

Protocol (e) I4V-MC-JAIN

A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Safety and Efficacy of Baricitinib in Combination with Topical Corticosteroids in Adult Patients with Moderate-to-Severe atopic Dermatitis Who Have Experienced Failure to Cyclosporine or Are Intolerant to, or Have Contradiction to Cyclosporine

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Who Have Experienced Failure to Cyclosporine or Are
Intolerant to, or Have Contraindication to, Cyclosporine**

BREEZE-AD4

EUDRA CTA 2017-004574-34

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Baricitinib (LY3009104)

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1. Synopsis

Title of Study:

A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Safety and Efficacy of Baricitinib in Combination with Topical Corticosteroids in Patients with Moderate-to-Severe Atopic Dermatitis Who Have Experienced Failure to Cyclosporine or are Intolerant to, or have Contraindication to, Cyclosporine.

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). Presentation is varied, but includes skin manifestations and pruritus, with associated sleep disturbances and subsequent skin infections. The course of disease includes relapses of varying duration and severity.

Mild AD can be controlled by appropriate skin care and topical treatments; moderate and severe AD usually require additional treatments such as phototherapy or systemic immunosuppressants (Wollenberg et al. 2016). Cyclosporine A (CyA) has been approved for the treatment of patients with severe AD in Europe and for the treatment of patients with resistance to existing therapies in Japan and is used off-label in the United States (US) and other geographies (Bieber and Straeter 2015). Cyclosporine A is usually considered a first-line option for patients requiring immunosuppressive treatment. However, the safety profile of CyA limits its use to the short-term treatment of acute flares; for chronic severe AD, treatment duration should not exceed 1 year (Bieber and Straeter 2015). Hence, there is a need for alternative therapy for patients with moderate-to-severe AD requiring systemic therapies.

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

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
To test the hypothesis that baricitinib 4-mg + TCS or baricitinib 2-mg + TCS is superior to placebo + TCS in the treatment of moderate-to-severe AD	<ul style="list-style-type: none"> Proportion of patients achieving EASI75 at Week 16
Key Secondary <i>These are prespecified objectives that will be adjusted for multiplicity</i>	
To test the hypothesis that baricitinib 1-mg + TCS is superior to placebo + TCS in the treatment of patients with moderate-to-severe AD	<ul style="list-style-type: none"> Proportion of patients achieving EASI75 at Week 16
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as measured by improvement of signs and symptoms of AD	<ul style="list-style-type: none"> Proportion of patients achieving IGA of 0 or 1 with a ≥ 2-point improvement at 16 weeks Proportion of patients achieving EASI90 at 16 weeks Percent change from baseline in EASI score at 16 weeks Proportion of patients achieving SCORAD75 at 16 weeks
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as assessed by patient-reported outcome measures.	<ul style="list-style-type: none"> Proportion of patients achieving a 4-point improvement in Itch NRS at 16, 4, 2, and 1 weeks Mean change from baseline in the score of Item 2 of the ADSS at 16 weeks and 1 week. Mean change from baseline in Skin Pain NRS at 16 weeks
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as measured by improvement of signs and symptoms of AD	<ul style="list-style-type: none"> Proportion of patients achieving IGA of 0 or 1 with a ≥ 2-point improvement from baseline at Week 24 Proportion of patients achieving EASI75 at 24 weeks
Other Secondary <i>These are prespecified objectives that will not be adjusted for multiplicity</i>	
To test the hypothesis that baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS is superior to placebo + TCS in the treatment of moderate-to-severe AD	<ul style="list-style-type: none"> Proportion of patients achieving IGA of 0 or 1 with a ≥ 2-point improvement at Week 4 and Week 52. Proportion of patients achieving EASI75 at Week 4 and Week 52
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as measured by improvement in signs and symptoms of AD	<ul style="list-style-type: none"> 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 Proportion of patients achieving SCORAD90 at 16 weeks Mean change from baseline in body surface area affected at 16 weeks

	<ul style="list-style-type: none"> • Proportion of patients developing skin infections requiring antibiotic treatment by Week 16 • Mean number of days without use of background TCS over 16 weeks • Mean gram quantity of background TCS used over 16 weeks (tube weights)
<p>To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as assessed by patient-reported outcome measures</p>	<ul style="list-style-type: none"> • Percent change from baseline in Itch NRS at Weeks 52, 24, 16, 4, and 1 • Proportion of patients achieving a 4-point improvement in Itch NRS at 24 weeks • Mean change from baseline in the total score of the POEM at 16 weeks • Mean change from baseline in the PGI-S-AD scores at 16 weeks • Mean change from baseline in the HADS total scores at 16 weeks • Mean change from baseline in the DLQI total scores at 16 weeks • Mean change from baseline in the WPAI-AD total scores at 16 weeks • Mean change from baseline in the EQ-5D-5L total scores at 16 weeks
<p>Substudy: Randomized Downtitration <i>These are prespecified objectives that will be not be adjusted for multiplicity</i></p>	
<p>All Patients Entering the Substudy To evaluate the change in clinical response after treatment downtitration from baricitinib</p> <ul style="list-style-type: none"> • 4-mg to 2-mg compared with patients who are rerandomized to remain on baricitinib 4-mg • 2-mg to 1-mg compared with patients randomized to remain on baricitinib 2-mg <p>Patients Entering the Substudy with IGA 0 or 1 To evaluate the change in clinical response after treatment downtitration from baricitinib</p> <ul style="list-style-type: none"> • 4-mg to 2-mg compared with patients who are rerandomized to remain on baricitinib 4-mg • 2-mg to 1-mg compared with patients randomized to remain on baricitinib 2-mg 	<ul style="list-style-type: none"> • Proportion of patients with a response of IGA 0, 1, or 2 assessed at 16 weeks after rerandomization (Week 68) and Week 104 • Proportion of patients with a response of IGA 0 or 1 assessed at 16 weeks after rerandomization (Week 68) and Week 104 • Proportion of patients with a response of EASI75 from baseline assessed at 16 weeks after rerandomization (Week 68) and Week 104 • Time to retreatment (time to IGA \geq3)
<p>Patients Not Entered into Substudy <i>These are prespecified objectives that will not be adjusted for multiplicity</i></p>	
<p>All Patients</p> <ol style="list-style-type: none"> 1. To evaluate the long-term effect of baricitinib dose on clinical measures <p>Patients with IGA 0 or 1</p> <ol style="list-style-type: none"> 2. To evaluate the long-term effect of baricitinib dose on clinical measures 	<ul style="list-style-type: none"> • Proportion of patients with a response of IGA 0, 1, or 2 assessed at Weeks 68 and 104 • Proportion of patients with a response of IGA 0 or 1 assessed at Weeks 68 and 104 • Proportion of patients with a response of EASI75 assessed at Weeks 68 and 104

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D-5L = the European Quality of Life–5 Dimensions 5 Levels; HADS = Hospital Anxiety Depression Scale; IGA = Investigator’s Global Assessment; NRS = Numeric Rating Scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; TCS = topical corticosteroids; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

Summary of Study Design:

Study I4V-MC-JAIN (JAIN) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of baricitinib 1-mg once daily (QD), 2-mg QD, and 4-mg QD compared with placebo in patients with moderate-to-severe AD who are receiving background topical corticosteroid (TCS) treatment and who have experienced failure to cyclosporine or are intolerant to, or have a contraindication to, cyclosporine.

The study consists of 5 periods:

Period 1: Screening Period (Visit 1), up to 5 weeks prior to randomization

Period 2: 52-week Double-Blind Treatment Period: from Week 0 (Baseline; Visit 2) up to Week 52 (Visit 14)

Period 3: 52-week Double-Blind, Long-Term Extension Period: from Week 52 (Visit 14) to Week 104 (Visit 22)

a. Randomized Down-Titration Substudy (Week 52)

Responders who are eligible to enter the substudy will be rerandomized as follows:

- baricitinib 4-mg treatment group 1:1 to baricitinib 2-mg, or baricitinib 4-mg.
- baricitinib 2-mg treatment group 1:1 to baricitinib 1-mg, or baricitinib 2-mg.

b. Responders who are not eligible to enter the randomized downtitration will continue on the treatment regimen assigned at baseline; however, rerandomization to either 4-mg or 2-mg baricitinib is available for the placebo, baricitinib 2-mg, and 1-mg treatment groups if patients have a worsening of symptoms.

c. Nonresponders in the placebo, baricitinib 2-mg, or baricitinib 1-mg treatment groups will be rerandomized at a 1:1 ratio to baricitinib 4-mg or baricitinib 2-mg QD at Week 52. After rerandomization, patients will remain on the same dose of baricitinib for the remainder of the study. Nonresponders who were randomized to baricitinib 4-mg will remain on 4-mg.

Period 4: Bridging Extension: from Week 104 (Visit 22) and up to Week 200 (Visit 28). Subjects who have completed Week 104 and have not met criteria of permanent discontinuation will have the possibility to remain in the trial for up to 96 additional weeks (up to Week 200).

Period 5: Post-Treatment Follow-Up Period: from last treatment period visit or early termination visit (ETV) to 4 weeks after the last dose of investigational product.

Treatment Arms and Duration:

At baseline, patients will be randomized at a 1:1:2:1 ratio to receive placebo QD, baricitinib 1-mg QD, baricitinib 2-mg QD, or baricitinib 4-mg QD for up to 200 weeks.

Number of Patients:

Planned enrollment is 500 patients ≥ 18 years of age.

Statistical Analysis

Unless otherwise specified, the efficacy and health outcome analyses will be conducted on the intent-to-treat population and safety analyses will be conducted on those patients who receive at least 1 dose of investigational product.

Treatment comparisons of discrete efficacy variables will be made using a logistic regression analysis with treatment, baseline disease severity (vIGA AD) and baseline score in the model. Region may be added to the model if patient numbers allow. The proportions and 95% confidence interval (CI) for the treatment comparisons will be reported. If a patient needs to use rescue medication, the data from that point forward will be considered missing and missing data will be imputed using the nonresponder imputation (NRI) method. Additional analyses will be conducted using all observed data regardless of whether rescue medication was used or not.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed-effects models for repeated measures (MMRM) model with treatment, baseline severity (vIGA AD), visit, and treatment-by-visit interaction as fixed categorical effects and baseline score and baseline score-by-visit interaction as fixed continuous effects. Region may be added to the model if patient numbers allow. An unstructured covariance matrix will be used to model the within-patient variance–covariance errors. Type III sums of squares for the least squares means (LSMs) will be used for the statistical comparison and contrasts will be set up within the model to compare treatment groups at specific time points of interest.

Fisher exact test will be used for all adverse events (AEs), baseline, discontinuation, and other categorical safety data. Continuous vital signs and laboratory values will be analyzed by an analysis of covariance (ANCOVA) with treatment and baseline values in the model.

2. Schedule of Activities

Table JAIN.1. Schedule of Activities

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension					PTFU	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28/ ETA	801 ^a	
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	204	
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	28±4
Inclusion and exclusion review	X	X																												
Informed consent	X																													
Clinical Assessments																														
Demographics	X																													
Medical history	X																													
Substance Use (alcohol, tobacco)	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	X	X	X	X	X	X	X	X	X
Height	X																													
Vital signs (BP and Pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X																													
Symptom-directed physical examination ^b		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (single)	X																													
Chest x-ray ^c (posterior–anterior view)	X																													
TB test ^d	X																													

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension					PTFU
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28/ ETA	801 ^a
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	204
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	28±4
Read PPD if applicable (48 to 72 hours after PPD)	X ^e																												
Pre-existing Conditions	X																												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ePRO (patient diary) dispensed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X												
ePRO (patient diary) returned		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X ^f	
Randomization/ rerandomization ^g		X												X ^g															
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Dispensed		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X
Weigh and dispense background TCS (tubes with cap) ^h		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Weigh and record returned background TCS (tubes with cap) ^h			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X ⁱ	
Scales																													
IGA	X	X	X	X	X	X	X	X	X	X	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	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	X	X	X	X	X	X	X	X	X	X
Health Outcomes Measures and Other																													

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension					PTFU	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28/ ETA	801 ^a	
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	204	
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	28±4	
Questionnaires ^h																														
Itch NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X ^f		
Skin Pain NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X ^f		
ADSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X ^f		
PGI-S-AD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X										X ^f		
POEM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X	X		X		X		X			X		X		X	X						X ^r	X ^r	
EQ-5D-5L		X	X	X	X	X	X	X		X		X		X			X		X		X	X						X ^r	X ^r	
WPAI-AD		X	X	X	X	X	X	X		X		X		X			X		X		X	X						X ^r	X ^r	
SF-36		X			X	X	X	X		X		X		X			X		X		X	X						X ^r	X ^r	
C-SSRS and Self-Harm Supplement ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-Up Form ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																														
Lipids (Fasting Visit) ^k		X					X			X		X		X			X		X		X	X	X	X	X	X	X	X	X	
Clinical Chemistry ^l	X	X			X	X	X	X		X	X	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	X	X	X	X	X	X	X	X	
Serum Pregnancy ^m	X																													
FSH ⁿ	X																													
TSH	X																													
HIV	X																													
HCV Antibody ^o	X																													
HBV testing	X																													
HBV DNAP	X							X		X			X			X		X		X	X	X	X	X	X	X	X	X	X	

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension					PTFU	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28/ ETa	801 ^a	
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	204	
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	28±4	
Urinalysis	X	X			X	X	X	X		X	X	X		X			X		X		X	X						X ^r	X ^r	
Urine Pregnancy ^m		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics: blood		X										X																		
Serum immunoglobulin (IgE)		X			X			X		X	X		X									X						X ^r		
Exploratory storage samples (serum and plasma)		X			X			X		X	X		X									X						X ^r		
RNA and biomarkers: blood		X			X			X		X	X		X									X						X ^r		

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale 11 categories suicidal ideation/suicidal behavior; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EQ-5D-5L = the European Quality of Life–5 Dimensions 5 Levels; ET = early termination; ePRO = electronic patient-reported outcomes (device); FSH = follicle-stimulating hormone; HADS = Hospital Anxiety Depression Scale; HCV = hepatitis C virus; HBV = hepatitis B virus; HIV = human immunodeficiency virus; ICF = informed consent form; IGA = Investigator’s Global Assessment; IgE = immunoglobulin E; IP = investigational product; IWRS = interactive web-response system; NRS = Numeric Rating Scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PPD = purified protein derivative; PTFU = post-treatment follow-up; SF-36 = Medical Outcomes Study 36-item short-form health survey; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TCS = topical corticosteroids; TSH = thyroid-stimulating hormone; V = visit; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

- a An early termination visit should be conducted if patient discontinues from the study before Week 200. Visit 801 is the post-treatment follow-up visit, which occurs after the patient has been off baricitinib/study drug 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 28/ET; Visit 801 (follow-up visit) is not required. ET visit activities do not need to be duplicated if occurring at the time of a scheduled visit.
- b The symptom-directed physical examination may be repeated at the investigator's discretion any time a patient presents with physical complaints.
- c A posterior–anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available.
- d TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. See Exclusion Criterion [40] for description of TB testing. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally. (Note: Exception: Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing but must have a chest x-ray at screening.)
- e If PPD testing was chosen to test for TB, then the patient must return and PPD test read 48 to 72 hours after Visit 1 (post-PPD).
- f Applies to ET Visit if conducted prior to Week 68 only.
- g At Week 52, patients who are eligible for the randomized downtitration substudy and nonresponders will be rerandomized as described in Section 5.1.3.
- h The following measures (Itch NRS, Skin Pain NRS, ADSS, PGI-S-AD, POEM, DLQI, HADS, EQ-5D-5L, WPAI-AD, SF-36) should be completed prior to any clinical assessments being performed on days when study visits occur.
- i Suicidal ideation and behavior subscales excerpt – Adapted for the assessment of 11 preferred ideation and behavior categories.
- j The Self-Harm Follow-Up Form is required only if triggered by the Self-Harm Supplement Form.
- k Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Unscheduled lipid testing can be performed at the discretion of the investigator.
- l Clinical chemistry will include the following value calculated from serum creatinine: estimated glomerular filtration rate (eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine 2009 equation).
- m For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and at all subsequent study visits after Visit 3. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.
- n For female patients ≥ 40 and < 60 years of age who have had a cessation of menses for at least 12 months, an FSH test will be performed to confirm nonchildbearing potential (FSH ≥ 40 mIU/mL).
- 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.
- q Beyond Week 104, low and mid potency TCS will no longer be provided by the sponsor.
- r Only applicable to ET visits and V801 before Period 4.

NOTE: Patients completing V22 and planning to sign the ICF for amendment (e) can participate as long as they have not completed a V801.

3. Introduction

3.1. Background

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

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

Whereas mild AD can be controlled by appropriate skin care and topical anti-inflammatory treatments (topical corticosteroids [TCS] and topical calcineurin inhibitors [TCIs]), moderate and severe AD usually require additional treatments such as phototherapy or systemic immunosuppressants (Wollenberg et al. 2016).

Cyclosporine A (CyA) has been approved for the treatment of patients with severe AD in most European countries and for AD not controlled with existing therapies in Japan and is used off-label in the US and other geographies (Bieber and Straeter 2015). Cyclosporine A is usually considered a first-line option for patients requiring immunosuppressive treatment. However, the safety profile of CyA limits its use to the short-term treatment of acute flares; for chronic severe AD, treatment duration should not exceed 1 year (Bieber and Straeter 2015). Hence, there is a need for alternative therapy for patients with moderate-to-severe AD requiring systemic therapies, particularly those who have experienced failure to cyclosporine or are intolerant to, or have contraindication to, cyclosporine.

Until recently, there were no Food and Drug Administration (FDA)-approved systemic treatments for patients with moderate-to-severe AD, with the exception of systemic corticosteroids. In March 2017, Dupixent (dupilumab) injection, an IgG4 monoclonal antibody that inhibits interleukin (IL)-4 and IL-13, was approved by the FDA for this patient population (Dupixent package insert, 2017). In the European Union, only cyclosporine has been approved for the treatment of patients with severe AD (Bieber and Straeter 2015). A recently completed Phase 2 study (I4V-MC-JAHG [JAHG]) evaluated the safety and efficacy of baricitinib (a Janus

kinase [JAK] inhibitor) in AD and results showed significant improvement in disease severity compared to placebo and no new safety concerns were identified.

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

Baricitinib has been administered as single doses ranging from 1- to 40-mg and as repeat oral doses ranging from 2- to 20-mg to healthy subjects. Baricitinib has also been administered to patients with RA at doses up to 15-mg daily for 4 weeks, 10-mg daily for 24 weeks, 8-mg daily for 76 weeks, and lower doses up to 4-mg daily for up to approximately 7 years. Through 13 February 2019, nearly 3861 patients have been treated with baricitinib within the RA program at doses of 2-mg once daily (QD) or 4-mg QD. Of these, more than 2700 patients have been treated with baricitinib for more than a year and more than 2100 patients have been treated with baricitinib for more than 2 years.

3.2. Benefit/Risk Assessment

CCI [REDACTED]

[REDACTED]

[REDACTED]

CCI



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

3.3. Study Rationale

The underlying cause of AD is not completely understood. Loss-of-function mutations in the gene for filaggrin (filament aggregating protein), a key protein in terminal differentiation of the epidermis contributing to barrier function, has been identified as the strongest genetic risk factor for AD in European populations, but is only observed in about half of Caucasian patients whereas other variants of FLG are found in different ethnicities. (Palmer et al. 2006). At a cellular level, AD is characterized by excessive T cell activation caused by genetic and environmental factors, leading to significant skin infiltration by T cells and dendritic cells. The cytokine thymic stromal lymphopoietin (TSLP) is thought to act as a master switch that triggers the initiation and maintenance of AD (Moniaga et al. 2013; Ziegler et al. 2013). Overexpression of TSLP in keratinocytes, the most prevalent cell type in the skin, triggers robust itch-evoked scratching and the development of an AD-like skin phenotype in mice (Li et al. 2005). In addition to directly inducing itch by activating sensory neurons in the skin, TSLP also enhances maturation and differentiation of dendritic cells and naive CD4+ T cells and induces production of Th2-related cytokines involved in AD pathogenesis (Wilson et al. 2013; Divekar and Kita 2015). Thymic stromal lymphopoietin and other key cytokines involved in AD pathogenesis, such as IL-4, IL-13, IL-5, IL-22, and IL-31, signal through receptors associated with intracellular

JAK1/JAK2/tyrosine kinase 2 (TYK2) signaling (Ziegler et al. 2013; Nomura and Kabashima 2015).

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

4. Objectives and Endpoints

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

Table JAIN.2. Objectives and Endpoints

Objectives	Endpoints
Primary	
To test the hypothesis that baricitinib 4-mg + TCS or baricitinib 2-mg + TCS is superior to placebo + TCS in the treatment of moderate-to-severe AD	<ul style="list-style-type: none"> Proportion of patients achieving EASI75 at Week 16
Key Secondary <i>These are prespecified objectives that will be adjusted for multiplicity</i>	
To test the hypothesis that baricitinib 1-mg + TCS is superior to placebo + TCS in the treatment of patients with moderate-to-severe AD	<ul style="list-style-type: none"> Proportion of patients achieving EASI75 at Week 16
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as measured by improvement of signs and symptoms of AD	<ul style="list-style-type: none"> Proportion of patients achieving IGA of 0 or 1 with a ≥ 2 point improvement at 16 weeks Proportion of patients achieving EASI90 at 16 weeks Percent change from baseline in EASI score at 16 weeks Proportion of patients achieving SCORAD75 at 16 weeks
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as assessed by patient-reported outcome measures	<ul style="list-style-type: none"> Proportion of patients achieving a 4-point improvement in Itch NRS at 16, 4, 2, and 1 weeks Mean change from baseline in the score of Item 2 of the ADSS at 16 weeks and 1 week. Mean change from baseline in Skin Pain NRS at 16 weeks
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as measured by improvement of signs and symptoms of AD	<ul style="list-style-type: none"> Proportion of patients achieving IGA of 0 or 1 with a ≥ 2-point improvement from baseline at Week 24 Proportion of patients achieving EASI75 at 24 weeks
Other Secondary <i>These are prespecified objectives that will not be adjusted for multiplicity</i>	
To test the hypothesis that baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS is superior to placebo + TCS in the treatment of moderate-to-severe AD	<ul style="list-style-type: none"> Proportion of patients achieving IGA of 0 or 1 with a ≥ 2-point improvement at Week 4 and Week 52 Proportion of patients achieving EASI75 at Week 4 and Week 52
To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as measured by improvement in signs and symptoms of AD	<ul style="list-style-type: none"> 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

	<ul style="list-style-type: none"> • Proportion of patients achieving SCORAD90 at 16 weeks • Mean change from baseline in body surface area (BSA) affected at 16 weeks • Proportion of patients developing skin infections requiring antibiotic treatment by Week 16 • Mean number of days without use of background TCS over 16 weeks • Mean gram quantity of background TCS used over 16 weeks (tube weights)
<p>To compare the efficacy of baricitinib 4-mg + TCS, baricitinib 2-mg + TCS, or baricitinib 1-mg + TCS to placebo + TCS in AD during the double-blind placebo-controlled treatment period as assessed by patient-reported outcome measures</p>	<ul style="list-style-type: none"> • Percent change from baseline in Itch NRS at Weeks 52, 24, 16, 4, and 1 • Proportion of patients achieving a 4-point improvement in Itch NRS at 24 weeks • Mean change from baseline in the total score of the POEM at 16 weeks • Mean change from baseline in the PGI-S-AD scores at 16 weeks • Mean change from baseline in HADS total scores at 16 weeks • Mean change from baseline in the DLQI total scores at 16 weeks • Mean change from baseline in the WPAI-AD total scores at 16 weeks • Mean change from baseline in the EQ-5D-5L total scores at 16 weeks
<p>Substudy: Randomized Downtitration <i>These are prespecified objectives that will be not be adjusted for multiplicity</i></p>	
<p>All Patients Entering the Substudy To evaluate the change in clinical response after treatment downtitration from baricitinib</p> <ul style="list-style-type: none"> • 4-mg to 2-mg compared with patients who are rerandomized to remain on baricitinib 4-mg • 2-mg to 1-mg compared with patients randomized to remain on baricitinib 2-mg <p>Patients Entering the Substudy with IGA 0 or 1 To evaluate the change in clinical response after treatment downtitration from baricitinib</p> <ul style="list-style-type: none"> • 4-mg to 2-mg compared with patients who are rerandomized to remain on baricitinib 4-mg • 2-mg to 1-mg compared with patients randomized to remain on baricitinib 2-mg 	<ul style="list-style-type: none"> • Proportion of patients with a response of IGA 0, 1, or 2 assessed at 16 weeks after rerandomization (Week 68) and Week 104 • Proportion of patients with a response of IGA 0 or 1 assessed at 16 weeks after rerandomization (Week 68) and Week 104 • Proportion of patients with a response of EASI75 from baseline assessed at 16 weeks after rerandomization (Week 68) and Week 104 • Time to retreatment (time to IGA \geq3)
<p>Patients Not Entered into Substudy <i>These are prespecified objectives that will not be adjusted for multiplicity</i></p>	

<p>All Patients</p> <p>1. To evaluate the long-term effect of baricitinib dose on clinical measures</p> <p>Patients with IGA 0 or 1</p> <p>2. To evaluate the long-term effect of baricitinib dose on clinical measures</p>	<ul style="list-style-type: none"> • Proportion of patients with a response of IGA 0, 1, or 2 assessed at Weeks 68 and 104 • Proportion of patients with a response of IGA 0 or 1 assessed at Weeks 68 and 104 • Proportion of patients with a response of EASI75 assessed at Weeks 68 and 104
<p>Exploratory Endpoints may include evaluating the response to baricitinib treatment regimens on clinical measures and patient-reported outcomes. These endpoints may include dichotomous endpoints or change from baseline for the following measures: IGA, EASI, SCORAD, POEM, DLQI, WPAI-AD, EQ-5D-5L, Itch NRS, ADSS Item 1, 2, 3 scores, Skin Pain NRS, SF-36, PGI-S-AD. Patients continuing on placebo as responders will be assessed during the long-term extension for relevant efficacy endpoints. Assessments of efficacy may be performed beyond Week 104 up to Week 200. The timing of the data lock(s) for the analysis of the efficacy data from the randomized withdrawal sub-study will be determined by the retreatment rates (see Section 10.3.7).</p>	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5D-5L = the European Quality of Life–5 Dimensions 5 Levels; HADS = Hospital Anxiety Depression Scale; IGA = Investigator’s Global Assessment; NRS = Numeric Rating Scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; SF-36 =Medical Outcomes Study 36-item short-form health survey; SCORAD = SCORing Atopic Dermatitis; TCS = topical corticosteroids; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

5. Study Design

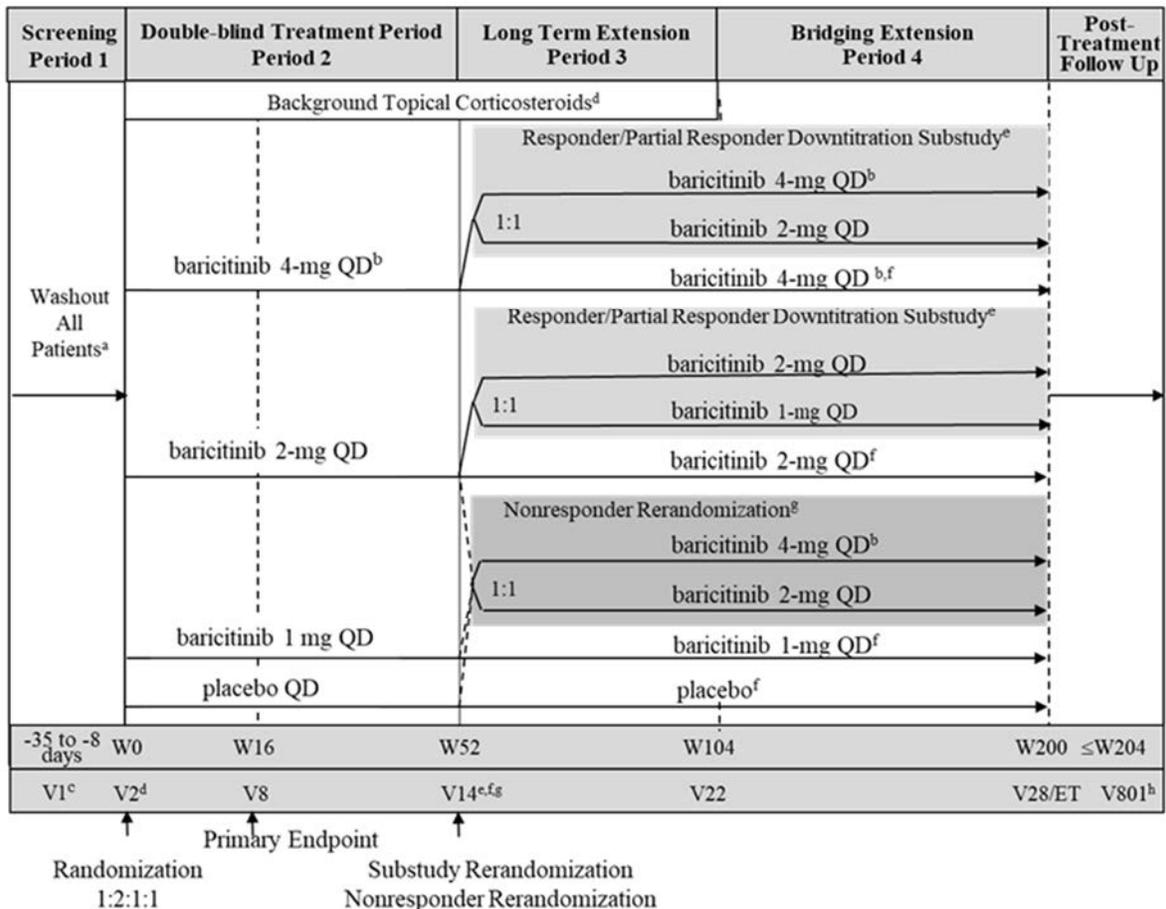
5.1. Overall Design

Study I4V-MC-JAIN (JAIN) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of baricitinib 1-mg QD, 2-mg QD, and 4-mg QD in combination with TCS in patients with moderate-to-severe atopic dermatitis (AD) who have experienced failure of cyclosporine, or are intolerant to, or have a contraindication to, cyclosporine. The study is divided into 5 periods: a 5-week Screening period, a 1-year Double-Blind Treatment period (Week 0 through Week 52), a 1-year double-blind, long-term extension (Week 52 through Week 104) that includes a randomized downtitration substudy, a bridging extension that may last up to 96 weeks (Week 104 to up to Week 200) and a 4-week Post-Treatment Follow-Up period.

Approximately 500 patients ≥ 18 years of age will be randomized at a 1:1:2:1 ratio to receive placebo QD, baricitinib 1-mg QD, baricitinib 2-mg QD, or baricitinib 4-mg QD (100 patients in the placebo group; 100 patients each in the baricitinib 1-mg and 4-mg groups; and 200 patients in the baricitinib 2-mg treatment group). Patients will be stratified at randomization according to disease severity (Investigator's Global Assessment [IGA] 3 versus 4) and geographic region if the planned country allocation justifies.

All procedures to be conducted during the study, including timing of all procedures, are indicated in the Schedule of Activities (Section 2). Section 9.4.4 describes collection of laboratory samples; [Appendix 2](#), [Appendix 4](#), and [Appendix 5](#) list the specific laboratory tests that will be performed for this study. Study governance considerations are described in detail in [Appendix 3](#). Section 10.3.7.1 outlines information regarding the data monitoring committee (DMC) and interim analyses.

[Figure JAIN.1](#) illustrates the study design.



Abbreviations: AD = atopic dermatitis; eGFR = estimated glomerular filtration rate; ET = early termination; IGA = Investigator’s Global Assessment; IP = investigational product; PPD = purified protein derivative; QD = once daily; TB = tuberculosis; TCS = topical corticosteroids; V = visit; W = week.

^a Applicable to patients taking topical treatments (excluding emollients) or systemic treatments for AD at the time of screening.

^b Maximum dose of baricitinib for patients with renal impairment (defined as eGFR <60 mL/min/1.73 m²) will be 2-mg QD.

^c Patients for whom PPD skin test for the evaluation of TB infection was performed at V1 must return and PPD test must be read 48 to 72 hours after Visit 1 (post-PPD).

^d At Visit 2 (W0) and up to Visit 22 (W104), patients will be supplied with mild- and moderate-potency TCS to be applied per the guidelines in Section 7.7.2.

^e At Week 52, responders (IGA 0 or 1) and partial responders (IGA 2) who were assigned to baricitinib 4-mg or 2-mg, at randomization, are currently receiving investigational product (does not currently have study drug interrupted), and have not used high- or ultra-high-potency TCS in the previous 14 days will be enrolled into the downtitration substudy. If a patient in the substudy has an IGA ≥3 during Periods 3 or 4, they will be retreated automatically with their presubstudy baricitinib dose for the remainder of the study.

^f At Week 52, responders (IGA 0 or 1) and partial responders (IGA 2) in the baricitinib 4-mg or baricitinib 2-mg treatment groups who are not eligible for the randomized downtitration substudy and those who are in the baricitinib 1-mg or placebo groups will remain on their current dose of investigational product. If worsening of AD symptoms occurs any time during Periods 3 or 4 such that a patient's IGA is ≥ 3 , with the exception of patients in the baricitinib 4-mg group, they will be rerandomized automatically at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD. Rerandomization will only occur once. Patients in the baricitinib 4-mg group will remain on 4-mg.

^g Beginning at Visit 14 (Week 52), nonresponders (IGA ≥ 3) in the placebo, baricitinib 1-mg or baricitinib 2-mg treatment groups will be rerandomized at a 1:1 ratio to baricitinib 4-mg or baricitinib 2-mg QD. Nonresponders randomized to baricitinib 4-mg at baseline will remain on 4-mg. After rerandomization, patients will remain on the same dose of baricitinib for the remainder of the study.

^h Occurs approximately 28 days after the last dose of IP. Not required for patients who have been off drug for 28 days or more at the time of their last visit.

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

5.1.1. Period 1: Screening and Baseline Period

The duration of the Screening Period is between 8 and 35 days prior to Visit 2 (Week 0). At Visit 1, the patient will sign the informed consent form (ICF) prior to any study assessments, examinations, or procedures being performed (see [Appendix 3](#)). 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 read the skin test. Prior to randomization, treatments for AD will be washed out: 5 half-lives for biologic treatments, 4 weeks for systemic treatments, and 2 weeks for topical treatments (not including emollients). Patients will be required to use emollients daily during the 14 days preceding randomization and throughout the study. On study visit days, patients are requested not to apply emollients until after the assessments are completed. If patients have been using emollients daily at the time of screening, then those cumulative days can be utilized to meet inclusion criterion [9]. Additionally, collection of data through daily diaries will be required throughout the screening period. The baseline for the daily PRO assessments will be the average score of the 7 days prior to randomization; thus the minimum screening window was set at 8 days.

All eligible patients who have not previously received the herpes zoster vaccine by screening will be encouraged (per local guidelines) to do so prior to randomization. Refer to the exclusion criterion [29] in Section 6 for additional information regarding herpes zoster vaccinations. Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination of those ≥ 18 years of age with nonlive vaccines intended to prevent infectious disease prior to entering patients into the study.

Patients who meet all of the inclusion and none of the exclusion criteria (Section 6) will continue to Visit 2.

5.1.2. Period 2: Double-Blind Placebo-Controlled Treatment

At Visit 2 (Week 0, baseline), study eligibility for each patient will be reviewed, based on all inclusion and exclusion criteria (Section 6), and laboratory test results. Patients who meet all criteria will proceed to randomization and begin the 52-week double-blind, placebo-controlled treatment period.

At Visit 2, laboratory samples will be collected and all assessments should be completed before the patient takes the first dose of investigational product. The first dose of investigational product should be administered on-site.

Patients will be randomized at a 1:1:2:1 ratio to 1 of 4 treatment groups (placebo QD, baricitinib 1-mg QD, baricitinib 2-mg QD, or baricitinib 4-mg QD). Patients will also apply background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment) on active lesions, as described in Section 7.7.2 (Use of Topical Corticosteroids). Use of TCIs and/or crisaborole (where approved) will be permitted as background therapy on areas where application of TCS is considered inappropriate by investigator (e.g., face, neck, skin folds, genital areas; see Section 7.7.1 [Permitted Medications and Procedures]). High- or ultra-high potency TCS (Class I to III; see Appendix 7) and all systemic therapies used for treating AD will not be allowed, unless used as directed as part of rescue therapy (see guidelines in Section 7.7.5 [Rescue Therapy]) and only at the discretion of the investigator. Rescue to baricitinib will not occur during treatment Period 2.

Assessments of disease severity will be performed by the investigator at all study visits including unscheduled and early termination visits (ETVs). On study visit days, patients are requested not to apply emollients nor TCS until after the assessments are completed. Daily diary collection will continue through all 52 weeks of treatment in Period 2 of JAIN.

The primary efficacy endpoint will be at Week 16 (Visit 8). All patients who permanently discontinue investigational product prior to the primary endpoint, including patients rescued with other systemic medications, should remain in the study to complete the schedule of study visits per protocol up to Week 16 (primary endpoint), when they will complete an ETV. If the patient refuses to continue up to Week 16 and wishes to withdraw consent, an ETV should be completed as soon as logistically possible.

5.1.3. Period 3: Double-Blind, Long-Term Extension

Patients who complete the study through Week 52 will progress into the double-blind long-term extension phase through Week 104 (Visit 22). Daily diary collection will continue through Week 68 (Visit 18) of Period 3.

Concomitant use of background TCS therapy will continue during this treatment period as described in Section 7.7.2.

5.1.3.1. Randomized Downtitration Substudy at Week 52

At Week 52, all patients will be evaluated for substudy eligibility. To be eligible, a patient must meet all of the following criteria:

- have an IGA 0, 1 (Responder) or 2 (Partial responder) at Week 52
- have not used high- or ultra-high potency TCS in the last 14 days (potency classification in [Appendix 7](#))
- do not currently have study drug interrupted
- have been assigned to baricitinib 2-mg or 4-mg at baseline (assessed by interactive web-response system [IWRS])

Treatment

Treatment in the substudy is illustrated in [Figure JAIN.1](#). Patients eligible for the substudy will be rerandomized at a 1:1 ratio at Week 52 based on the baricitinib treatment group assigned at baseline:

- 4-mg QD rerandomized to baricitinib 4-mg QD, or baricitinib 2-mg QD
- 2-mg QD rerandomized to baricitinib 2-mg QD, or baricitinib 1-mg QD

Note: Intensification of emollients and TCS may be continued or initiated to control worsening and unacceptable symptoms of AD any time during this treatment period. For management of TCS, follow the guidelines in [Section 7.7.2](#).

Retreatment

During the substudy, if worsening of AD symptoms occurs such that IGA increases to ≥ 3 , the patient will be automatically retreated with their presubstudy baricitinib dose. When the IGA is ≥ 3 , the investigator should reinstate background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment), provided the patients are not currently using TCS, and may prescribe high- or ultra-high-potency TCS following the guidelines for use of Rescue Therapies ([Section 7.7.5](#) [Rescue Therapy]). An unscheduled visit may be needed to assess worsening of symptoms and to perform clinical safety and efficacy assessments immediately before retreatment.

Investigators will be aware of the patients not meeting the first 3 eligibility criteria for randomized downtitration substudy; however, they will not be aware of the patient's dose assigned at randomization. As such, IGA ≥ 3 will be the criterion for both retreatment (in the substudy) and rescue for patients not eligible for the substudy, as described below, to ensure that all patients are treated similarly and that the blinding to treatment group is preserved. In addition, all patients, regardless of whether entered into the substudy or not, will follow all study procedures in Period 3 to maintain the blind.

5.1.3.2. Patients Not Eligible for the Substudy

Beginning at Week 52,

- Patients with an IGA ≥ 3 who
 - are in the baricitinib 2-mg, 1-mg, and placebo treatment groups will be automatically rerandomized at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD.

- are in the baricitinib 4-mg treatment group will remain on 4-mg QD (see “Rescue during Period 3” Section 7.7.5.2).
- Patients with an IGA 0, 1, or 2 who
 - are in the baricitinib 4-mg or 2-mg treatment groups and who are not eligible for the substudy (i.e., have study drug interrupted at Week 52, or have received high- or ultra-high potency TCS in the previous 14 days), or are in the placebo or baricitinib 1-mg groups will continue in their current treatment group.
 - Patients who experience a worsening of symptoms of AD such that IGA increases to ≥ 3 will be rerandomized at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD. Patients in the baricitinib 4-mg group will remain on 4-mg.

This option for rescue is only available once for each patient and will be assigned by IWRS; investigators will remain blinded to treatment assignments. The investigator may reinstate background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment), provided the patients are not currently using TCS, and may prescribe high- or ultra-high-potency TCS following the guidelines for use of rescue therapies (see Section 7.7.5).

Once a patient has an IGA ≥ 3 in Period 3, the investigator will know that a patient is on the highest dose of baricitinib that he/she will receive in the study; therefore, if AD symptoms remain unacceptable then discontinuation should be considered.

5.1.4. Period 4: Bridging Extension

Patients who have completed Week 104 and have not met criteria for permanent discontinuation will have the possibility to remain in the trial for up to 96 additional weeks (up to Week 200).

During Period 4, patients will continue to receive the same treatment (baricitinib or placebo) they received during Period 3, and will have the same options for dose changes as Period 3 (if not already implemented in Period 3):

- Randomized Down titration substudy: the substudy will continue during Period 4. Therefore, patients who have not met the criterion for retreatment in Period 3 will have the possibility to be retreated with the baricitinib dose they received prior to the substudy if worsening of AD symptoms occurs such that IGA increases to ≥ 3 .
- Patients with an IGA 0, 1, or 2 at Week 52 and who were not eligible to the randomized downtitration, will be rerandomized at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD if they experience a worsening of symptoms of AD such that IGA increases to ≥ 3 , unless the randomized uptitration has already occurred in Period 3. Patients in the baricitinib 4-mg group will remain on 4-mg.

5.1.5. Period 5: Post-Treatment Follow-Up

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

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

Patients who have discontinued investigational product but remain in the study for more than 28 days without investigational product will have an ETV if they chose to discontinue early; however, a separate follow-up visit (Visit 801) is not required.

If a patient permanently discontinues investigational product for any reason before Week 16 (Visit 8), 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 (See Section 5.1.3).

5.2. Number of Participants

Approximately 500 participants will be enrolled; approximately 714 patients will be screened to achieve this enrollment.

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 patients with moderate-to-severe AD who have a history of failure to cyclosporine or who are intolerant to, or have contraindication to, cyclosporine, for whom a systemic treatment such as baricitinib may therefore be appropriate.

Topical corticosteroids are the first-line anti-inflammatory treatment, even for patients treated with systemic treatments. For this reason, this study will assess the efficacy of baricitinib in combination with background mild- to moderate-potency TCS, used as determined appropriate by the investigator.

Both EASI score and 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; Božek and Reich, 2017). 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 (for example, moderate to severe) and a 75% improvement from Baseline (EASI75) is a commonly used measure of treatment effect in AD clinical trials. The IGA scale that will be used in this trial, the validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD, referred to throughout the protocol as IGA) assesses AD severity using a 5-point scale (0 to 4). It was developed in partnership with a multi-stakeholder consortium, including experts in AD, industry partners, and academia. Development of the vIGA-AD also included the development of a training video and certification exam to ensure consistency across raters. The scale and all training materials are available to all other pharmaceutical companies, as well as any academic investigator interested in using the scale through the International Eczema Council.

During the screening period (Period 1), a washout of systemic and topical treatments for AD is incorporated prior to randomization to minimize confounding effects due to background treatment.

The 52-week double-blind, placebo-controlled treatment period (Period 2) is designed to evaluate the efficacy and safety of 3 doses of baricitinib relative to placebo, in combination with TCS, both in short-term and long-term treatment of patients with moderate-to-severe AD. Study JAIN will include the possibility to downtitrate baricitinib in patients who are responders (IGA 0 or 1) or partial responders (IGA 2) in the context of a randomized downtitration substudy starting at Week 52. Study JAIN will also evaluate the possibility to uptitrate nonresponders (IGA \geq 3) during Period 3.

A 1:1:2:1 randomization scheme of placebo, 1-mg baricitinib, 2-mg baricitinib, and 4-mg baricitinib was implemented in JAIN to obtain additional efficacy and safety data for the 2-mg dose of baricitinib relative to other studies conducted with baricitinib in AD.

All patients in Study JAIN will be assigned investigational product with concomitant mild- to moderate-potency TCS until Week 104 (Visit 22) and investigators may rescue patients who are experiencing unacceptable or worsening symptoms of AD with high- or ultra-high-potency TCS. (See Section 7.7.5 for all rescue options).

Topical rescue treatments (as outlined in Section 7.7.5) will be available during Study JAIN to facilitate the management of disease, as there are instances where patients will remain on the same dose of baricitinib during episodes of worsening.

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 for consistency with other studies in AD. This timing will allow adequate duration on a stable dose of baricitinib to assess the benefit/risk profile of the dose regimens.

During the long-term extension (Period 3), eligible patients will participate in a downtitration substudy. The objective of the substudy is to evaluate the possibility of maintaining efficacy with a lower dose of baricitinib in patients with response (IGA 0 or 1) or partial response (IGA 2) to baricitinib 2-mg QD or 4-mg QD in combination with TCS.

Period 4 will provide patients who have completed Week 104 visit and have not met criteria for permanent discontinuation, the possibility to remain in the trial for up to 96 additional weeks (up to Week 200). This will allow for additional long-term efficacy and safety information to be collected, and provide patients the opportunity to continue study treatment until the anticipated approval of baricitinib in this indication.

The Post-Treatment Follow-Up Period (Period 5) is for safety monitoring after the patient has been off investigational product for approximately 28 days.

5.5. Justification for Dose

The doses proposed for AD Phase 3 studies are baricitinib 1-mg, 2-mg, and 4-mg QD. These doses were chosen primarily based on the recently completed Phase 2 AD study, JAHG, and are additionally supported by pharmacokinetic (PK), safety, and efficacy data for baricitinib in Phase 2 and Phase 3 RA studies and a Phase 2 psoriasis study.

In the Phase 2 Study JAHG, 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.

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 2-mg dose particularly in the subgroup of patients with baseline EASI scores ≥ 16 . The 4-mg dose resulted in statistically significant improvement in these endpoints at Week 4 and this level of response was maintained through Week 16. Additionally, statistical significance for EASI75 for the 4-mg dose compared to placebo also occurred at Week 4, and this level of response was maintained through Week 16. A similar trend between the baricitinib 4-mg and 2-mg doses was observed in patients with RA. However, on other endpoints including EASI50, and EASI change from baseline, 2-mg and 4-mg doses show similar efficacy compared to placebo. Thus, based on available data, 3 doses will be included in Phase 3, including a 1-mg dose, to cover the range of exposures where clinical responses could be anticipated.

5.5.1. Rationale for Dose Adjustment for Renal Impairment

Baricitinib exposure increases with decreased renal function. Based on PK simulations of baricitinib exposures for the mild and moderate categories of renal function (stratified as estimated glomerular filtration rate [eGFR] 60 to <90 mL/min/1.73 m² and eGFR 30 to <60 mL/min/1.73 m², respectively), dose adjustment is not required for patients with eGFR ≥ 60 mL/min/1.73 m². Patients with eGFR <60 mL/min/1.73 m² who are randomized to the 4-mg dose will receive a dose of 2-mg QD, which will ensure that exposures do not exceed those of the 4-mg QD dose in patients with eGFR ≥ 60 mL/min/1.73 m². For patients randomized to the 2-mg dose or 1-mg dose, there will be no dose adjustment based on renal function. The dose adjustment for renal impairment will be managed by IWRS to ensure maintenance of the treatment blind. This study will not enroll patients with screening eGFR <40 mL/min/1.73 m². See Section 8.1.1 for eGFR thresholds that trigger interruption of investigational product.

The procedure for dose adjustment based on renal function (eGFR) during the study is detailed in Section 7.2.2.

6. Study Population

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

Study investigator(s) will 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.

6.1. Inclusion Criteria

Informed consent

- [1] are at least 18 years of age at the time of informed consent

Note: Use local requirements to provide consent if the age of adulthood is defined as >18 years

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

Type of Patient and Disease Characteristics

- [3] have a diagnosis of AD at least 12 months 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 (see [Appendix 6](#)).
- [4] have moderate-to-severe AD, including all of the following:
- EASI score ≥ 16 at Screening (Visit 1) and at randomization (Visit 2)
 - IGA score of ≥ 3 at Screening (Visit 1) and at randomization (Visit 2)
 - $\geq 10\%$ of BSA involvement at Screening (Visit 1) and at randomization (Visit 2)
- [5] have a history documented by a physician and/or investigator of an inadequate response to existing topical medications within 6 months preceding screening, defined as: inability to achieve good disease control (e.g., not able to achieve IGA ≤ 2) 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 ultra-high-potency TCS), whichever is shorter.
- [6] have a history documented by a physician and/or investigator of either:
- medical contraindications to cyclosporine:
 - Hypersensitivity to the active substance or to any of the excipients
 - Medical conditions (e.g., uncontrolled hypertension on medication)

- Use of prohibited concomitant medications: products containing hypericum perforatum (St John's Wort), medicines that are substrates of CYP3A4, multidrug efflux transporter P-glycoprotein and organic anion transporter proteins (OATP): bosentan, dabigatran etexilate, aliskiren, statins, angiotensin-converting-enzyme inhibitors, lercanidipine, etc.
 - Increased susceptibility to cyclosporine-induced renal damage (elevated creatinine) and liver damage (elevated function tests), or increased risk of serious infections.
- b. intolerance and/or unacceptable toxicity to cyclosporine (e.g., elevated creatinine, elevated liver function tests, uncontrolled hypertension, paresthesia, headache, nausea, hypertrichosis, etc.), or
- c. Inadequate response to cyclosporine (CyA) defined as failure to obtain good disease control (i.e., remission or low disease activity) within 6 weeks of treatment with CyA dosed at 2.5 to 5 mg/kg/day, or requirement for CyA at doses >5 mg/kg/day, or for a duration beyond that specified in the prescribing information (>1 year).
- [7] agree to discontinue use of the following excluded medications/treatments for at least 4 weeks prior to randomization (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. sedating systemic antihistamines, including but not limited to alimemazine, chlorphenamine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, ketotifen, and promethazine during Periods 1 and 2. Sedating antihistamines may be used during Period 3.

Note: Patients may use newer, less-sedating antihistamines (e.g., fexofenadine, loratadine, cetirizine) throughout the trial.
 - d. any other systemic therapy used to treat AD or symptoms of AD (approved or off-label use)
 - e. phototherapy, including therapeutic phototherapy (psoralen plus ultraviolet A, ultraviolet B, excimer laser) as well as self-treatment with tanning beds.
- [8] agree to discontinue use of the following excluded medications for at least 2 weeks prior to randomization (Visit 2):
- a. topical corticosteroids (TCS) or topical immune modulators (e.g., tacrolimus or pimecrolimus). Note: Mild- and moderate-potency TCS will be administered as concomitant therapy for all patients, beginning at Visit 2; refer to Section 7.7.1 and 7.7.2 for further information.

- b. topical phosphodiesterase type 4 (PDE-4) inhibitor (crisaborole)
- [9] have applied emollients daily for at least 14 days prior to randomization and agree to use emollient daily throughout the treatment period
- [10] Patients who are receiving chronic treatments to improve sleep should be on a stable dose for at least 2 weeks prior to screening as determined by the investigator. Sedating antihistamines (see above) are not permitted.

Patient Characteristics

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

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

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

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

- Highly effective birth control methods: oral, injectable, or implanted hormonal contraceptives (combined estrogen/progesterone or progesterone only, associated with inhibition of ovulation); intrauterine device or intrauterine system (e.g., progestin-releasing coil); or, vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Effective birth control methods: condom with a spermicidal foam, gel, film, cream, or suppository; occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository; or, oral hormonal contraceptives.

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

- c. Females of nonchildbearing potential are not required to use birth control and they are defined as:
- women ≥ 60 years of age or women who are congenitally sterile, or
 - women ≥ 40 and < 60 years of age who have had a cessation of menses for ≥ 12 months and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (≥ 40 mIU/mL or ≥ 40 IU/L), or women who are surgically sterile (i.e., have had a hysterectomy or bilateral oophorectomy or tubal ligation).

6.2. Exclusion Criteria

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

Medical Conditions Related to Atopic Dermatitis

- [12] 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
 - [13] have had an important side effect to TCS (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or treating physician that would prevent further use.
 - [14] 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 IV treatment for skin infections that may interfere with participation in the study
 - [15] a history of eczema herpeticum within 12 months prior to screening
 - [16] a history of 2 or more episodes of eczema herpeticum in the past
 - [17] patients who are currently experiencing a skin infection that requires treatment or is currently being treated with topical or systemic antibiotics
- Note: Patients may be rescreened at least 4 weeks after the date of their previous screen failure and at least 2 weeks after resolution of the infection.
- [18] 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)
 - [19] have been treated with the following therapies:
 - a. monoclonal antibody (e.g., ustekinumab, omalizumab, dupilumab) less than 5 half-lives prior to randomization

- b. any oral JAK inhibitor (e.g., tofacitinib, ruxolitinib) less than 4 weeks prior to randomization
- 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. intraarticular 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 throughout Study JAIN.

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

Medical Conditions in General

- [20] are largely or wholly incapacitated permitting little or no self-care, such as being bedridden
- [21] have uncontrolled arterial hypertension characterized by a repeated systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg in a seated position
- [22] 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 Eli Lilly and Company (Lilly) or its designee, would pose an unacceptable risk to the patient if he or she is participating in the trial.
- [23] are immunocompromised and, in the opinion of the investigator, at an unacceptable risk for participating in the study
- [24] have experienced any of the following within 12 weeks of screening: venous thromboembolic event (VTE), myocardial infarction (MI), unstable ischemic heart disease, stroke, or New York Heart Association Stage III/IV heart failure
- [25] have a history of recurrent (≥ 2) VTE or are considered at high risk of VTE as deemed by the investigator
- [26] have a history or presence of cardiovascular, respiratory, hepatic, gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other serious and/or unstable illness that, in the opinion of the investigator, could constitute an unacceptable risk when taking investigational product or interfere with the interpretation of data.
- [27] 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.

- a. Patients with cervical carcinoma in situ that has been appropriately treated with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study.
 - b. Patients with basal cell or squamous epithelial skin cancers that have been appropriately treated with no evidence of recurrence for at least 3 years may participate in the study.
- [28] have a current or recent and/or serious viral, bacterial, fungal, or parasitic infection, including but not limited to the following:
- a. symptomatic herpes zoster infection within 12 weeks prior to screening
 - b. a history of disseminated/complicated herpes zoster (e.g., multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or post-herpetic neuralgia)
 - c. symptomatic herpes simplex at the time of randomization
 - 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) and did not receive appropriate and documented prophylaxis for TB
 - f. evidence of active TB or have previously had evidence of active TB and did not receive appropriate and documented treatment
 - g. clinically serious infection or received IV antibiotics for an infection, within the past 4 weeks of randomization
- Note: A recent viral upper respiratory tract infection or uncomplicated urinary tract infection should not be considered clinically serious.
- h. any other active or recent infection within 4 weeks of randomization that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study
- [29] have been exposed to a live vaccine within 12 weeks prior to planned randomization or are expected to need/receive a live vaccine during the course of the study (with the exception of herpes zoster vaccination).
- Note: Patients eligible for herpes zoster vaccine (as per local guidelines) who have not received it prior to screening will be encouraged to do so prior to randomization; vaccination must occur >4 weeks prior to randomization and start of investigational product. Patients will be excluded if they were exposed to herpes zoster vaccination within 4 weeks of planned randomization.
- [30] have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within the 2 years prior to screening

- [31] 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:
- Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the “Suicidal Ideation” portion of the Columbia Suicide Severity Rating Scale (C-SSRS) or
 - Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the “Suicidal Ideation” portion of the C-SSRS or
 - 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. Of course, if this situation arises, it is likely the subject should be referred to a psychiatrist or appropriately trained professional.

- [32] 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

Other Exclusions

- [33] 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 currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- [35] have participated, within the last 30 days in a clinical study involving an investigational product. If the previous investigational product has a long half-life (2 weeks or longer), at least 3 months or 5 half-lives (whichever is longer) should have passed.
- [36] have previously been randomized in this study or any other study investigating baricitinib
- [37] 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, regardless of whether biological or legally adopted
- [38] are Lilly or Incyte employees or their designee

Diagnostic Assessments

- [39] 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
- [40] have evidence of active TB or latent TB
- a. have evidence of active TB, defined in this study as the following:
 - documented by a positive PPD test (≥ 5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening.
 - The 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. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.

Exception: Patients with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening.

- b. Have evidence of untreated/inadequately or inappropriately treated latent TB, defined in this study as the following:
 - documented to have a positive PPD test (≥ 5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
 - PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study); 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 considered to have latent TB. 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 considered to have latent TB (for purposes of this study).

Exception: Patients who have evidence of latent TB may be enrolled if he or she completes at least 4 weeks of appropriate treatment prior to randomization and agrees to complete the remainder of treatment while in the trial.

Exception: Patients with a history of latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening.

[41] have a positive test HBV infection defined as:

- a. positive for hepatitis B surface antigen (HBsAg), or
- b. positive for hepatitis B core antibody (HBcAb) and positive 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.

[42] have HCV infection (positive for anti-hepatitis C antibody with confirmed presence of HCV 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.

[43] have evidence of HIV infection and/or positive HIV antibodies

[44] 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 have TSH marginally outside the laboratory's normal reference range and are receiving stable thyroxine replacement therapy may participate if the treating physician has documented that the thyroxine replacement therapy is adequate for the patient.

[45] have any of the following specific abnormalities on screening laboratory tests:

- a. aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2 x the upper limit of normal (ULN)
- b. alkaline phosphatase (ALP) ≥ 2 x ULN
- c. total bilirubin ≥ 1.5 x the ULN
- d. hemoglobin < 10.0 g/dL (100.0 g/L)

- e. total white blood cell count <2500 cells/ μL ($<2.50 \times 10^3/\mu\text{L}$ or <2.50 GI/L)
- f. neutropenia (absolute neutrophil count [ANC] <1200 cells/ μL) ($<1.20 \times 10^3/\mu\text{L}$ or <1.20 GI/L)
- g. lymphopenia (lymphocyte count <750 cells/ μL) ($<0.75 \times 10^3/\mu\text{L}$ or <0.75 GI/L)
- h. thrombocytopenia (platelets $<100,000/\mu\text{L}$) ($<100 \times 10^3/\mu\text{L}$ or <100 GI/L)
- i. eGFR <40 mL/min/1.73 m² (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine 2009 equation)

Note: For cases with any of the aforementioned laboratory abnormalities (Exclusion Criteria [44] and [45]), 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 must sign a new ICF, repeat all necessary screening procedures, and will be assigned a new identification number.

If a patient undergoes rescreening, radiographic images acquired as part of initial screening and within 6 months of randomization may be used.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of placebo, baricitinib 1-mg, baricitinib 2-mg, and baricitinib 4-mg administered orally once a day. [Table JAIN.3](#) shows the treatment regimens.

Table JAIN.3. Treatment Regimens

Regimen	Investigational Product Supplied	Dose
Baricitinib 4-mg QD ^a	Baricitinib 4-mg tablets	3 tablets per day
	Placebo to match 2-mg tablets	
	Placebo to match 1-mg tablets	
Baricitinib 2-mg QD	Baricitinib 2-mg tablets	3 tablets per day
	Placebo to match 4-mg tablets	
	Placebo to match 1-mg tablets	
Baricitinib 1-mg QD	Baricitinib 1-mg tablets	3 tablets per day
	Placebo to match 4-mg tablets	
	Placebo to match 2-mg tablets	
Placebo QD	Placebo to match 4-mg tablets	3 tablets per day
	Placebo to match 2-mg tablets	
	Placebo to match 1-mg tablets	

Abbreviation: QD = once daily.

^a The baricitinib dose for patients randomized to the 4-mg QD treatment group who have renal impairment (defined as eGFR <60 mL/min/1.73 m²) will be 2-mg QD.

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

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

7.1.1. Packaging and Labeling

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

- 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.

Packaging for each dose will include 3 tablets per day. 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 JAIN.3](#).

Investigational product tablets will be provided in blister packs.

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

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized in a 1:1:2:1 ratio to receive placebo QD, baricitinib 1-mg QD, 2-mg QD, or 4-mg QD to double-blind treatment at Visit 2 (Week 0). Randomization will be stratified by geographic region if the planned country allocation justifies, and disease severity at baseline (IGA 3 versus 4). Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign cartons, each containing 4 blister packs of double-blind investigational product tablets to each patient, starting at Visit 2 (Week 0), and at each visit up to and including Visit 28 (Week 200). Site personnel will confirm that they have located the correct carton by entering a confirmation number found on the carton into the IWRS.

7.2.1. Selection and Timing of Doses

The investigational product (3 tablets from blister pack) should be taken once daily without regard to food and, if possible, at approximately the same time every day, usually at the start of the patient's day, to aid patient compliance.

7.2.2. Dose Adjustment for Renal Impairment

The rationale of dose adjustment for patients with documented renal impairment (defined as screening eGFR ≥ 40 to < 60 mL/min/1.73 m²) is detailed in Section [5.5.1](#).

The dose adjustment for renal impairment will be managed by IWRS to ensure maintenance of the treatment blind. The eGFR value from the screening visit (Visit 1) will be entered into IWRS at Visit 2, and IWRS will assign the treatment doses accordingly.

Patients with documented renal impairment (defined as screening eGFR ≥ 40 to < 60 mL/min/1.73 m²), who are randomized to the 4-mg active treatment arm will receive a dose of 2-mg QD by the IWRS. For patients randomized to the 2-mg dose or 1-mg dose, there will be no dose adjustment based on renal function.

No dose adjustment will be made for patients with screening eGFR ≥ 60 mL/min/1.73 m². These patients who are randomized to active treatment will receive their assigned dose, either baricitinib 4-mg, 2-mg, or 1-mg, respectively.

During the study, for patients with documented renal impairment when the subsequent eGFR falls < 30 mL/min/1.73 m², investigational product will be withheld until their eGFR becomes ≥ 40 mL/min/1.73 m², whereupon the investigational product dosing may resume. For patients with screening eGFR ≥ 60 mL/min/1.73 m², when the subsequent eGFR falls to < 40 mL/min/1.73 m², investigational product will be withheld until their eGFR becomes ≥ 50 mL/min/1.73 m², whereupon the investigational product dosing may resume (Section [8.1.1](#)).

7.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. All study assessments will be performed by study personnel who are blinded to the patient's treatment group. Except in clinical circumstances where unblinding is required, the patients, investigators, Lilly study team, and any personnel interacting directly with patients or investigative sites will remain blinded to baricitinib and placebo assignment until after completion of the double-blinded treatment periods. It is expected that the need for unblinding a patient's treatment prior to completion of the double-blinded 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. 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. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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

Processes to maintain blinding during the interim analysis conducted by the DMC are described in Section [10.3.7.1](#).

7.4. Dosage Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

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

Follow storage and handling instructions on the investigational product packaging.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit during the treatment period (Visit 4 through Visit 28) by counting returned tablets.

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

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

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

7.7. Concomitant Therapy

All concomitant medication, whether prescription or over the counter, used at baseline and/or during the course of the study, must be recorded on the Concomitant Medication electronic case report form (eCRF). Patients will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study. For AD therapies permitted as part of rescue therapy, see Section 7.7.5.

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 up to Week 104. After Week 104, the continued use of emollients is encouraged. Moisturizers with antipruritics or antiseptics are not permitted up to Week 104. 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.
- Background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment) are to be used on active lesions in Periods 2 and 3, as described in Section 7.7.2.
- High- or ultra-high-potency TCS are only permitted as rescue therapy as described in Section 7.7.5 (Rescue Therapy).
- During Period 4, concomitant use of TCS may be continued, as directed by the investigator, as per clinical practice.
- TCIs (e.g., tacrolimus and pimecrolimus), or topical PDE-4 inhibitor (i.e., crisaborole, where approved) are permitted in place of TCS 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.
- Phototherapy, including therapeutic phototherapy (psoralen and ultraviolet A, ultraviolet B, excimer laser), is permitted as rescue therapy in Periods 2 to 4 (see Section 7.7.5, Rescue Therapy); however, it requires a temporary interruption of investigational product (see Section 8.1.1).

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 seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations.

For those patients on stable dosing of prescription sleep medications 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 in the Concomitant Therapy of Special Interest eCRF.

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

7.7.2. Use of Topical Corticosteroids

A washout period of 14 days is required for all TCS prior to randomization at Visit 2.

At baseline (Week 0, Visit 2) and up to Week 104 (Visit 22), patients will receive triamcinolone 0.1% cream (or equivalent-potency TCS) and hydrocortisone 2.5% ointment (or equivalent-potency TCS). See “Choice of Background Topical Corticosteroid” below. Triamcinolone 0.1% cream (moderate-potency TCS) should be applied at least once daily to affected areas until lesions are under control (clear or almost clear). Patients should then switch to hydrocortisone 2.5% ointment (low-potency TCS) and treat previously affected areas once-daily for 7 days and then stop. Hydrocortisone 2.5% ointment (low-potency TCS) may also be used to replace triamcinolone 0.1% cream (moderate-potency TCS) on areas of thin skin (face, neck, folds, and genital areas) and areas with skin atrophy.

If lesions reappear during the course of the study, the patients should resume the once-daily applications of triamcinolone 0.1% cream (moderate-potency TCS) or hydrocortisone 2.5% ointment (low-potency TCS) as described above.

For patients whose lesions persist or worsen despite the use of emollients and low- and/or moderate-potency TCS and/or patients who require daily applications on large surfaces may be considered for topical rescue with high- or ultra-high-potency TCS (see Section 7.7.5 for details).

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.

After Week 104, use of TCS may be continued as directed by the investigator, as per clinical practice. Background TCS will no longer be provided nor reimbursed to study participants by the sponsor, unless required by local law.

Choice of Background Topical Corticosteroid

Where possible, triamcinolone cream 0.1% and/or hydrocortisone 2.5% ointment will be supplied by the sponsor for use as background TCS up to Week 104 (Visit 22). In the event of these specific TCS being unavailable, an alternate, equivalent-potency TCS may be provided by the sponsor (see below). Topical corticosteroid use, when supplied by the sponsor, should be recorded via weight of dispensed and returned tubes as indicated in the Schedule of Activities (Section 2). In the event that the sponsor is unable to supply TCS, commercially available triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment may be supplied by the sites.

- Where providing triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment is not possible, an equivalent-potency TCS cream and/or ointment that is in line with local practices can be supplied by the sites. Refer to [Appendix 7](#) for guidance on potency equivalence.
- Where possible, TCS use when supplied by the site should also be recorded via weight of dispensed and returned tubes, as indicated in the Schedule of Activities (Section 2); however, where this is not practical, this information does not need to be recorded, and will not be considered a protocol violation.
- If the TCS supplied by the sponsor is not considered suitable for an individual patient, an equivalent-potency TCS cream and/or ointment that is in line with local practices can be supplied by the sites. Refer to [Appendix 7](#) for guidance on potency equivalence.

Choice of High- and Ultra-High-Potency Topical Corticosteroids for Rescue

The use and choice of specific high- or ultra-high-potency TCS for rescue is at the discretion of the investigator and it will not be provided by the sponsor. The weights of dispensed and returned tubes of the high- and ultra-high-potency TCS are not required.

Other Topical Treatments

Investigators may also select to use TCIs and/or crisaborole in countries where approved, in place of TCS. If TCIs or crisaborole are prescribed, use should be limited to problem areas (e.g., face, neck, skin folds, genital areas, etc.).

Use of all topical treatments for AD must be recorded in the CRF.

7.7.3. Use of Antihistamines

Antihistamine ophthalmic preparations are permitted during the study.

During Period 2, nonsedating antihistamines are permitted, including, but not limited to, acrivastine, bilastine, cetirizine, desloratadin, fexofenadine, levocetirizine, loratadine, mizolastine, and rupatadine.

During Period 2, sedating antihistamines, including, but not limited to, alimemazine, chlorphenamine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, ketotifen, and promethazine, are **not** permitted and will require a 28-day washout prior to randomization.

During Periods 3, 4, and 5, there are no restrictions for antihistamine use; both sedating and nonsedating antihistamines are permitted.

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 investigational product will be permanently discontinued.

- topical antihistamines or sedating, systemic antihistamines in Period 2 (see Section 7.7.3, Use of Antihistamines, for additional information).
- self-treatment with tanning booth
- bleach baths (swimming in chlorinated pools is permitted)

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 investigational product is required.

- live vaccines (including Bacillus Calmette-Guérin [BCG] or herpes zoster), (see Exclusion Criterion [29])
 - For BCG vaccination, investigational product should be temporarily interrupted for 12 weeks.
 - For herpes zoster vaccination, investigational product should be temporarily interrupted for 4 weeks.
- 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 investigational product is required.
- probenecid: if a patient is inadvertently started on probenecid, investigational product should be temporarily interrupted, and can be resumed after the patient has discontinued probenecid. If a patient is not able to discontinue probenecid, then investigational product should be permanently discontinued.
- phototherapy, including therapeutic phototherapy (psoralen and ultraviolet A, ultraviolet B, excimer laser) as rescue therapy in Period 2 or 3. Investigational product should be temporarily interrupted until completion of the phototherapy.

Prohibited Medications Requiring Permanent Discontinuation of Investigational Product

- 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).

- 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).

Note: In the event that these prohibited medications were inadvertently used, agreement and documentation to continue investigational product must be sought from sponsor.

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 Period 2: Week 0 (Visit 2) up to Week 52 (Visit 14)

Control of AD symptoms should be attempted by avoiding exacerbating factors, intensifying emollient applications, and using only the permitted study treatments, including background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment) (see Section [7.7.2](#)).

Rescue with High- and Ultra-High-Potency TCS

Patients whose lesions persist or worsen despite the use of emollients and background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment) and/or patients who require prolonged applications of triamcinolone 0.1% cream (moderate-potency TCS) on large surfaces may be considered for rescue to high- or ultra-high-potency TCS (see [Appendix 7](#) for TCS potency).

High- or ultra-high-potency TCS may be used once daily for up to 14 consecutive days or 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 high- or ultra-high-potency TCS should be stopped, and low- and/or moderate-potency TCS (e.g., triamcinolone 0.1%, hydrocortisone 2.5% ointment) should be used once daily for an additional 7 days, then stopped.

Patients rescued with high- or ultra-high-potency TCS will continue to take investigational product and use of topical rescue therapy will be documented in the eCRF.

Rescue with Phototherapy

Patients may also be rescued with phototherapy at the discretion of the investigator. Patients rescued with phototherapy will remain in the study and be required to temporarily interrupt use of investigational product until completion of the phototherapy (see Section [8.1.1](#) for Temporary Interruption of Investigational Product).

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). These patients will be required to discontinue investigational product and proceed to the ETV before initiating systemic treatment. However, patients rescued to systemic therapies prior to the primary endpoint (Week 16) should be encouraged to continue with study visits and assessments through Visit 8.

7.7.5.2. Rescue during Periods 3 and 4: from Week 52 (Visit 14) to Week 200 (Visit 28)

In Period 3, all patients will continue to use concomitant background TCS (e.g., triamcinolone 0.1% cream and hydrocortisone 2.5% ointment) as described in Section 7.7. In Period 4, use of concomitant may continue as directed by the investigator, as per clinical practice. All patients may be rescued at any time with high- or ultra-high-potency TCS or phototherapy as described in Section 7.7.

As mentioned in Sections 5.1.3 and 5.1.4, patients who reach an IGA ≥ 3 after entry into the randomized downtitration substudy will be automatically retreated with their presubstudy dose of baricitinib.

Patients not eligible for the substudy and who present with an IGA ≥ 3 at Week 52 or anytime thereafter will automatically be rerandomized at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD, but this will only occur once. Patients randomized to baricitinib 4-mg QD at baseline (Week 0, Visit 2) will stay on this dose for the remainder of the trial regardless of IGA.

Patients whose disease cannot be controlled by the measures described above may be rescued to systemic therapies (conventional systemics or biologics). Whenever possible during this Period, it is recommended to wait for at least 4 weeks after the visit at which the patient has reached IGA ≥ 3 to initiate rescue with systemic therapies.

Patients rescued with high- or ultra-high-potency TCS will continue to take investigational product and use of topical rescue therapy will be documented in the eCRF.

Patients rescued with phototherapy will remain in the trial and will be required to temporarily interrupt the use of investigational product until completion of the phototherapy.

Patients who need rescue with systemic therapies (conventional systemics or biologics) during Period 3 will be required to discontinue investigational product and to proceed to the ETV before initiating systemic treatment.

7.8. Treatment after the End of the Study

Period 4 will provide patients who have completed Week 104 visit and have not met criteria for permanent discontinuation, the possibility to remain in the trial for up to 96 additional weeks (up to Week 200) and thus provide patients the opportunity to continue study treatment until the anticipated approval of baricitinib in this indication.

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 Interruption of Investigational Product

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

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in [Table JAIN.4](#), 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 are 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 JAIN.4](#) may be restarted at the discretion of the investigator.

Table JAIN.4. Medical and Laboratory 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/ μ L (<2.00x10 ³ / μ L or <2.00 GI/L)	WBC count \geq 2500 cells/ μ L (\geq 2.50x10 ³ / μ L or \geq 2.50 GI/L)
ANC <1000 cells/ μ L (<1.00x10 ³ / μ L or <1.00 GI/L)	ANC \geq 1200 cells/ μ L (\geq 1.20x10 ³ / μ L or \geq 1.20 GI/L)
Lymphocyte count <500 cells/ μ L (<0.50x10 ³ / μ L or <0.50 GI/L)	Lymphocyte count \geq 750 cells/ μ L (\geq 0.75x10 ³ / μ L or \geq 0.75 GI/L)
Platelet count <75,000/ μ L (<75x10 ³ / μ L or <75 GI/L)	Platelet count \geq 100,000/ μ L (\geq 100x10 ³ / μ L or \geq 100 GI/L)
eGFR <40 mL/min/1.73 m ² (from serum creatinine) for patients with screening eGFR \geq 60 mL/min/1.73 m ²	eGFR \geq 50 mL/min/1.73 m ²
eGFR <30 mL/min/1.73 m ² (from serum creatinine) for patients with screening eGFR \geq 40 to <60 mL/min/1.73 m ²	eGFR \geq 40 mL/min/1.73 m ²
ALT or AST >5 x ULN	ALT and AST return to <2 x ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin \geq 10 g/dL (\geq 100.0 g/L)
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection

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

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

For specific guidance on temporary interruption of investigational product after use of a prohibited medication, please refer to Section 7.7.4, Prohibited Medications and Procedures.

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

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

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

8.1.2. Permanent Discontinuation from Investigational Product

Investigational product should be permanently discontinued if the patient is rescued with systemic therapies to treat AD and/or the patient requests to discontinue investigational product.

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

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

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

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

- white blood cell count <1000 cells/ μ L ($1.00 \times 10^3/\mu$ L or 1.00 GI/L)
- ANC <500 cells/ μ L ($0.50 \times 10^3/\mu$ L or 0.50 GI/L)
- lymphocyte count <200 cells/ μ L ($0.20 \times 10^3/\mu$ L or 0.20 GI/L)
- hemoglobin <6.5 g/dL (<65.0 g/L).

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

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

- pregnancy
- malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- hepatitis B virus DNA is detected with a value above limit of quantitation or 2 sequential tests return a value of below the limit of quantitation (see Section 9.4.8).
- certain prohibited medications are taken per Section 7.7.4, Prohibited Medications and Procedures.
- development of a VTE

Note: Patients who develop a VTE may have additional follow up and testing recommended (see Appendix 8).

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

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor clinical research physician (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 investigational product. Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

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

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

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

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

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

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

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessment

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

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

9.1.2. Secondary Efficacy Assessments

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

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

9.1.2.2. SCORing Atopic Dermatitis

The SCORing Atopic Dermatitis (SCORAD) index uses the rule of nines to assess disease extent and evaluates 6 clinical characteristics to determine disease severity: (1) erythema, (2) edema/papulation, (3) oozing/crusts, (4) excoriation, (5) lichenification, and (6) dryness. The SCORAD index also assesses subjective symptoms of pruritus and sleep loss. These 3 aspects: extent of disease, disease severity, and subjective symptoms combine to give a maximum possible score of 103 (Stalder and Taieb 1993; Oranje et al 2007).

9.1.3. Health Outcomes and Quality-of-Life Measures

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

9.1.3.1. Hospital Anxiety Depression Scale

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

9.1.3.2. Patient-Oriented Eczema Measure

The POEM is a simple, 7-item, patient-administered scale that assesses disease severity in children and adults. Patients respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the last week. Response categories include “No days,” “1 to 2 days,” “3 to 4 days,” “5 to 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).

9.1.3.3. 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.” The overall severity of a patient’s itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al. 2015; Kimball et al. 2016).

9.1.3.4. 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. Patients 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.

9.1.3.5. 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.” The 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.

9.1.3.6. Patient Global Impression of Severity

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

9.1.3.7. Dermatology Life Quality Index

The DLQI is a simple, patient-administered, 10-item, validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the “last week.” Response categories include “not at all,” “a lot,” and “very much,” with corresponding scores of 1, 2, and 3, respectively, and unanswered (“not relevant”) responses scored as 0. Scores range from 0 to 30, with higher scores indicating greater impairment of QoL. A DLQI total score of 0 to 1 is considered as having no effect on a patient’s health-related QoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2015).

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

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

9.1.3.9. Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis

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

9.1.3.10. Medical Outcomes Study 36-Item Short Form Health Survey Version 2 Acute (SF-36)

The SF-36v2 Acute measure is a subjective, generic, health-related QoL instrument that is patient reported and consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality (Ware and Sherbourne 1992). Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale, with higher scores indicating better health status or functioning. In addition, 2 summary scores, the PCS (physical component score) and the MCS (mental component score), will be evaluated based on the 8 SF-36v2 Acute domains.

9.1.4. Appropriateness of Assessments

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

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

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

cause-and-effect relationship between the investigational product, study device and/or study procedure, and the AE. The investigator answers yes/no when making this assessment.

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

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

9.2.1. Serious Adverse Events

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

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

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

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

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

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

9.2.2. Adverse Events of Special Interest

Adverse events of special interest will include the following:

- infections (including TB, herpes zoster, or opportunistic infections)
- malignancies (except for successfully treated basal or squamous cell skin carcinoma)
- hepatic events (see Section 9.4.10)
- 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 investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

Refer to the IB.

9.4. Safety

Any clinically significant findings from 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 should be measured according to the Schedule of Activities (Section 2).

9.4.3. Physical Examination

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. Laboratory Tests

For each patient, laboratory tests detailed in [Appendix 2](#) should be conducted according to the Schedule of Activities (Section 2). With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

9.4.5. Columbia Suicide Severity Rating Scale

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

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception 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. Chest x-ray and Tuberculosis Testing

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

Investigators should follow local guidelines for monitoring patients for TB if a patient is at high risk for acquiring TB or reactivation of latent TB.

9.4.8. Hepatitis B Virus DNA Monitoring

Patients who are HBcAb positive and HBV DNA negative (undetectable) at Visit 1 will require periodic measurement of HBV DNA as per study schedule (Section 2), regardless of their hepatitis B surface antibody (HBsAb) status.

The following actions should be taken in response to HBV DNA test results:

- If a single result is obtained with a value “below limit of quantitation,” the test should be repeated within approximately 2 weeks. If the repeat test result is “target not detected,” 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 investigational product (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 DMC (an advisory group for this study formed to protect the integrity of data; refer to Interim Analyses section [Section 10.3.7]) can conduct additional analyses of the safety data.

The Lilly clinical research physician will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical

research physician will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist and periodically review trends in safety data and laboratory analytes. Any concerning trends in frequency or severity noted by an investigator and/or Lilly (or designee) may require further evaluation.

All deaths and SAE reports will be reviewed 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 investigational product, only Lilly Global Patient Safety will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this trial and minimize any potential for bias while providing for appropriate safety monitoring.

Investigators will monitor vital signs and carefully review findings that may be associated with cardiovascular 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 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.

9.4.10. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥ 3 x ULN, ALP ≥ 2 x ULN, or elevated TBL ≥ 2 x ULN, liver testing ([Appendix 4](#)) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator 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.

Discontinuation criteria of investigational products, either temporary interruption or permanent discontinuation, due to abnormal ALT, AST, TBL, or ALP, are detailed in [Section 8.1](#).

9.4.10.1. Hepatic Safety Data Collection

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

- elevation of serum ALT to ≥ 5 x ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2 x ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥ 2 x ULN on 2 or more consecutive blood tests

- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

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

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenetics

9.7.1. *Blood Samples for Pharmacogenetic Research*

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

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

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.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable

examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Blood samples for 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 for a maximum of 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.

9.9. Medical Resource Utilization and Health Economics

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

10. Statistical Considerations

10.1. Sample Size Determination

Study JAIN will aim to enroll 500 patients ≥ 18 years of age. Ignoring stratification, the proposed sample size will ensure a $>90\%$ power based on the Chi-square test to detect an absolute difference of approximately 25% between the 4-mg baricitinib and the placebo treatment groups, and the 2-mg baricitinib and the placebo treatment groups, each using a 2-sided alpha of 0.025 and assuming approximately 20% placebo response rate for the primary endpoint. These assumptions are based on what was observed in the Phase 3 study (JAIY).

Sample size and power estimates were obtained from nQuery[®] Advisor 7.0.

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.

Unless otherwise specified, safety analyses will be conducted on all randomized patients who receive at least 1 dose of investigational product they were randomized to in Study JAIN and who did not discontinue from the study for the reason “Lost to Follow-up” at the first postbaseline visit.

Patients will be analyzed for efficacy, health outcomes, and safety according to the treatment to which they were assigned. Further details will be described in the SAP, including but not limited to, additional populations for the randomized down-titration substudy. Significant protocol violations will be described in the SAP.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. 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. 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. Treatment comparisons of discrete efficacy variables between baricitinib and placebo will be made using a logistic regression analysis with baseline disease severity (vIGA AD), baseline score and treatment group in the model. Region may be added as an additional factor if the planned country allocation justifies, and stratification has not resulted in empty strata. This will be finalized in the SAP. If appropriate, treatment-by-region interaction may be added to the

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 the effect) or qualitative (the treatment is beneficial for some but not all regions). The percentages, difference in percentages, and 95% confidence interval (CI) of the difference in percentages will be reported. The p-value from the Fisher exact test will also be produced. Additional relative measures, for example, odds ratio, may be reported as appropriate.

When evaluating continuous measures over time, a restricted maximum likelihood-based mixed model for repeated measures (MMRM) will be used. The model will include treatment, baseline severity (vIGA AD), visit, and treatment-by-visit interaction as fixed categorical effects and baseline score and baseline score-by-visit interaction as fixed continuous effects. Region may be added as an additional factor if the planned country allocation justifies. 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 disease severity, treatment group, and baseline value in the model. Region may be added as an additional factor if the planned country allocation justifies. Type III tests for LSMs will be used for statistical comparison between treatment groups. The LSM difference, standard error, p-value, and 95% CI may also be reported. The methods used to handle missing data will be specified in the SAP.

Time-to-event analysis may be done and would be analyzed using a Cox proportional hazards model with disease severity and treatment group in the model. Region may be added as an additional factor if the planned country allocation justifies. Hazard ratio with CIs may be reported. Kaplan–Meier curves may also be produced. Diagnostic tests for checking the validity of the proportional hazards assumption may be performed and these would be described in detail in the SAP. If the assumption of proportional hazards is not justified, nonproportionality may be modeled by stratification, as the most likely variable that interacts with time is categorical, that is, disease severity.

Fisher 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.

10.3.1.1. Missing Data Imputation

- 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 EASI50/75/90 from the time of discontinuation and onward. Patients who receive rescue therapy (high or ultra-high potency TCS, phototherapy, or systemic therapies for treatment of AD, see Section 7.7.5) will be analyzed as nonresponders from the point of rescue and onward. An additional analysis will be performed that includes all available data regardless of whether rescue medication was given or not.
- Continuous variables such as EASI and SCORAD scores will be assumed to be missing from the point of rescue or discontinuation and then an MMRM analysis will be performed. An additional analysis will be performed that includes all available data regardless of whether rescue medication was given or not.
- Last observed carried forward: An additional analysis will be performed that uses the last observed value 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.

There will be further discussion on the relevant estimands including appropriate methods for analysis and imputation of missing data in the SAP. This will include specifications of additional sensitivity analyses for the primary and key secondary endpoints such as tipping point as well as a reference-based multiple imputation method.

10.3.1.2. Adjustment for Multiple Comparisons

Multiplicity controlled analyses will be conducted on the primary and major secondary endpoints in order 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). Details of the specific graphical testing scheme (including 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 4-mg + TCS patients achieving EASI75 at Week 16
- proportion of baricitinib 2-mg + TCS patients achieving EASI75 at Week 16

Key Secondaries:

- proportion of baricitinib 1-mg + TCS patients achieving EASI75 at Week 16

Evaluated for 4-mg + TCS, 2-mg + TCS, and 1-mg + TCS:

- proportion of patients achieving IGA of 0 or 1 and ≥ 2 -point improvement from baseline at 16 weeks
- proportion of patients achieving EASI90 at 16 weeks
- percent change from baseline in EASI score at 16 weeks
- proportion of patients achieving SCORAD75 at 16 weeks
- proportion of patients achieving a 4-point improvement in Itch NRS at 16 weeks
- proportion of patients achieving a 4-point improvement in Itch NRS at 4 weeks
- proportion of patients achieving a 4-point improvement in Itch NRS at 2 weeks
- proportion of patients achieving a 4-point improvement in Itch NRS at 1 week
- mean change from baseline in the total score of Item 2 of the ADSS at 16 weeks
- mean change from baseline in the total score of Item 2 of the ADSS at 1 week
- mean change from baseline in Skin Pain NRS at 16 weeks
- proportion of patients achieving IGA of 0 or 1 with a ≥ 2 -point improvement at Week 24
- proportion of patients achieving EASI75 at 24 weeks.

10.3.1.3. Adjustment for Unblinding of Primary Analyses 24-Week Data

When all patients have completed their Week 24 assessments, the primary analysis for the purpose of regulatory submission will be made. The evaluation of the primary and key secondary endpoints will be adjusted for multiplicity.

Although the regulatory submission team will be unblinded to the 24-week data and to patient treatment assignments, they will not have access to efficacy data after 24 weeks until all patients have completed Week 52. In order to maintain the blind for efficacy data beyond Week 24, post-lock activities will incorporate appropriate security measures, including restricted provision of data. The study team preparing for the submission is authorized to evaluate unblinded efficacy and safety analyses. Study sites will not receive any patient level efficacy and safety information. Unblinding details will be specified in a separate unblinding plan document to ensure proper firewalls between the study team and study sites.

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, and along with their reason for discontinuation. Reasons for discontinuation from the study will be summarized by treatment group. This will be done for Period 2 and Period 3 of the study. Additional summaries that may be produced for other populations will be documented in the SAP. Reasons for discontinuation from the study will be summarized by treatment group and compared between groups with Fisher exact test.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group for Period 2 and Period 3 of Study JAIN. Additional summaries that may be produced for other populations will be documented in the SAP. 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. The medications will be coded accordingly.

10.3.2.4. Treatment Compliance

Treatment compliance with the randomly assigned study medication will be evaluated at every clinic visit through the counts of returned investigational product tablets. A patient will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses during the study, i.e., 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, i.e., compliance $\geq 120\%$.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy measure is categorical outcome of EASI75 at Week 16. EASI75 is defined as having an improvement of at least 75% from baseline. Primary analysis will be conducted using a logistic regression as described above with treatment and the stratification variables (disease severity; region as appropriate) in the model, to test the treatment difference in proportion. Nonresponder imputation for missing data as described above will be used.

Additional analysis of the primary efficacy outcome will include analyzing the outcome as observed, i.e., 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, i.e., using the same logistic regression model. Nonresponder imputation will be used for these analyses unless otherwise noted.

- IGA score of 0 or 1 (clear or almost clear skin) and ≥ 2 -point improvement from baseline at Week 16. Besides NRI, this outcome will also be analyzed using observed cases, that is, whether rescue medication was given.
- EASI75 at Week 52, Week 24, and Week 4. EASI75 is defined as having an improvement of at least 75% from baseline. Besides NRI, this outcome will also be analyzed using observed cases, i.e., 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. 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.
- 4-point improvement in Itch NRS at 24 weeks, 16 weeks, 4 weeks, 2 weeks, and 1 week
- IGA score of 0 or 1 (clear or almost clear skin) and ≥ 2 -point improvement from baseline at Week 52, Week 24, and Week 4
- IGA of 0 at 16 weeks

The following continuous measures will be analyzed with the MMRM model described above unless otherwise noted. Contrasts within the MMRM model 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 Items 1, 2 and 3
 - EASI score
 - SCORAD score
 - Body Surface Area
 - Itch NRS
 - Skin Pain NRS
 - POEM total score
 - PGI-S-AD
 - HADS
 - DLQI total score
 - WPAI-AD
 - EQ-5D-5L

The EASI total score and SCORAD total score will also be analyzed as observed, i.e., 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 high- or ultra-high-potency TCS

- Patients requiring rescue with systemic treatments

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

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

10.3.4. Safety Analyses

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

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

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

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

The incidence and average duration of investigational product interruptions will be summarized and compared descriptively among treatment groups. Various techniques may be used to estimate the effects of investigational product interruptions on safety measures. Further analyses may be performed and will be planned in the SAP.

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

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Other Analyses

10.3.6.1. Health Economics

The health outcome measures will be analyzed using methods described for continuous or categorical data as described for efficacy measures in Section 9.1.3. More detailed analytical methods will be described in the SAP.

10.3.6.2. 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 (disease severity; region as appropriate), the subgroup variable (e.g., sex), and the subgroup-by-treatment interaction. If the interaction is statistically significant at $\alpha = 0.10$, the nature of the interaction will be explored, that is, within each subgroup the treatment effect will be estimated. Similarly, for the continuous variables of EASI, the MMRM model will include additional variables for subgroup and the subgroup by treatment interaction.

Treatment effects for subgroups defined by IGA, age, race, sex, and region (as appropriate) will be assessed and reported regardless of whether the interaction test is significant or not.

10.3.7. Interim Analyses

10.3.7.1. Data Monitoring Committee

A DMC will oversee the conduct 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 dermatology, 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 data, etc. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients. The DMC may recommend continuation of the study, as designed; temporary suspension of enrollment; or the discontinuation of a particular dose regimen or the entire study. Although 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.

10.3.7.2. Adjudication Committee

A blinded Clinical Event Committee will adjudicate potential MACE (cardiovascular death, MI, stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary

revascularization such as coronary artery bypass graft or percutaneous coronary intervention), venous thrombotic events, and noncardiovascular deaths. Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the Charter.

10.3.7.3. Unblinded Study Team for the Primary Analyses for Regulatory Submission

A limited number of pre-identified individuals will have access to the 24-week unblinded data when all the patients complete Week 24 assessments. These individuals will not have access to efficacy data after 24 weeks until all patients have completed Week 52. In order to maintain the blind for efficacy data beyond Week 24, post-lock activities will incorporate appropriate security measures, including restricted provision of data. Only the blinded study team will communicate with sites on regular trial conduct issues, and study sites will not receive any patient level efficacy and safety information from the primary analyses for submission.

10.3.7.4. Other Interim Analyses

Besides DMC members and Unblinded Study Team for the Primary Analyses 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 primary analysis or final database lock for preparation of regulatory documents. Interim locks will be conducted at various timepoints to support regulatory submissions and scientific disclosures. The timing of the data lock(s) for the analysis of the efficacy data from the sub-study will be determined by the retreatment rates. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AD	atopic dermatitis
ADSS	Atopic Dermatitis Sleep Scale
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
blinding/masking	<p>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.</p> <p>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.</p>
BSA	body surface area
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRS	clinical research physician
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
CyA	cyclosporine A
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.
EQ-5D-5L	the European Quality of Life–5 Dimensions–5 Levels
ERB	ethical review board
ETV	early termination visit
FDA	the Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HADS	Hospital Anxiety Depression Scale
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
IGA	Investigator’s Global Assessment
IL	interleukin
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
INR	international normalized ratio

Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IWRS	interactive web-response system
JAK	Janus kinase
LSM	least squares mean
MACE	major adverse cardiovascular events
MI	myocardial infarction
MMRM	mixed-effects model of repeated measures
NRI	nonresponder imputation
NRS	Numeric Rating Scale
PDE-4 inhibitor	phosphodiesterase type 4 inhibitor
PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PPD	purified protein derivative
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QD	once daily
QoL	quality of life
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
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
ULN	upper limit of normal
US	United States
VAS	visual analog scale
vIGA-AD	validated Investigator's Global Assessment for Atopic Dermatitis
VTE	venous thromboembolic event
WPAI-AD	the Work Productivity and Activity Impairment–Atopic Dermatitis

Appendix 2. Clinical Laboratory Tests

Hematology^{a,b}

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Absolute reticulocyte count
Mean cell volume
Mean cell hemoglobin
Mean cell hemoglobin concentration
Leukocytes (WBC)
Platelets

Absolute counts of:

Neutrophils, segmented
Neutrophils, juvenile (bands)
Lymphocytes
Monocytes
Eosinophils
Basophils

Urinalysis^{a,b,d}

Color
Specific gravity
pH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood
Leukocyte esterase
Nitrite

Lipids^{a,c}

Total cholesterol
Low-density lipoprotein
High-density lipoprotein
Triglycerides

Clinical Chemistry^{a,b}**Serum Concentrations of:**

Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Creatinine
Cystatin C
Uric acid
Calcium
Glucose
Albumin
Total protein
Estimated glomerular filtration rate (eGFR)^e
Creatine phosphokinase (CPK)

Other Tests^a

Hepatitis B Surface antigen (HBsAg)^f
Anti-Hepatitis B Core antibody (HBcAb)^f
HBV DNA^k
Anti-Hepatitis B Surface antibody (HBsAb)^f
Human immunodeficiency virus (HIV)^f
Hepatitis C antibody^{f,g}
Thyroid-stimulating hormone (TSH)
Exploratory storage samples (serum, plasma and mRNA)
Pregnancy Test^h
Follicle-stimulating hormone^{f,i}
Serum immunoglobulin (IgE)
QuantiFERON[®]-TB Gold or T-SPOT[®].TB^j
PPD (local testing)

Abbreviations: eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; 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 12 hours 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 for serum creatinine calculated by the central laboratory 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.
- ^h For all women of childbearing potential, a serum pregnancy test will be performed at Visit 1 and a local urine pregnancy test will be performed at 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 To confirm postmenopausal status for women ≥ 40 and < 60 years of age who have had a cessation of menses, an FSH test will be performed. Nonchildbearing potential is defined as an FSH ≥ 40 mIU/mL and a cessation of menses for at least 12 months.
- ^j The QuantiFERON[®]-TB Gold test is the preferred alternative to the PPD test for the evaluation of TB infection, and it may be used instead of the PPD test or T-SPOT[®].TB test and may be read locally. If the QuantiFERON[®]-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.
- ^k HBV DNA testing will be done in those patients who are HBcAb+ at screening.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. *Informed Consent*

The investigator is responsible for:

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

Appendix 3.1.2. *Recruitment*

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

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

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

- the protocol and related amendments and addenda, current Investigator's Brochure (IB), and updates during the course of the study

- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

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

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

Appendix 3.1.5. Investigator Information

Physicians with a specialty in dermatology 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

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

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

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

Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate

- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

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

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

Appendix 3.2.1. Data Capture System

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

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

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

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

Case report form data will be encoded and stored in InForm. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

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

Appendix 3.3. Study and Site Closure***Appendix 3.3.1. Discontinuation of Study Sites***

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I4V-MC-JAIN is described in the 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

Hemoglobin
 Hematocrit
 RBC
 WBC
 Neutrophils, segmented
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
 Platelets

Hepatic Chemistry^a

Total bilirubin
 Direct bilirubin
 Alkaline phosphatase
 ALT
 AST
 GGT
 CPK

Haptoglobin^a

Hepatic Coagulation^a

Prothrombin Time
 Prothrombin Time, INR

Hepatic Serologies^{a,b}

Hepatitis A antibody, total
 Hepatitis A antibody, IgM
 Hepatitis B surface antigen
 Hepatitis B surface antibody
 Hepatitis B Core antibody
 Hepatitis C antibody
 Hepatitis E antibody, IgG
 Hepatitis E antibody, IgM

Anti-nuclear antibody^a

Alkaline Phosphatase Isoenzymes^a

Anti-smooth muscle antibody (or anti-actin antibody)^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate 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. 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 9.4.10	Section 9.4.10	Section 8.1.1	Section 8.1.2
ALT/ AST	≥2x ULN	ALT ≥3x ULN (ALT only)	ALT ≥5x ULN on ≥2 consecutive tests (ALT only)	≥5x ULN	<ul style="list-style-type: none"> • >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	≥2x ULN	≥2x ULN on ≥2 consecutive tests	No applicable criteria	<ul style="list-style-type: none"> • >3x ULN • >2.5x ULN AND TBL >2x ULN • >2.5x ULN with symptoms^a
TBL	≥1.5x ULN	≥2x ULN	≥2x ULN (excluding Gilbert's syndrome)	No applicable criteria	<ul style="list-style-type: none"> • 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 6. 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 the following:

- 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 et al. (2014).

Appendix 7. Classification of Potency for Topical Corticosteroids

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

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

Appendix 8. 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 = factor Xa;
MTHFR = methylene tetrahydrofolate reductase; PT = prothrombin time; PTT = partial thromboplastin time.

**Appendix 9. Protocol Amendment I4V-MC-JAIN(e)
Summary**

**A Phase 3, Multicenter, Double-Blind, Randomized,
Placebo-Controlled Study Evaluating the Safety and
Efficacy of Baricitinib in Combination with Topical
Corticosteroids in Adult Patients with
Moderate-to-Severe Atopic Dermatitis Who Have
Experienced Failure to Cyclosporine or Are Intolerant to,
or Have Contraindication to, Cyclosporine**

Overview

Protocol I4V-MC-JAIN(d) has been amended. This amendment is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the council of the European Union. The new protocol is indicated by amendment (e) 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 table below. In addition, minor typographical corrections not affecting the content have been made in the document.

Amendment Summary for Protocol I4V-MC-JAIN Amendment (e)

Section # and Name	Description of Change	Brief Rationale
Section 1	A bridging extension period was added between the Long-Term Extension (Period 3) and the Post-Treatment Follow-Up Period (Period 4). The Post-Treatment Follow-Up Period was renamed Period 5.	The Bridging extension period will allow for additional long-term safety information on the IP to be collected and will provide to study participants the opportunity to continue study treatment until commercial availability of baricitinib in this indication in the respective countries or for a maximum of 96 additional weeks.
Section 1 and Section 10.3 1	Text was added to provide additional detail of the logistic regression analysis.	Text was added to clarify that baseline disease severity would be assessed via investigator's global assessment and that baseline score will also be included in the model.
Section 2 - Table JAIN.1.	Included an additional six visits to reflect the bridging extension period. Added collection of PGI-S-AD up to Week 68.	Updated to reflect the extension of the duration of the trial by approximately two years (up to Week 200). To align with the collection of the other PROs on the ediaries.
Section 4 – Table JAIN.2.	Exploratory efficacy analysis wording was added to the Exploratory Endpoints section.	Updated to indicate that additional efficacy analyses may be performed beyond Week 104.
Section 5.1 and Figure JAIN.1.	Reflected the addition of the bridging extension period (now Period 4). Figure JAIN.1 was updated to include the additional period.	Updated to reflect the extension of the duration of the trial by approximately two years (up to Week 200).
Section 5.1.4	Replaced by the design details of the Bridging Extension Period. The Post-Treatment Follow-Up Period design details are now presented in Section 5.1.5.	Text was added to clarify that treatments received during Period 4 are essentially a continuation of the treatment options available in treatment Period 3.

<p>Section 5.4</p>	<p>Text was added to provide rationale for the bridging extension period.</p> <p>Specified that Background TCS will be assigned until Week 104.</p>	<p>Period 4 will give to patients who have completed Week 104 visit and have not met criteria for permanent discontinuation the possibility to remain in the trial for a maximum of 96 additional weeks (up to Week 200). This will provide additional long term efficacy and safety information.</p> <p>The requirement for concomitant background TCS is limited to Period 2 and 3. During Period 4, concomitant use of TCS may be continued, as directed by the investigator, as per clinical practice.</p>
<p>Section 7.2, Section 7.6, and Section 7.7.3</p>	<p>Visit, Week, and Period numbers were updated to be consistent with the additional visits (additional period).</p>	<p>To reflect the extension of the treatment period with the addition of Period 4 (Bridging extension).</p>
<p>Section 7.7.1</p>	<p>Updated language specifying which periods medications and procedures referred to and added text to specify that, during Period 4, concomitant use of TCS may be continued, as directed by the investigator, as per clinical practice.</p>	<p>Updated to clarify the requirement and restrictions relative to the use of emollient and TCS during the different Periods.</p>
<p>Section 7.7.2</p>	<p>Specified that in Period 4, use of concomitant TCS may be continued as directed by the investigator.</p>	<p>In Period 4, TCS use is allowed as directed by the investigator and TCS will not be provided by the sponsor.</p>
<p>Section 7.7.4</p>	<p>Removed allergen immunotherapy from prohibited procedures</p>	<p>Due to the extended duration of the study, the sponsor anticipates some patients may require allergen immunotherapy for allergic conditions.</p>
<p>Section 7.7.5.2</p>	<p>Clarified that the same rules for the management of rescue therapy in Period 3 will apply to Period 4.</p>	<p>Patients in Period 4 will have the same possibility of rescue therapies as in Period 3.</p>
<p>Section 7.8</p>	<p>Detailed objectives of Period 4 and conditions underwhich patients can enter Period 4.</p>	<p>The trial duration is increased for up to 96 additional weeks to give to patients the possibility to remain in the trial until baricitinib is approved for the treatment of AD and becomes reimbursed or a negative regulatory opinion is received.</p>

Section 8.1.1 - Table JAIN.4.	Removed wording allowing to resume IP after institution of appropriate treatment of a first VTE.	Permanent discontinuation of IP is required after occurrence of any VTE in the study.
Section 8.1.2	Specified that patients will be discontinued from investigational product if a VTE develops and added a note regarding followup testing.	Permanent discontinuation of IP is required after occurrence of any VTE in the study.
Section 8.2	Specified that the study may be terminated in a specific country after baricitinib is approved for the treatment of AD and becomes reimbursed or a negative regulatory opinion is received in that country.	To align with the objectives of the extension of the duration of the trial.
Section 9.4.8	Clarified the existing wording concerning the periodic monitoring of HBV DNA for patients who are HBc Antibody positive at Screening which is described in the SOA.	To correct the discrepancy between section 9.4.8 and the SOA table.
Section 10.3.7.4	Section created to clarify that other interim analyses may be conducted to support regulatory submissions and scientific disclosures.	To align with regulatory submissions and disclosures plans.
Appendix 3.3.2	Wording was added to clarify that the study may be terminated 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.	To align with the objectives of the extension of the duration of the trial.

Revised Protocol Sections

<p>Note: Deletions have been identified by strikethroughs. Additions have been identified by the use of <u>underscore</u>.</p>
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1. Synopsis

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Summary of Study Design:

Study I4V-MC-JAIN (JAIN) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of baricitinib 1-mg once daily (QD), 2-mg QD, and 4-mg QD compared with placebo in patients with moderate-to-severe AD who are receiving background topical corticosteroid (TCS) treatment and who have experienced failure to cyclosporine or are intolerant to, or have a contraindication to, cyclosporine.

The study consists of 54 periods:

Period 1: Screening Period (Visit 1), up to 5 weeks prior to randomization

Period 2: 52-week Double-Blind Treatment Period: from Week 0 (Baseline; Visit 2) up to Week 52 (Visit 14)

Period 3: 52-week Double-Blind, Long-Term Extension Period: from Week 52 (Visit 14) to Week 104 (Visit 22)

d. Randomized Down-Titration Substudy (Week 52)

Responders who are eligible to enter the substudy will be rerandomized as follows:

- baricitinib 4-mg treatment group 1:1 to baricitinib 2-mg, or baricitinib 4-mg.
- baricitinib 2-mg treatment group 1:1 to baricitinib 1-mg, or baricitinib 2-mg.

e. Responders who are not eligible to enter the randomized downtitration will continue on the treatment regimen assigned at baseline; however, rerandomization to either 4-mg or 2-mg baricitinib is available for the placebo, baricitinib 2-mg, and 1-mg treatment groups if patients have a worsening of symptoms.

f. Nonresponders in the placebo, baricitinib 2-mg, or baricitinib 1-mg treatment groups will be rerandomized at a 1:1 ratio to baricitinib 4-mg or baricitinib 2-mg QD at Week 52. After rerandomization, patients will remain on the same dose of baricitinib for the remainder of the study. Nonresponders who were randomized to baricitinib 4-mg will remain on 4-mg.

Period 4: Bridging Extension: from Week 104 (Visit 22) and up to Week 200 (Visit 28). Subjects who have completed Week 104 and have not met criteria of permanent discontinuation will have the possibility to remain in the trial for up to 96 additional weeks (up to Week 200).

Period 45: Post-Treatment Follow-Up Period: from last treatment period visit or early termination visit (ETV) to 4 weeks after the last dose of investigational product.

Treatment Arms and Duration:

At baseline, patients will be randomized at a 1:1:2:1 ratio to receive placebo QD, baricitinib 1-mg QD, baricitinib 2-mg QD, or baricitinib 4-mg QD for up to ~~404~~200 weeks.

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Statistical Analysis

Unless otherwise specified, the efficacy and health outcome analyses will be conducted on the intent-to-treat population and safety analyses will be conducted on those patients who receive at least 1 dose of investigational product.

Treatment comparisons of discrete efficacy variables will be made using a logistic regression analysis with treatment ~~and~~, baseline disease severity (vIGA AD) and baseline score in the model. Region may be added to the model if patient numbers allow. The proportions and 95% confidence interval (CI) for the treatment comparisons will be reported. If a patient needs to use rescue medication, the data from that point forward will be considered missing and missing data will be imputed using the nonresponder imputation (NRI) method. Additional analyses will be conducted using all observed data regardless of whether rescue medication was used or not.

Treatment comparisons of continuous efficacy and health outcome variables will be made using mixed-effects models for repeated measures (MMRM) model with treatment, baseline severity (vIGA AD), visit, and treatment-by-visit interaction as fixed categorical effects and baseline score and baseline score-by-visit interaction as fixed continuous effects. Region may be added to the model if patient numbers allow. An unstructured covariance matrix will be used to model the within-patient variance–covariance errors. Type III sums of squares for the least squares means (LSMs) will be used for the statistical comparison and contrasts will be set up within the model to compare treatment groups at specific time points of interest.

2. Schedule of Activities

Table JAIN.1. Schedule of Activities

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension						PTFU
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22/ ETA	23	24	25	26	27	28/ ETA	801a	
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	10820 4	
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	28±4
Inclusion and exclusion review	X	X																												
Informed consent	X																													
Clinical Assessments																														
Demographics	X																													
Medical history	X																													
Substance Use (alcohol, tobacco)	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	X	X	X	X	X	X	X	X	X
Height	X																													
Vital signs (BP and Pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X																													
Symptom-directed physical examination ^b		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (single)	X																													
Chest x-ray ^c (posterior–anterior view)	X																													
TB test ^d	X																													
Read PPD if applicable (48 to 72)	X ^e																													

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension						PTFU
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22/ ETA	23	24	25	26	27	28/ ETA	801a	
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	10820 4	
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	28±4
hours after PPD)																														
Pre-existing Conditions	X																													
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ePRO (patient diary) dispensed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X													
ePRO (patient diary) returned		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				xf							xf	
Randomization/ rerandomizationg		X												Xg																
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Dispensed		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	
Weigh and dispense background TCS (tubes with cap)q		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
Weigh and record returned background TCS (tubes with cap)q			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							xf	
Scales																														
IGA	X	X	X	X	X	X	X	X	X	X	X	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	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	X	X	X	X	X	X	X	X	X	X	X

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension						PTFU	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22/ ETA	23	24	25	26	27	28/ ETA	801a		
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	10820 4		
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	28±4	
Health Outcomes Measures and Other Questionnaires ^h																															
Itch NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X ^f						<u>X</u> ^f		
Skin Pain NRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X ^f						<u>X</u> ^f		
ADSS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X ^f						<u>X</u> ^f		
PGI-S-AD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>					X						<u>X</u> ^f		
POEM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	X
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	X
HADS	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X								<u>X</u> ^r	X ^r	
EQ-5D-5L		X	X	X	X	X	X		X		X		X		X		X		X	X	X								<u>X</u> ^r	X ^r	
WPAI-AD		X	X	X	X	X	X		X		X		X		X		X		X	X	X								<u>X</u> ^r	X ^r	
SF-36		X			X	X	X		X		X		X		X		X		X	X	X								<u>X</u> ^r	X ^r	
C-SSRS and Self-Harm Supplement ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	X
Self-Harm Follow-Up Form ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	X
Laboratory Assessments																															
Lipids (Fasting Visit) ^k		X					X			X		X		X		X		X		X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	X	
Clinical Chemistry ^l	X	X			X	X	X	X		X	X	X		X		X		X		X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	X	
Hematology	X	X			X	X	X	X		X	X	X		X		X		X		X	X	X	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	<u>X</u>	X	
Serum Pregnancy ^m	X																														
FSH ⁿ	X																														
TSH	X																														

	Period 1: Screening	Period 2: Double-blind Treatment Period												Period 3: Long-Term Extension										Period 4: Bridging Extension						PTFU
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22/ ETA	23	24	25	26	27	28/ ETA	801a	
Weeks from Randomization	-8 to -35 days	0	1	2	4	8	12	16	20	24	32	40	48	52	56	60	64	68	76	84	92	104	120	136	152	168	184	200	10820 4	
Visit tolerance interval (days)		0	±2	±2	±2	±2	±4	±4	±4	±5	±5	±5	±5	±5	±4	±4	±4	±4	±5	±5	±5	±5	±7	±7	±7	±7	±7	±7	±7	28±4
HIV	X																													
HCV Antibody ^o	X																													
HBV testing	X																													
HBV DNAP	X							X		X			X			X		X		X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X			X	X	X	X		X	X	X		X			X		X		X	X							X	X
Urine Pregnancy ^m		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics: blood		X										X																		
Serum immunoglobulin (IgE)		X			X			X		X	X		X									X							X	
Exploratory storage samples (serum and plasma)		X			X			X		X	X		X									X							X	
RNA and biomarkers: blood		X			X			X		X	X		X									X							X	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale 11 categories suicidal ideation/suicidal behavior; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EQ-5D-5L = the European Quality of Life–5 Dimensions 5 Levels; ET = early termination; ePRO = electronic patient-reported outcomes (device); FSH = follicle-stimulating hormone; HADS = Hospital Anxiety Depression Scale; HCV = hepatitis C virus; HBV = hepatitis B virus; HIV = human immunodeficiency virus; ICF = informed consent form; IGA = Investigator’s Global Assessment; IgE = immunoglobulin E; IP = investigational product; IWRS = interactive web-response system; NRS = Numeric Rating Scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PPD = purified protein derivative; PTFU = post-treatment follow-up; SF-36 =Medical Outcomes Study 36-item short-form health survey; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TCS = topical corticosteroids; TSH = thyroid-stimulating hormone; V = visit; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

- a An early termination visit should be conducted if patient discontinues from the study before Week ~~104~~200. Visit 801 is the post-treatment follow-up visit, which occurs after the patient has been off baricitinib/study drug 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 ~~22~~28/ET; Visit 801 (follow-up visit) is not required. ET visit activities do not need to be duplicated if occurring at the time of a scheduled visit.
- b The symptom-directed physical examination may be repeated at the investigator's discretion any time a patient presents with physical complaints.
- c A posterior–anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available.
- d TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. See Exclusion Criterion [40] for description of TB testing. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally. (Note: Exception: Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing but must have a chest x-ray at screening.)
- e If PPD testing was chosen to test for TB, then the patient must return and PPD test read 48 to 72 hours after Visit 1 (post-PPD).
- f Applies to ET Visit if conducted prior to Week 68 only.
- g At Week 52, patients who are eligible for the randomized downtitration substudy and nonresponders will be rerandomized as described in Section 5.1.3.
- h The following measures (Itch NRS, Skin Pain NRS, ADSS, PGI-S-AD, POEM, DLQI, HADS, EQ-5D-5L, WPAI-AD, SF-36) should be completed prior to any clinical assessments being performed on days when study visits occur.
- i Suicidal ideation and behavior subscales excerpt – Adapted for the assessment of 11 preferred ideation and behavior categories.
- j The Self-Harm Follow-Up Form is required only if triggered by the Self-Harm Supplement Form.
- k Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Unscheduled lipid testing can be performed at the discretion of the investigator.
- l Clinical chemistry will include the following value calculated from serum creatinine: estimated glomerular filtration rate (eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine 2009 equation).
- m For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and at all subsequent study visits after Visit 3. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.
- n For female patients ≥ 40 and < 60 years of age who have had a cessation of menses for at least 12 months, an FSH test will be performed to confirm nonchildbearing potential (FSH ≥ 40 mIU/mL).
- 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.
- q Beyond Week 104, low and mid potency TCS will no longer be provided by the sponsor.
- r Only applicable to ET visits and V801 before Period 4.

NOTE: Patients completing V22 and planning to sign the ICF for amendment (e) can participate as long as they have not completed a V801.

4.0. Objectives and Endpoints

Table JAIN.2. Objectives and Endpoints

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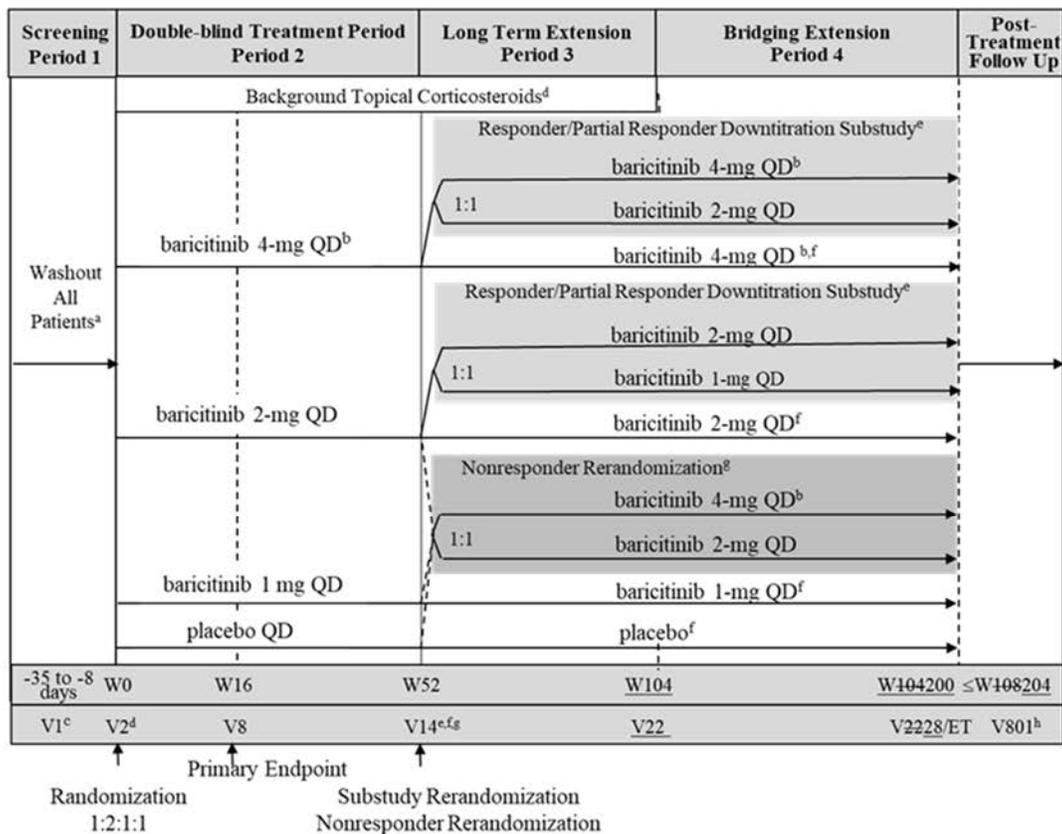
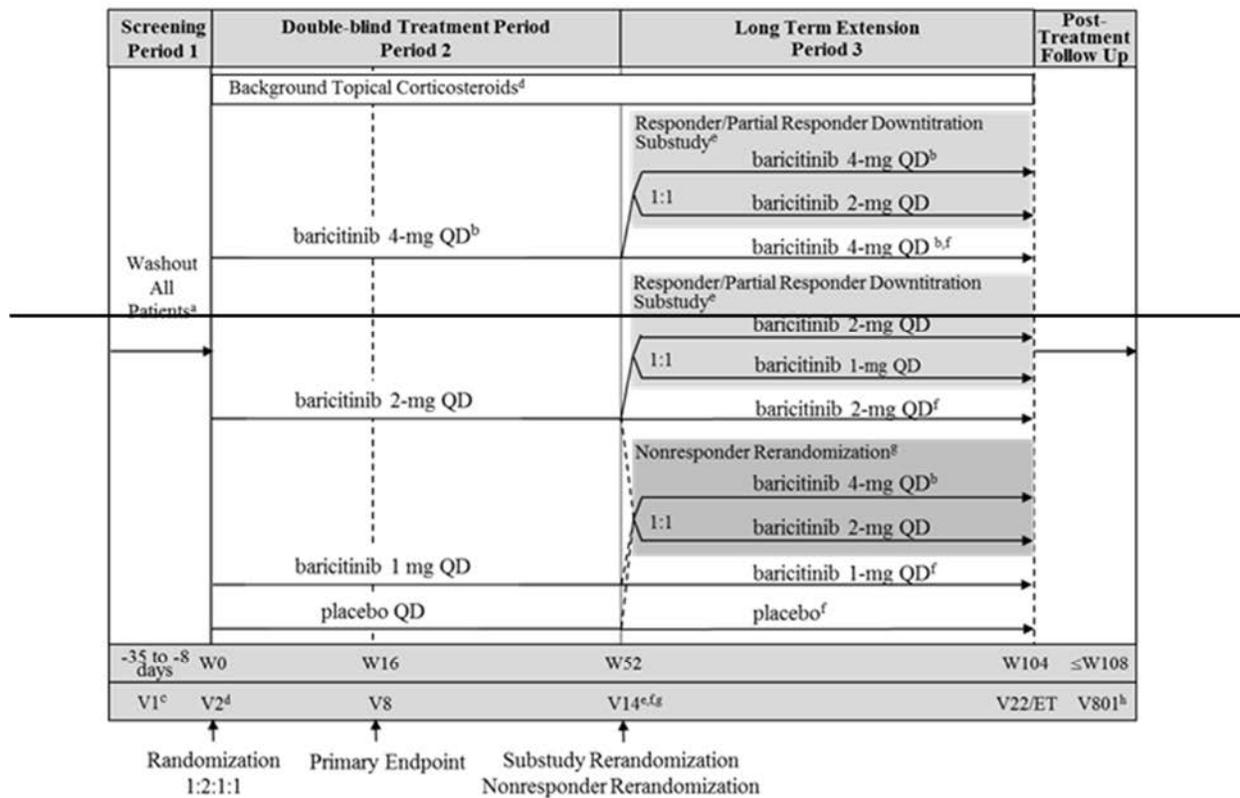
Exploratory Endpoints may include evaluating the response to baricitinib treatment regimens on clinical measures and patient-reported outcomes. These endpoints may include dichotomous endpoints or change from baseline for the following measures: IGA, EASI, SCORAD, POEM, DLQI, WPAI-AD, EQ-5D-5L, Itch NRS, ADSS Item 1, 2, 3 scores, Skin Pain NRS, SF-36, PGI-S-AD. Patients continuing on placebo as responders will be assessed during the long-term extension for relevant efficacy endpoints. Assessments of efficacy may be performed beyond Week 104 up to Week 200. The timing of the data lock(s) for the analysis of the efficacy data from the randomized withdrawal sub-study will be determined by the retreatment rates (see Section 10.3.7).

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5.1. Overall Design

Study I4V-MC-JAIN (JAIN) is a Phase 3, multicenter, double-blind, randomized, placebo-controlled study evaluating the safety and efficacy of baricitinib 1-mg QD, 2-mg QD, and 4-mg QD in combination with TCS in patients with moderate-to-severe atopic dermatitis (AD) who have experienced failure of cyclosporine, or are intolerant to, or have a contraindication to, cyclosporine. The study is divided into 45 periods: a 5-week Screening period, a 1-year Double-Blind Treatment period (Week 0 through Week 52), a 1-year double-blind, long-term extension (Week 52 through Week 104) that includes a randomized downtitration substudy, a bridging extension that may last up to 96 weeks (Week 104 to up to Week 200) and a 4-week Post-Treatment Follow-Up period.

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Abbreviations: AD = atopic dermatitis; eGFR = estimated glomerular filtration rate; ET = early termination; IGA = Investigator's Global Assessment; IP = investigational product; PPD = purified protein derivative; QD = once daily; TB = tuberculosis; TCS = topical corticosteroids; V = visit; W = week.

- a Applicable to patients taking topical treatments (excluding emollients) or systemic treatments for AD at the time of screening.
- b Maximum dose of baricitinib for patients with renal impairment (defined as eGFR <60 mL/min/1.73 m²) will be 2-mg QD.
- c Patients for whom PPD skin test for the evaluation of TB infection was performed at V1 must return and PPD test must be read 48 to 72 hours after Visit 1 (post-PPD).
- d At Visit 2 (W0) and up to Visit 22 (W104), patients will be supplied with mild- and moderate-potency TCS to be applied per the guidelines in Section 7.7.2.
- e At Week 52, responders (IGA 0 or 1) and partial responders (IGA 2) who were assigned to baricitinib 4-mg or 2-mg, at randomization, are currently receiving investigational product (does not currently have study drug interrupted), and have not used high- or ultra-high-potency TCS in the previous 14 days will be enrolled into the downtitration substudy. If a patient in the substudy has an IGA ≥ 3 during Periods 3 or 4, they will be retreated automatically with their presubstudy baricitinib dose for the remainder of the study.
- f At Week 52, responders (IGA 0 or 1) and partial responders (IGA 2) in the baricitinib 4-mg or baricitinib 2-mg treatment groups who are not eligible for the randomized downtitration substudy and those who are in the baricitinib 1-mg or placebo groups will remain on their current dose of investigational product. If worsening of AD symptoms occurs any time during Periods 3 or 4 thereafter such that a patient's IGA is ≥ 3 , with the exception of patients in the baricitinib 4-mg group, they will be rerandomized automatically at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD. Rerandomization will only occur once. Patients in the baricitinib 4-mg group will remain on 4-mg.
- g Beginning at Visit 14 (Week 52), nonresponders (IGA ≥ 3) in the placebo, baricitinib 1-mg or baricitinib 2-mg treatment groups will be rerandomized at a 1:1 ratio to baricitinib 4-mg or baricitinib 2-mg QD. Nonresponders randomized to baricitinib 4-mg at baseline will remain on 4-mg. After rerandomization, patients will remain on the same dose of baricitinib for the remainder of the study.
- h Occurs approximately 28 days after the last dose of IP. Not required for patients who have been off drug for 28 days or more at the time of their last visit.

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

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5.1.4 Period 4: Bridging Extension

Patients who have completed Week 104 and have not met criteria for permanent discontinuation will have the possibility to remain in the trial for up to 96 additional weeks (up to Week 200).

During Period 4, patients will continue to receive the same treatment (baricitinib or placebo) they received during Period 3, and will have the same options for dose changes as Period 3 (if not already implemented in Period 3):

- Randomized Down titration substudy: the substudy will continue during Period 4. Therefore, patients who have not met the criterion for retreatment in Period 3 will have the possibility to be retreated with the baricitinib dose they received prior to the substudy if worsening of AD symptoms occurs such that IGA increases to ≥ 3 .
- Patients with an IGA 0, 1, or 2 at Week 52 and who were not eligible to the randomized downtitration, will be rerandomized at a 1:1 ratio to baricitinib 2-mg QD or baricitinib 4-mg QD if they experience a worsening of symptoms of AD such that IGA increases to ≥ 3 , unless the randomized uptitration has already occurred in Period 3. Patients in the baricitinib 4-mg group will remain on 4-mg.
- Patients with an IGA 0, 1, or 2 at Week 52 and who were not eligible to the randomized downtitration, will be rerandomized at a 1:1 ratio to baricitinib 2 mg QD or baricitinib 4-mg QD if they experience a worsening of symptoms of AD such that IGA increases to ≥ 3 , unless the randomized uptitration has already occurred in Period 3. Patients in the baricitinib 4 mg group will remain on 4 mg.

5.1.45.1.5 Period 45: Post Treatment Follow-Up

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

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5.4. Scientific Rationale for Study Design

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All patients in Study JAIN will be assigned investigational product with concomitant mild- to moderate-potency TCS until Week 104 (Visit 22) and investigators may rescue patients who are experiencing unacceptable or worsening symptoms of AD with high- or ultra-high-potency TCS. (See Section 7.7.5 for all rescue options).

Topical rescue treatments (as outlined in Section 7.7.5) will be available during Study JAIN to facilitate the management of disease, as there are instances where patients will remain on the same dose of baricitinib during episodes of worsening.

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 for consistency with other studies in AD. This timing will allow adequate duration on a stable dose of baricitinib to assess the benefit/risk profile of the dose regimens.

During the long-term extension (Period 3), eligible patients will participate in a downtitration substudy. The objective of the substudy is to evaluate the possibility of maintaining efficacy with a lower dose of baricitinib in patients with response (IGA 0 or 1) or partial response (IGA 2) to baricitinib 2-mg QD or 4-mg QD in combination with TCS.

Period 4 will provide patients who have completed Week 104 visit and have not met criteria for permanent discontinuation, the possibility to remain in the trial for up to 96 additional weeks (up to Week 200). This will allow for additional long-term efficacy and safety information to be

collected, and provide patients the opportunity to continue study treatment until the anticipated approval of baricitinib in this indication.

The Post-Treatment Follow-Up Period (Period 4~~5~~) is for safety monitoring after the patient has been off investigational product for approximately 28 days.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized in a 1:1:2:1 ratio to receive placebo QD, baricitinib 1-mg QD, 2-mg QD, or 4-mg QD to double-blind treatment at Visit 2 (Week 0). Randomization will be stratified by geographic region if the planned country allocation justifies, and disease severity at baseline (IGA 3 versus 4). Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign cartons, each containing 4 blister packs of double-blind investigational product tablets to each patient, starting at Visit 2 (Week 0), and at each visit up to and including Visit ~~2228~~ (Week-104~~200~~). Site personnel will confirm that they have located the correct carton by entering a confirmation number found on the carton into the IWRS.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit during the treatment period (Visit 4 through Visit ~~2228~~) by counting returned tablets.

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 up to Week 104. After Week 104, the continued use of emollients is encouraged. Moisturizers with antipruritics or antiseptics are not permitted up to Week 104. 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.
- Background TCS therapy (e.g., triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment) are to be used on active lesions in Periods 2 and 3, as described in Section 7.7.2.
- ~~During Periods 2 and 3, h~~High- or ultra-high-potency TCS are only permitted as rescue therapy as described in Section 7.7.5 (Rescue Therapy).
- During Period 4, concomitant use of TCS may be continued, as directed by the investigator, as per clinical practice.
- TCIs (e.g., tacrolimus and pimecrolimus), or topical PDE-4 inhibitor (i.e., crisaborole, where approved) are permitted in place of TCS 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.
- Phototherapy, including therapeutic phototherapy (psoralen and ultraviolet A, ultraviolet B, excimer laser), is permitted as rescue therapy in Periods ~~2 or 3~~ to 4 (see

Section 7.7.5, Rescue Therapy); however, it requires a temporary interruption of investigational product (see Section 8.1.1).

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7.7.2. Use of Topical Corticosteroids

A washout period of 14 days is required for all TCS prior to randomization at Visit 2.

At baseline (Week 0, Visit 2) and up to Week 104 (Visit 22), patients will receive triamcinolone 0.1% cream (or equivalent-potency TCS) and hydrocortisone 2.5% ointment (or equivalent-potency TCS)...

After Week 104, use of TCS may be continued as directed by the investigator, as per clinical practice. Background TCS will no longer be provided nor reimbursed to study participants by the sponsor, unless required by local law.

Choice of Background Topical Corticosteroid

Where possible, triamcinolone cream 0.1% and/or hydrocortisone 2.5% ointment will be supplied by the sponsor for use as background TCS up to Week 104 (Visit 22). In the event of these specific TCS being unavailable, an alternate, equivalent-potency TCS may be provided by the sponsor (see below). Topical corticosteroid use, when supplied by the sponsor, should be recorded via weight of dispensed and returned tubes as indicated in the Schedule of Activities (Section 2). In the event that the sponsor is unable to supply TCS, commercially available triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment may be supplied by the sites.

7.7.3. Use of Antihistamines

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During Periods 3, ~~and 4,~~ and 5, there are no restrictions for antihistamine use; both sedating and nonsedating antihistamines are permitted.

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 investigational product will be permanently discontinued.

- topical antihistamines or sedating, systemic antihistamines in Period 2 (see Section 7.7.3, Use of Antihistamines, for additional information).
- ~~allergen immunotherapy~~
- self-treatment with tanning booth
- bleach baths (swimming in chlorinated pools is permitted)

7.7.5.2. Rescue during Periods 3 and 4: from Week 52 (Visit 14) to Week 104 200 (Visit 228)

In Period 3, all patients entering Period 3 will continue to use concomitant background TCS (e.g., triamcinolone 0.1% cream and hydrocortisone 2.5% ointment) as described in Section 7.7. In Period 4, use of concomitant may continue as directed by the investigator, as per clinical practice. All patients and may be rescued at any time with high- or ultra-high-potency TCS or phototherapy as described in Section 7.7.

As mentioned in Sections 5.1.3, and 5.1.4, patients who reach an IGA ≥ 3 after entry into the randomized downtitration substudy will be automatically retreated with their presubstudy dose of baricitinib.

...

7.8. Treatment after the End of the Study

Period 4 will provide patients who have completed Week 104 visit and have not met criteria for permanent discontinuation, the possibility to remain in the trial for up to 96 additional weeks (up to Week 200) and thus provide patients the opportunity to continue study treatment until the anticipated approval of baricitinib in this indication.

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.

8.1.1. Temporary Interruption of Investigational Product

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Table JAIN.4. Medical and Laboratory 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/ μ L (<2.00x10 ³ / μ L or <2.00 GI/L)	WBC count \geq 2500 cells/ μ L (\geq 2.50x10 ³ / μ L or \geq 2.50 GI/L)
ANC <1000 cells/ μ L (<1.00x10 ³ / μ L or <1.00 GI/L)	ANC \geq 1200 cells/ μ L (\geq 1.20x10 ³ / μ L or \geq 1.20 GI/L)
Lymphocyte count <500 cells/ μ L (<0.50x10 ³ / μ L or <0.50 GI/L)	Lymphocyte count \geq 750 cells/ μ L (\geq 0.75x10 ³ / μ L or \geq 0.75 GI/L)
Platelet count <75,000/ μ L (<75x10 ³ / μ L or <75 GI/L)	Platelet count \geq 100,000/ μ L (\geq 100x10 ³ / μ L or \geq 100 GI/L)
eGFR <40 mL/min/1.73 m ² (from serum creatinine) for patients with screening eGFR \geq 60 mL/min/1.73 m ²	eGFR \geq 50 mL/min/1.73 m ²
eGFR <30 mL/min/1.73 m ² (from serum creatinine) for patients with screening eGFR \geq 40 to <60 mL/min/1.73 m ²	eGFR \geq 40 mL/min/1.73 m ²
ALT or AST >5 x ULN	ALT and AST return to <2 x ULN, and IP is not

	considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥10 g/dL (≥100.0 g/L)
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection
Clinical features of VTE (such as deep vein thrombosis or pulmonary embolism) are present ^a	After evaluation and institution of appropriate treatment of VTE ^b

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

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

~~^b If after evaluation and institution of appropriate treatment the investigator deems that the patient is still at significant risk, or if this would constitute a second VTE for the patient, then IP should be discontinued permanently.~~

...

8.1.2. Permanent Discontinuation from Investigational Product

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

- pregnancy
- malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- hepatitis B virus DNA is detected with a value above limit of quantitation or 2 sequential tests return a value of below the limit of quantitation (see Section 9.4.8).
- ~~• confirmed second VTE~~
- certain prohibited medications are taken per Section 7.7.4, Prohibited Medications and Procedures.
- development of a VTE

Note: Patients who develop a VTE may have additional follow up and testing recommended (see Appendix 8).

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8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

...

- 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.

...

9.4.8. Hepatitis B Virus DNA Monitoring

Patients who are HBcAb positive and HBV DNA negative (undetectable) at Visit 1 will require periodic measurement of HBV DNA as per study schedule (Section 2) Week 16 (Visit 8) or ETV, regardless of their hepatitis B surface antibody (HBsAb) status.

10.3.1. General Statistical Considerations

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All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. Treatment comparisons of discrete efficacy variables between baricitinib and placebo will be made using a logistic regression analysis with baseline disease severity (vIGA AD), baseline score and treatment group in the model. Region may be added as an additional factor if the planned country allocation justifies, and stratification has not resulted in empty strata. This will be finalized in the SAP. If appropriate, treatment-by-region interaction may be added to the 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 the effect) or qualitative (the treatment is beneficial for some but not all regions). The percentages, difference in percentages, and 95% confidence interval (CI) of the difference in percentages will be reported. The p-value from the Fisher exact test will also be produced. Additional relative measures, for example, odds ratio, may be reported as appropriate.

When evaluating continuous measures over time, a restricted maximum likelihood-based mixed model for repeated measures (MMRM) will be used. The model will include treatment, baseline severity (vIGA AD), visit, and treatment-by-visit interaction as fixed categorical effects and baseline score and baseline score-by-visit interaction as fixed continuous effects. Region may be added as an additional factor if the planned country allocation justifies. 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.

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10.3.7.4 Other Interim Analyses

Besides DMC members and Unblinded Study Team for the Primary Analyses 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 primary analysis or final database lock for preparation of regulatory documents. Interim locks will be conducted at various timepoints to support regulatory submissions and scientific disclosures. The timing of the data lock(s) for the analysis of the efficacy data from the sub-study will be determined by the

retreatment rates. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

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

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Appendix 3.3. Study and Site Closure

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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. 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.

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