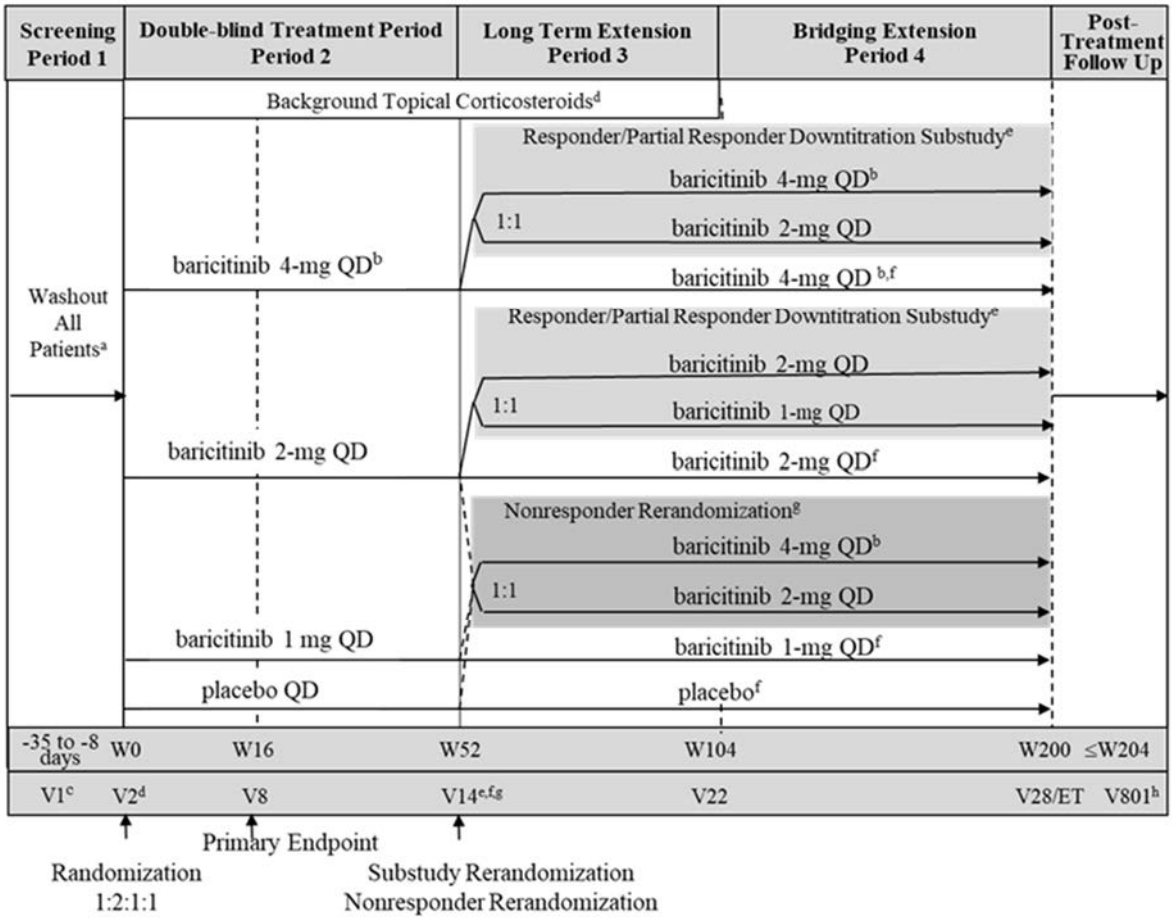
Objective(s)/Endpoints:

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	• Proportion of patients achieving EASI75 at Week 16
Key Secondary *These are prespecified objectives that will be adjusted for multiplicity*	
To test the hypothesis that baricitinib 1-mg + TCS is superior to placebo + TCS in the treatment of patients with moderate-to-severe AD	• 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	• 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.	• 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	• 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 *These are prespecified objectives that will not be adjusted for multiplicity*	
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	• 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	• 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

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/ ET[a]**	**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**
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
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
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
12-lead ECG (single)	X																												
Chest x-ray[c] (posterior–anterior view)	X																												
TB test[d]	X																												

	• 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)
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	• 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
Substudy: Randomized Downtitration *These are prespecified objectives that will be not be adjusted for multiplicity*	
All Patients Entering the Substudy To evaluate the change in clinical response after treatment downtitration from baricitinib • 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 **Patients Entering the Substudy with IGA 0 or 1** To evaluate the change in clinical response after treatment downtitration from baricitinib • 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	• 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 ≥3)
Patients Not Entered into Substudy *These are prespecified objectives that will not be adjusted for multiplicity*	



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 m^2) 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.

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 ≥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.

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.

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

	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/ ET[a]**	**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		
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	
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								
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						X[r]	
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																													

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:

	• 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)
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	• 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
Substudy: Randomized Downtitration *These are prespecified objectives that will be not be adjusted for multiplicity*	
All Patients Entering the Substudy To evaluate the change in clinical response after treatment downtitration from baricitinib • 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 **Patients Entering the Substudy with IGA 0 or 1** To evaluate the change in clinical response after treatment downtitration from baricitinib • 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	• 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 ≥3)
Patients Not Entered into Substudy *These are prespecified objectives that will not be adjusted for multiplicity*	
All Patients 1. To evaluate the long-term effect of baricitinib dose on clinical measures **Patients with IGA 0 or 1** 2. To evaluate the long-term effect of baricitinib dose on clinical measures	• 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

All Patients 1. To evaluate the long-term effect of baricitinib dose on clinical measures **Patients with IGA 0 or 1** 2. To evaluate the long-term effect of baricitinib dose on clinical measures	• 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
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).	

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.

[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.

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 m^2 and eGFR 30 to <60 mL/min/1.73 m^2, respectively), dose adjustment is not required for patients with eGFR ≥60 mL/min/1.73 m^2. Patients with eGFR <60 mL/min/1.73 m^2 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 m^2. 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 m^2. 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.

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

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

	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/ ET[a]**	**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
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
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[i]	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
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 DNA[p]	X							X			X			X			X		X		X	X	X	X	X	X	X	X	X

- 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 reinitiate 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.