical outcome assessment; EQ-5D-Y = European Quality of Life-5 Dimensions-Youth version; IDQOL = Infant's Dermatitis Quality of Life Index; NRS = Numeric Rating Scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; PK = pharmacokinetic; POEM = Patient Oriented Eczema Measure; PRISM = Parent-Reported Itch Severity Measure; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; SCORAD = SCORing Atopic Dermatitis; TCS = topical corticosteroids; VAS = visual analogue scale; vIGA-AD = validated Investigator's Global Assessment for Atopic Dermatitis; WPAI-AD-CG = Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis Caregiver.

Appendix 7. 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 9.4.9.1	Section 9.4.9.1	Section 8.1.1	Section 8.1.2
ALT/AST	≥2x ULN	ALT ≥3x ULN	ALT ≥5x ULN on ≥2 consecutive tests	>5x ULN	• >8x ULN • >5x ULN for >2 weeks • >3x ULN AND TBL >2x ULN or INR >1.5 • >3x ULN with symptoms[a]
ALP	≥2x ULN (unless allowed after discussion with Sponsor)	≥2x ULN (for patients with baseline <2x ULN)	≥2x ULN on ≥2 consecutive tests (for patients with baseline <2x ULN)	No applicable criteria	• >3x ULN (unless allowed after discussion with Sponsor) • >2.5x ULN AND TBL >2x ULN • >2.5x ULN with symptoms[a]
TBL	≥1.5x ULN (unless allowed after discussion with Sponsor)	≥2x ULN (for patients with baseline <1.5 ULN)	≥2x ULN (excluding Gilbert's syndrome)	No applicable criteria	• ALT or AST >3x ULN AND TBL >2x ULN • ALP >2.5x ULN AND TBL >2x 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 8. American Academy of Dermatology: Criteria for the Diagnosis and Assessment of Atopic Dermatitis

Features to be considered in diagnosis of patients with atopic dermatitis:

Essential Features—Must be present:

- pruritus
- eczema (acute, subacute, chronic)
    - typical morphology and age-specific patterns*
    - chronic or relapsing history

*Patterns include:

1)facial, neck, and extensor involvement in infants and children
2)current or previous flexural lesions in any age group
3)sparing of the groin and axillary regions

Important Features—Seen in most cases, adding support to the diagnosis:

- early age of onset
- atopy
    - personal and/or family history
    - Immunoglobulin E reactivity
- xerosis

Associated Features—These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
- keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- ocular/periorbital changes
- other regional findings (e.g., perioral changes/periauricular lesions)
- perifollicular accentuation/lichenification/prurigo lesions

Exclusionary Features—It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:

- scabies
- seborrheic dermatitis
- contact dermatitis (irritant or allergic)
- ichthyoses
- cutaneous T-cell lymphoma
- psoriasis
- photosensitivity dermatoses
- immune deficiency diseases
- erythroderma of other causes

Source: Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Silverman RA, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W, Sidbury R. Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014b;70(2):338-351.

Appendix 9. 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 acetate	Cream 1%
		Methylprednisolone acetate	Cream 0.25%
		Hydrocortisone	Lotion, cream, or ointment 2.5%

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

Appendix 10. Provisions for Changes in Study Conduct During Exceptional Circumstances

Exceptional circumstances, such as pandemics or natural disasters, may cause disruptions to the conduct of the study. Examples of such disruptions include limitations in the ability to conduct study procedures or ability to have on-site participant visits.

To mitigate the risk of participants missing visits, to allow participants to safely continue in the study, and to maintain the data integrity of the study in the case of an exceptional circumstance, **sites may implement changes to the conduct of the study on a case-by-case basis following sponsor's written approval and if permitted by local regulations. These provisions for changes in study conduct are temporary and will be repealed once the restrictions are lifted and the clinical site can comply with requirements of the protocol without the provisions described in this appendix.** Good clinical practice compliance and minimization of risks to study integrity are important considerations. Ensuring the safety of study participants is the prevailing consideration.

Additional written guidance will be provided by the sponsor in the event written approval is granted for changes in study conduct.

The following changes in study conduct captured in this appendix will not be considered protocol deviations. Missing data will be captured as protocol deviation(s).

1. Remote visit (telephone/telemedicine)

Telephone or technology-assisted virtual visits (telemedicine) to complete appropriate assessments are acceptable if in-person site visits are not possible. The study site should capture the visit location and method with a specific explanation for any data missing because of missed in-person site visits in source document and eCRF.

Examples of assessments that may be completed via telephone/telemedicine visit include the following:

- AEs and product complaints
- concomitant medications
- review study participant diary (including study drug compliance)
- C-SSRS (Since Last Visit Version), Self-Harm Supplement Form, and Self-Harm Follow-up Form (if applicable).

2. Mobile home health visit

Mobile visits may be performed as home visits (e.g., at participants' homes) if travel to the site is not possible due to exceptional circumstances. Mobile visits will be performed by a qualified home nursing service provider or trained site personnel, following sponsor written approval and if permitted by local regulations. Procedures performed may include, but are not limited to, collecting blood and urine samples, conducting physical assessments,

administering PROs, and collecting health information. Please note that requirements related to the reporting of SAEs remain unchanged. Every effort should be made for the participant to return to on-site visits as soon as reasonably possible, while ensuring the safety of the participant and investigational site staff.

Additional consent from the participant will be obtained for those who participate in home health services.

3. Investigational product and ancillary supplies (including participant diaries)

In cases when a patient is unable to come to the site to receive trial supplies during a normal on-site visit, the site should work with the sponsor to determine appropriate actions to receive trial supplies. This may include a participant coming to the site to receive trial supplies only from site staff without full completion of a visit, a participant-approved designee coming to the site to receive trial supplies on a participant's behalf, or delivery to a participant's home.

The following requirements must be met:

- sponsor approves the alternative method of delivery, taking local regulatory requirements into consideration
- participant consents verbally to alternate method of delivery
- site confirms the participant's receipt of the trial supplies
- site/sponsor confirms appropriate ethics review board notification
- alternate delivery of IP should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged.
- when delivering supplies to a participant's home,
    - participant consent must include provision of any personal information
    - site/sponsor should ensure oversight of the shipping process to ensure accountability and product quality (i.e., storage conditions and intact packaging upon receipt)
- additional instructions should be provided to the participant on how to return any unused or completed trial supplies.

4. Local laboratory option

In exceptional circumstances, to ensure patient safety and with the sponsor's prior written approval, local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with local regulations. Clinically significant laboratory findings must be recorded as an adverse event in the AE eCRF.

5. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at Visit 1 are valid for a maximum of 90 days. Therefore, the following rules will be applied for participants who are paused in an active, nonrandomized status due to exceptional circumstances:

- Paused for less than 90 days from Visit 1 to Visit 2: The participant will proceed to the next study visit per the Schedule of Activities in the protocol and Visit 2 (randomization visit) must be conducted within 90 days from Visit 1.
    - The site should proceed with the next visit if eligibility criteria are confirmed and document the reason for delay in the eCRF.
    - Due to the pause in screening, sites should also reconfirm each participant's consent and document in the source documentation.
- Paused for more than 90 days from Visit 1 to Visit 2: The participant must be discontinued from the study and rescreened. The screening procedures per the Schedule of Activities in the protocol should be followed (starting at Visit 1) to ensure participant eligibility by randomization visit (Visit 2). Before rescreening, the participant must sign a new ICF and receive a new identification number through IWRS. Patients who screen fail due to enrollment being paused for more than 90 days may rescreen within 4 weeks of the screen fail with specific guidance from the sponsor, and this will not be considered a protocol deviation.

6. Increasing visit window(s) for primary and secondary endpoint visits

- During Study Period 3 (post-randomization and up to but not including the primary endpoint [Visit 8]), visit windows may be extended up to a total of 28 days upon specific guidance from the sponsor.
- Participants should complete primary endpoint visit (Visit 8/Study Period 3) and the final study endpoint visit (Visit 27/Study Period 4) as per original schedule whenever possible and safe to do so, at the investigator's discretion. However, in order to maximize the ability for such on-site visits, minimize missing data, and preserve the intended conduct of the study, the visit windows may be brought forward no sooner than 14 days or extended up to 28 days, upon specific guidance from the sponsor.
- During the long-term extension (Study Period 4) and the Post-treatment follow-up (Visit 801/Study Period 5), visit windows may be extended up to 12 weeks upon specific guidance from the sponsor.
- Upon specific guidance from the sponsor, assessments (e.g., x-rays) may be collected at visits not designated on the Schedule of Activities if the scheduled procedures were missed at visits when the patient could not attend an on-site visit.
- For participants requiring the visit windows to be extended, additional study drug may need to be provided to avoid study drug interruption and maintain overall integrity of the trial. Additional consent from the participant per local regulations will be obtained for those participants who will be dispensed additional study drug during the study treatment periods.

7. Documentation

a. Changes to study conduct

Changes to study conduct will be documented as the following:

- Sites will need to identify and document the details of how all participants, visits methods, and activities conducted were affected by exceptional circumstances. All dispensing/shipment records of IP and relevant communications, including delegation, should be filed with site trial records.
- The site should document the participant's verbal consent for having remote visits and remote dispensing of IP, ancillaries and diaries, prior to implementation of these activities.
- Source document(s) that are generated at an off-site location (e.g., participant's home) should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

b. Missing data and other protocol deviations

The study site should capture specific explanation for any missing data and other protocol deviations in source documents and eCRF. While protocol deviations may be unavoidable in an exceptional circumstance, documentation of deviations and missing data will be important for data analysis and reporting.

Details of changes in analyses to specifically accommodate exceptional circumstances will be further described in the study SAP.

8. Informing ERBs

The sponsor and study investigators will notify ERBs as soon as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation.

Appendix 11. Additional Procedures for Countries Participating in the PK Lead-in Period (Study Period 2)

This appendix applies for countries participating in the PK lead-in period (Study Period 2) of Study JAIP. Additions are designated using underline. Deletions are designated using ~~strikethrough~~.

Additional venous blood samples for pharmacokinetic (PK) concordance testing (i.e., to assess concordance between PK micro blood samples and venous blood samples) have been included. In addition, clarification related to allowance for re-dispensing of open-label bottles of tablets during Study Period 2 has been included.

Section 9.5. Pharmacokinetics

Protocol Section 9.5.1. Open-label PK Lead-in (Study Period 2)

Blood samples will be collected during the Open-label PK Lead-in period using a commercially available microsampling device (see Schedule of Activities below). These blood samples will be used to determine the concentrations of baricitinib using a validated bioanalytical method. The timing will be as follows:

- At Visit 2 (Week 0/Day 1), patients will take their first dose of IP in the clinic, and PK samples will be collected 15 minutes and 1 hour postdose.
- On Day 2 and thereafter: patients will take their IP once daily at home. Patients should be instructed to take their dose at approximately the same time each day.
- On Day 4, patients will take their IP at home, and PK samples will be collected at 2 hours and 4 hours postdose. If PK samples are not collected on Day 4, they may be collected on the following days up to and including the date of Visit 3 (Week 1).
- On Day 11, a PK sample will be collected BEFORE the IP is taken. Immediately after the PK sample is collected, the patient will take the IP, and PK samples will be collected at 30 minutes and 6 hours postdose. If PK samples are not collected on Day 11, they may be collected on the following days up to and including the date of Visit 4 (Week 2). All PK samples must be completed before the patient leaves the clinical site at Visit 4.

~~One patient in the older age group may be selected to provide 1 venous blood sample to assess concordance between venous blood samples and microsamples.~~ At least 5 patients in the older age group will be selected to provide 2 venous blood samples to assess concordance between venous blood samples and microsamples. The venous blood samples for concordance testing will be collected at Visit 2 at the same time as the 1 hour microsample and at Visit 3 or 4 (on site) at the same time as one of the planned microsample collections. During Study Period 2, the actual date and 24-hour clock time of the PK sample collection, and the date and time of the last 2 doses of IP will be recorded. For samples drawn on Day 4 and 11, the 2 previous doses should be the dose given on the day of the PK sample collection and the dose given the previous day.

5. Schedule of Activities

Table JAIP.6. Schedule of Activities for Patients Participating in the Open-label PK Lead-in

	Screening	Open-label PK Lead-in				Long-term Extension Treatment											~~PTF/U~~
	Period 1	Period 2				Period 4											~~Period 5~~
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ ~~ET~~[a]**	~~801~~
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	~~28 ±4 after last dose~~
Procedures																	
IWRS	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	~~X~~
IP tablets dispensed (patients ≥10 years old) *The bottle dispensed at Visit 2 should be re-dispensed at Visit 3 and 4 (Study Period 2).		X	X*	X*		X	X	X	X	X	X	X	X	X	X		
IP suspension dispensed (patients <10 years old)		X				X		X	X	X	X	X	X	X	X		
Baricitinib plasma concentration (PK sample)[r]		X	X	X													

[r] PK samples will be collected as described in Section 9.5.1.

Appendix 12. EU-Specific Requirements

In this appendix, additions are designated using underline. Deletions are designated using ~~strikethrough~~.

12.1. CCI -Specific Requirements

This section provides the following additional information to investigators or their designees in the CCI

- Hormonal contraception can only be prescribed to female patients of childbearing potential aged 15 years and over. The investigator or his/her designee should alert the parents/caregivers of patients younger than 15 years of age of the possible adverse reactions to the fetus in case of pregnancy.
- Total sexual abstinence is included in the list of highly effective birth control methods.
- A QuantiFERON®-TB Gold test or the T-SPOT® TB test should be used for patients with known vaccination history with Bacillus Calmette–Guérin (BCG) vaccination. The PPD test will remain an option for patients who do not have vaccination history with BCG vaccine. This allows younger patients without a history of BCG vaccination to be enrolled where use of the QuantiFERON®-TB Gold test may exceed the blood volume restrictions.

Section 6.1. Inclusion Criteria

Patient Characteristics

[8] are male or nonpregnant, nonbreastfeeding female patients

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 the opposite sex.

Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 4 weeks following the last dose of IP. Periodic abstinence such as calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception.

Otherwise, patients and their partners of childbearing potential must agree to use 2 effective methods of contraception, where at least 1 form is highly effective for the entirety of the study and for at least 4 weeks following the last dose of IP.

In the [redacted] hormonal contraception may be required (i.e., prescribed) only for female patients of childbearing potential aged 15 years and over. The investigator or his/her designee should alert the parents/caregivers of patients younger than 15 years of age of the possible adverse reactions to the fetus in case of pregnancy.

The following contraception methods are considered acceptable (the patient and their partner should choose 2, and 1 must be highly effective [defined as less than 1% failure rate per year when used consistently and correctly]):

- Highly effective birth control methods:
  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, intravaginal or implantable
  - Intrauterine device (IUD)/intrauterine hormone-releasing system (IUS)
  - Vasectomized partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
  - Total sexual abstinence (as defined above)
- Effective birth control methods:
  - Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
  - Diaphragm with spermicide
  - Cervical sponge
  - Cervical cap with spermicide
  - Oral contraceptives that do not inhibit ovulation

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

Adolescent females who have started menses (even one cycle and any amount of spotting) are considered to be of childbearing potential.

Females of nonchildbearing potential are not required to use birth control and they are defined as:

- Females who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis, or have not started menses (and are not sexually active)

Section 6.2. Exclusion Criteria

Diagnostic Assessments

[37] Patients with evidence of active TB or latent TB based on medical history and clinical features are excluded. In addition, if the following criteria are met, the patient will be excluded:

- positive PPD test (i.e., ≥5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), and/or
  - **NOTE:** The PPD test should only be used in patients where blood volume restrictions do not allow for the use of the QuantiFERON®-TB Gold test or T-SPOT® TB test AND the patient does not have a history of BCG vaccination.
- QuantiFERON®-TB Gold test or T-SPOT® TB test (as available and if compliant with local TB guidelines) ~~may~~ should be used instead of the PPD test unless blood volume restrictions do not allow for the use of the QuantiFERON®-TB Gold test or T-SPOT® TB test AND the patient does not have a history of BCG vaccination. If the test results are positive, the patient will be excluded. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be excluded.

Section 9.4.7. Tuberculosis Testing

Patients will be tested at screening (Visit 1) for evidence of active or latent TB as described in the exclusion criteria. Investigators should follow local guidelines for monitoring.

The purified protein derivative (PPD) test will remain an option for patients who do not have vaccination history with BCG vaccine. The rationale for allowing the PPD test is primarily for younger children where use of the QuantiFERON®-TB Gold test may exceed the blood volume restrictions, so in younger patients without a history of BCG vaccination, the PPD test would be acceptable.

Section 2. Schedule of Activities

Table JAIP.7. Schedule of Activities for Patients Participating in the Open-label PK Lead-in

	Screening	Open-label PK Lead-in				Long-term Extension Treatment											PTF/U
	Period 1	Period 2				Period 4											Period 5
Visit number	**1**	**2**	**3**	**4**	**Patient Transitions Directly to Visit 9 (Period 4)**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19/ ET[a]**	**801**
Weeks from initiation of baricitinib treatment		**0**	**1**	**2**		**4**	**12**	**16**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	
Visit tolerance interval (days)	-8 to -35		±2	±2		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ±4 after last dose
Procedures																	
TB test[d] QuantiFERON®-TB Gold test or T-SPOT® TB test are preferred	X																
Read PPD if applicable (48–72 hours post PPD)[e] PPD test may be used only for patients without BCG vaccination AND for whom blood volume restrictions apply.	X																

d TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally.

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

Table JAIP.8. Schedule of Activities for Patients Randomized to Double-blind Treatment in Study Period 3

	Screening	Double-blinded Treatment							Long-term Extension Treatment											~~PTF/U~~
	Period 1	Period 3							Period 4											~~Period 5~~
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19~~/ ET~~[a]**	**~~801~~**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**	
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	~~28 ±4 after last dose~~
Procedures																				
TB test[d] QuantiFERON®-TB Gold test or T-SPOT® TB test are preferred	X																			
Read PPD if applicable (48–72 hours post PPD)[e] PPD test may be used only for patients without BCG vaccination AND for whom blood volume restrictions apply.	X																			

d TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally.

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

12.2. CCI Specific Requirements

This section includes regularly scheduled pregnancy tests for female patients in CCI and to clarify the reassessment of benefit-risk for patients to remain in the trial after Week 16.

Section 2. Schedule of Activities

The following modification has been made to Section 2; see Footnote n.

Table JAIP.2. Schedule of Activities for Patients Randomized to Double-Blind Treatment in Study Period 3

…

	Screening	Double-blinded Treatment							Long-term Extension Treatment										
	Period 1	Period 3							Period 4										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Laboratory Assessments																			
Serum Pregnancy[n]	X																		

…

[n] Pregnancy tests prior to first dose of investigational product for females ≥10 years old of age (<10 years at investigator discretion) if menarche reached or if there is reason to believe the patient is sexually active. Pregnancy test results from Visit 2 must be known prior to first dose of investigational product. A serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and at all subsequent study visits after Visit 3. When the interval between scheduled visits exceeds 4 weeks, patients will undergo urine pregnancy self-testing at home approximately every 4 weeks (testing kits to be provided). During these intervisit periods, the site will call the patient approximately every 4 weeks to obtain her pregnancy test results. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

Section 5.1.4. ***Period 4: Long-Term Extension Treatment Period***

…

All Patients:

…

The benefit/risk profile will be reassessed throughout the study and patients may be discontinued at any time. In particular, during the long-term extension period, the investigators should continue to assess the benefit/risk profile of patients to remain in the trial after Week 16. For a patient having safety and tolerability issues, or one who is not achieving adequate treatment response, investigators should use clinical judgment on whether to continue or discontinue patient participation in the study.

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Absolute Reticulocyte Count	
Mean cell volume	Total bilirubin
Mean cell hemoglobin	
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
	Bone alkaline phosphatase[l]
Platelets	Alanine aminotransferase (ALT)
Absolute counts of:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Blood urea nitrogen (BUN)
Neutrophils, juvenile (bands)	Creatinine
	Cystatin C
Lymphocytes	Uric acid
Monocytes	Calcium
Eosinophils	Glucose
Basophils	Albumin
	Total protein
	Estimated glomerular filtration rate (eGFR)[e]
	Creatine phosphokinase (CPK)
	Gamma-glutamyl transferase (GGT)
Urinalysis[a,b,d]	
Color	**Other Tests**[a]
Specific gravity	Hepatitis B Surface antigen (HBsAg)[f]
pH	Anti-Hepatitis B Core antibody (HBcAb)[f]
Protein	HBV DNA[k]
Glucose	Anti-Hepatitis B Surface antibody (HBsAb)[f]
Ketones	Human immunodeficiency virus (HIV)[f]
Bilirubin	Hepatitis C antibody[f,g]
Urobilinogen	Thyroid-stimulating hormone (TSH)
Blood	Exploratory storage samples (serum, plasma and mRNA)
Leukocyte esterase	Pregnancy Test[h]
Nitrite	Gonadal hormone (estradiol for females, and testosterone for males[i]
	Serum immunoglobulin (IgG, and IgE)
	IGF-1 and IGFBP-3
Lipids[a,c]	QuantiFERON®-TB Gold or T-SPOT®.TB[j]
Total cholesterol	PPD (local testing)
Low-density lipoprotein	Baricitinib plasma levels
High-density lipoprotein	
Triglycerides	

Abbreviations: HBV = hepatitis B virus; IGFBP-3 = insulin-like growth factor binding protein-3; PPD = purified protein derivative; RBC = red blood cell; TB = tuberculosis; 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] Fasting lipid profile. Patients should not eat or drink anything except water for 4 to 12 hours (depending on age and weight as specified in Section 9.4.3) prior to test. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

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

[e] eGFR calculated by Bedside Schwartz 2009 formula.

[f] Test required at Visit 1 only to determine eligibility of patient for the study.

[g] A positive hepatitis C antibody (Hep C antibody) result will be confirmed with an alternate hepatitis C method (HCV RNA).

[h] For all females of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a local urine pregnancy test will be performed at Visit 2 and at all subsequent study visits after Visit 3. When the interval between scheduled visits exceeds 4 weeks, patients will undergo urine pregnancy self-testing at home approximately every 4 weeks (testing kits to be provided). During these intervisit periods, the site will call the patient approximately every 4 weeks to obtain her pregnancy test results. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

[i] Gonadal hormones will be collected for patients aged 8 to <18 years.

[j] The QuantiFERON®-TB Gold test is the preferred alternative to the PPD test for the evaluation of TB infection. In countries where the QuantiFERON®-TB Gold test or T-SPOT® is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT® must be performed locally. If the QuantiFERON®-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

[k] HBV DNA testing will be done in those patients who are HBcAb+ at screening.

[l] Collection of a sample for bone alkaline phosphatase may be requested by the Sponsor as a reflex test if the alkaline phosphatase result is high.

12.3. CCI Specific Requirements

This section provides the following additional information to investigators or their designees in CCI :

- Additional details on the strategies implemented to minimize patient pain and distress as much as possible.
- Complete physical examinations to be conducted at additional time points.
- Electrocardiograms to be conducted at additional time points.
- Additional description of the Investigator's Global Assessment (IGA) scale and investigator qualifications.
- Additional requirements related to x-ray collection based on the feedback from the Bundesamt für Strahlenschutz (BfS) or CCI Federal Office for Radiation Protection.
- Incorporated additional imaging requirements related to monitoring bone/cartilage growth based on the request from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) or Federal Institute for Drugs and Medical Devices.
- Incorporated the addition of measurement of tibial length based on request from BfArM.
- Incorporated option for knee x-ray if magnetic resonance imaging (MRI) of the knee is not possible.
- Schedule of Activities was updated to be consistent with the treatment period in amendment b of the main protocol, JAIP. For clarity, text has been updated to make MRI collection consistent with x-ray collection by stopping when skeletal maturity has been confirmed by the investigator.

Section 2. Schedule of Activities

Table JAIP.1. Schedule of Activities for Patients Randomized to Double-blind Treatment in Study Period 3

	Screening	Double-blinded Treatment							Long-term Extension Treatment										
	Period 1	Period 3							Period 4										
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Weeks from randomization		**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**40**	**52**	**64**	**76**	**88**	**100**	**112**	**124**
Visit tolerance interval (days)	-8 to -35		±2	±2	±2	±4	±4	±4	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Physical examination[u]	X							X			X	X	X	X	X	X	X	X	X
12-lead ECG (single)	X							X				X			X		X		X
Left hand x-ray[l]		X						X					X		X		X		X
Tibial length measurement		X						X			X	X	X	X	X	X	X	X	X
MRI of the knee (or x-ray of the knee if MRI is not possible)[l, t]		X								X			X		X		X		X

	Long-term Extension Treatment												PTF/U
	Period 4 – Extended (Patients Randomized to Double-Blind Treatment at Visit 2)												Period 5
Visit number	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27[s]**	**28[s]**	**29[s]**	**30[s]**	**31[s]/ET[a]**	**801**
Weeks from randomization	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**	**256**	**268**	
Visit tolerance interval (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	28 ±4 after last dose
Physical examination[u]	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG (single)		X		X		X		X		X		X	
Left hand x-ray[l]		X		X		X		X		X		X	
Tibial length measurement	X	X	X	X	X	X	X	X	X	X	X	X	
MRI of the knee (or x-ray of the knee if MRI is not possible)[l, t]		X		X		X		X		X		X	

Abbreviations: ECG = electrocardiogram; ET = early termination; IP = investigational product; MRI = magnetic resonance imaging; PTF/U = post treatment follow up

a An early termination visit should be conducted if patient discontinues from the study before Visit 27. Visit 801 is the post-treatment follow-up visit, which occurs after the patient has been off 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 27/ET; Visit 801 (follow-up visit) is not required.

l Left hand and knee x-rays or knee MRI at an early termination visit ~~is~~ are not required if previously taken within 6 months of the early termination visit. For patients with radiologically proven completed skeletal maturity, left hand x-rays and knee x-rays or MRI are not required (see Section 9.4.9.3 below).

t X-ray of the knee may be completed instead of MRI of the knee if MRI is not possible (see Section 9.4.9.3 below).

u Symptomatic findings on bones and joints must be followed up appropriately by investigators.

Section 9. Study Assessments and Procedures

Investigators will provide age-appropriate explanations to all children prior to any assessment or procedure. Investigators should assess and monitor physical pain and distress at each visit.

Section 9.1.1. Primary Efficacy Assessments

Detailed description of the vIGA

The IGA scale is proposed as primary endpoint in this program and measures the clinician's impression of overall disease severity at a single time point. In contrast to EASI and SCORAD, which are based on numerical scoring, IGA is intended to provide a snapshot of disease severity easily understandable by physicians and patients (e.g., ranging from clear skin to severe disease). The IGA is a commonly used scale in clinical trials in adult and pediatric patients. The vIGA has been provided to other pharmaceutical industry sponsors and investigators at no cost with quick adoption by other sponsor companies in Phase 1, 2, and 3 clinical trials, broadening the use of the scale across clinical sites.

The IGA used in this study is the vIGA-AD (referred to as the IGA throughout the protocol). For the purposes of this study, AD severity will be defined using the IGA. The IGA scale with descriptors is shown below.

Investigator's Global Assessment (IGA) Scale

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.

Investigator Qualifications

Investigators will be required to be certified to complete vIGA training for the JAIP study. The certification process includes reviewing a video that describes the scale and provides guidance on how to rate patients and will use images of AD patients' affected skin. After reviewing the video, the PI must complete a certification examination including rating of 20 photographs of AD patients' skin with descriptions of the area affected. The investigators must pass the examination with a score of 70% or greater to receive certification as a vIGA rater for Study JAIP. Investigators must be recertified approximately every 2 years.

Section 9.4.3. Laboratory Tests

To minimize pain, distress, and fear, investigators will be trained and experienced in clinical research with children. Sampling will only be performed by trained staff as described below. Lilly will provide training to sites on blood sample volumes, in keeping with local procedures and standards of care.

Blood sampling should be consolidated whenever possible. With the exception of Visit 2 (baseline), where 3 venipunctures will be needed (predose chemistry/hematology, and PK samples at 15 minutes and 1-hour postdose), it is anticipated that only 1 venipuncture will be required per visit in order to collect required blood tests. The timing of sampling and number of sampling attempts should be minimized, in keeping with local guidelines and procedures. For example, it is recommended that after one unsuccessful attempt, another experienced person should take over the procedure.

Section 9.4.9.3. Growth Monitoring

- Left hand x-rays will be collected to assess effects on bone age.
    - Left hand x-rays will be collected at the time points shown in the SOA above. An appropriate physician at the clinical site will read the x-ray image, and if it is determined that the patient does not have growth potential (that is, the patient has completed skeletal maturity), then no further left hand x-rays will be required. That is, as soon as a left hand x-ray for a study patient shows mature skeletal findings, no further left hand x-rays are required for the patient for the remainder of the patient's participation in the study. The clinical sites will document the decision that a patient has reached skeletal maturity.
- Magnetic resonance imaging (MRI) of the knee will be collected to monitor bone/cartilage growth.
    - MRI of the knee will be collected approximately every 6 months as shown in the SoA above. A central vendor will be used for reading of MRI images. An appropriate physician at the clinical site will read the MRI image, and if it is determined that the patient does not have growth potential (that is, the patient has completed skeletal maturity), then no further knee MRI will be required. The clinical sites will document the decision that a patient has reached skeletal maturity.
    - An x-ray of the knee (anteroposterior) may be collected in place of the MRI in cases where MRI is not possible (e.g., site does not have MRI access; sedation is required; MRI is not medically advisable in the opinion of the investigator; or parents/patients do not consent). The clinical site will document the rationale for collecting x-rays versus MRIs. An appropriate physician at the clinical site will read the x-ray image, and if it is determined that the patient does not have growth potential (that is, the patient has completed skeletal maturity), then no further knee x-rays will be required. The clinical sites will document the decision that a patient has reached skeletal maturity.
- Tibial length measurement will be collected as an additional assessment of growth.

- Tibial length will be measured approximately every 3 months as shown in the SOA above. Guidance on measuring tibial length will be provided by the Sponsor.

Appendix 13. Guidance for Blood Sampling When Volume Restrictions May Apply

This appendix applies for all countries participating in Study JAIP and is anticipated to be applicable for patients 2 to <8 years old and particularly for patients 10 to <20 kg in body weight; however, it may be used for older patients if local regulations require restrictions on blood volumes.

Due to blood volume restrictions, some laboratory samples may not be collected (for example, exploratory storage samples and genetic and biomarker samples). Laboratory samples should be collected as described in a sponsor-provided weight-based prioritization chart.

Additional allowances to accommodate blood volume restrictions may include, but are not limited to the following:

- Blood draws for Visit 1 and Visit 2 may be divided over 2 days if the 24-hour blood volume limit is exceeded.
- The pharmacogenetics (DNA) sample may be collected after Visit 1 at the earliest visit where blood volumes allow.
- HBV DNA will be collected as a reflex test prior to Visit 2 and is only required for patients who are positive for hepatitis B core antibody (HBcAb).
- HCV RNA will be collected as a reflex test prior to Visit 2 and is only required for patients who are positive for HCV antibody.

Appendix 14. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [b]: (06-Aug-2020)

Overall Rationale for the Amendment

Protocol I4V-MC-JAIP - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Outpatient Study Evaluating the Pharmacokinetics, Efficacy, and Safety of Baricitinib in Pediatric Patients with Moderate-to-Severe Atopic Dermatitis- has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table. Editorial revisions with no impact on protocol design or implementation were also made. These revisions are not noted in this protocol amendment summary except where contained in a section with substantive changes.

There are 3 main changes incorporated into this protocol amendment:

- Addition of knee imaging and increased frequency of hand x-ray requirements related to monitoring bone growth and clarification of assessment of any symptomatic areas of bones/joints were included based on regulatory feedback. In addition, baseline assessment of sexual maturation was included based on regulatory feedback.
- Extension of the duration of treatment for all patients.
- Guidance for study implementation under exceptional circumstances, such as pandemics or natural disasters.

Amendment Summary for Protocol I4V-MC-JAIP Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis Section 2 Schedule of Activities Section 3.3 Benefit/Risk Assessment Section 4 Objectives and Endpoints Section 5.1 Overall Design Section 8.2 Discontinuation from the Study Section 10.3.3.2 Secondary Analyses Section 10.3.3.3 Tertiary/Exploratory Analyses	Increased the treatment period from 2 to 4 years, additional exploratory objectives were included for timepoints in the extended treatment period, and relevant updates were included to describe possible termination of the study in a specific geography after commercial availability or negative regulatory opinion.	Based on data from completed adult Phase 3 studies and initial data from Study JAIP which support risk/benefit in pediatric patients, the treatment period was increased from 2 to 4 years. Secondary and tertiary/expoloratory IGA and EASI objectives were aligned with this change. This extension of treatment will allow for continued efficacy and safety data collection and will allow patients to continue to receive baricitinib treatment for up to an additional 2 years until baricitinib

Section # and Name	Description of Change	Brief Rationale
		is commercially available for this population or not approved. Clarification was added related to termination of the study in a specific geography after commercial availability of baricitinib in that geography or after negative regulatory opinion.
Section 2 Schedule of Activities Section 9.4.3 Laboratory Tests Appendix 10	Added provisional language for participation in the study during exceptional circumstances such as the Coronavirus disease 2019 (COVID-19) pandemic. Included provision for home visits to collect laboratory tests.	Appendix 10 describes the types of changes to study conduct that will be possible during exceptional circumstances. These changes to study conduct will only be implemented with approval from the sponsor and if permitted by local regulations. Provision was made for home visits for patient convenience specifically to collect laboratory tests during the study if approved by the sponsor and if permitted by local regulations.
Section 2 Schedule of Activities Section 9.4.4.1 Tanner Staging Scale Section 9.4.9.3 Growth Monitoring	Addition of knee imaging approximately every 6 months. Increased frequency of hand x-ray to approximately every 6 months. Added baseline Tanner Staging Scale.	Imaging procedures were included or increased in frequency based on feedback from regulatory agencies for additional monitoring of bone growth and assessment of symptomatic areas of bones/joints. Baseline assessment of sexual maturity (Tanner Staging) was included based on feedback from regulatory agencies.
Section 11 References	Addition of references for Tanner Staging	References to support addition of Tanner Staging were included.

Signature Page for VV-CLIN-074361 v1.0

Approval	PPD PPD 14-Feb-2023 12:52:37 GMT+0000

Approval	PPD PPD 14-Feb-2023 16:08:51 GMT+0000

Signature Page for VV-CLIN-074361 v1.0