Clinical Study Protocol Addendum Version 7 I4V-MC-JAHN

A Phase 3 Multicenter, Double-Blind Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Adult Patients with Atopic Dermatitis

NCT03334435

Approval Date: 13-June-2018

1. Protocol Addendum I4V-MC-JAHN(7) A Phase 3 Multicenter, Double-Blind Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Adult Patients with Atopic Dermatitis

BREEZE-AD3

EudraCT Number: 2017-000873-35

Baricitinib (LY3009104)

This addendum is to be performed in addition to or in place of procedures required by protocol I4V-MC-JAHN(a) or any subsequent amendments to that protocol.

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Protocol Addendum (7) Electronically Signed and Approved by Lilly on date provided below.

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3. Rationale for Addendum

Addendum I4V-MC-JAHN(7) (JAHN[7]) contains additions to be conducted as an addendum to the long-term extension Study I4V-MC-JAHN (JAHN) and will only apply to a selected number of participating sites. All sites participating in the addendum may enroll patients directly into JAHN(7) and all patients will receive open-label baricitinib 2-mg.

As baricitinib 2-mg dose showed statistically significant improvements compared to placebo in the Phase 2 study of baricitinib in atopic dermatitis (AD) (Study I4V-MC-JAHG), it is anticipated that this dose will provide the benefit needed to meet the primary and secondary efficacy measures in the feeder studies and in Study JAHN. Given recent regulatory feedback with regard to minimum number of exposures for appropriate evaluation of benefit-risk for each registered dose, the goal of JAHN(7) is to provide 2-mg as a treatment to additional patients and to further increase the long-term exposure safety database for this dose.

4. Protocol Additions

4.1. Overview of Protocol Additions

JAHN(7) applies to JAHN(a) and all subsequent amendments (referred to throughout as the main protocol).

This addendum adds a separate open-label treatment arm for approximately 250 patients to enroll directly into Study JAHN without having first completed a feeder study. Patients entered in JAHN(7) will complete a screening period (up to 5 weeks in duration). If all inclusion criteria and none of the exclusion criteria are met, patients may enroll into JAHN(7) where they will receive open-label baricitinib 2-mg for 52 weeks during treatment period 1. Patients in JAHN(7) will be eligible to participate in the randomized withdrawal and down-titration substudy during treatment period 2 as described in the main protocol. The screening procedures and inclusion/exclusion criteria in this addendum are all the same as those utilized in the feeder studies to ensure inclusion of the same patient population. All study procedures starting at Visit 1 are the same as the main protocol.

The Schedule of Activities (Attachment 1) and Clinical Laboratory Tests (Attachment 2) have been updated to accommodate the screening period and apply to patients participating in JAHN(7).

4.2. Objectives and Endpoints

The objectives of this addendum are to estimate the effect of starting baricitinib 2-mg on clinical measures during treatment period 1. The data will be analyzed separately from patients in the main protocol.

Secondary objectives for treatment period 2 (Weeks 52 to 104) will be assessed similar to those described in Section 4 of the main protocol; however, as patients in JAHN(7) will not have an originating study baseline, data collected during screening or at Visit 1 of JAHN(7) will be used as baseline for efficacy assessments.

Additional efficacy endpoints will be assessed as exploratory measures and will be described in the statistical analysis plan (SAP). As with the main study, collection of safety data is an important component of this addendum (see Section 9.2 and 9.4 of the main protocol).

Objectives	Endpoints
Primary	
To estimate the effect of starting baricitinib 2-mg on clinical measures and patient-reported outcomes.	• Proportion of patients with a response of IGA 0, 1, or 2 assessed at Week 16
Secondary (Weeks 0-52)	
To estimate the effect of starting baricitinib 2-mg on clinical measures and patient-reported outcomes.	• Proportion of patients with a response of IGA 0, 1, or 2 assessed at Weeks 4, 24, and 52 • Proportion of patients with a response of IGA 0 or 1 assessed at Weeks 4, 16, 24, and 52 • Proportion of patients achieving response of EASI 75 from baseline assessed at Weeks 4, 16, 24, and 52 • Proportion of patients with a 4-point improvement from baseline of JAHN(7) in Itch NRS at 16 weeks

Abbreviation: EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = numeric rating scale.

4.3. Study Design

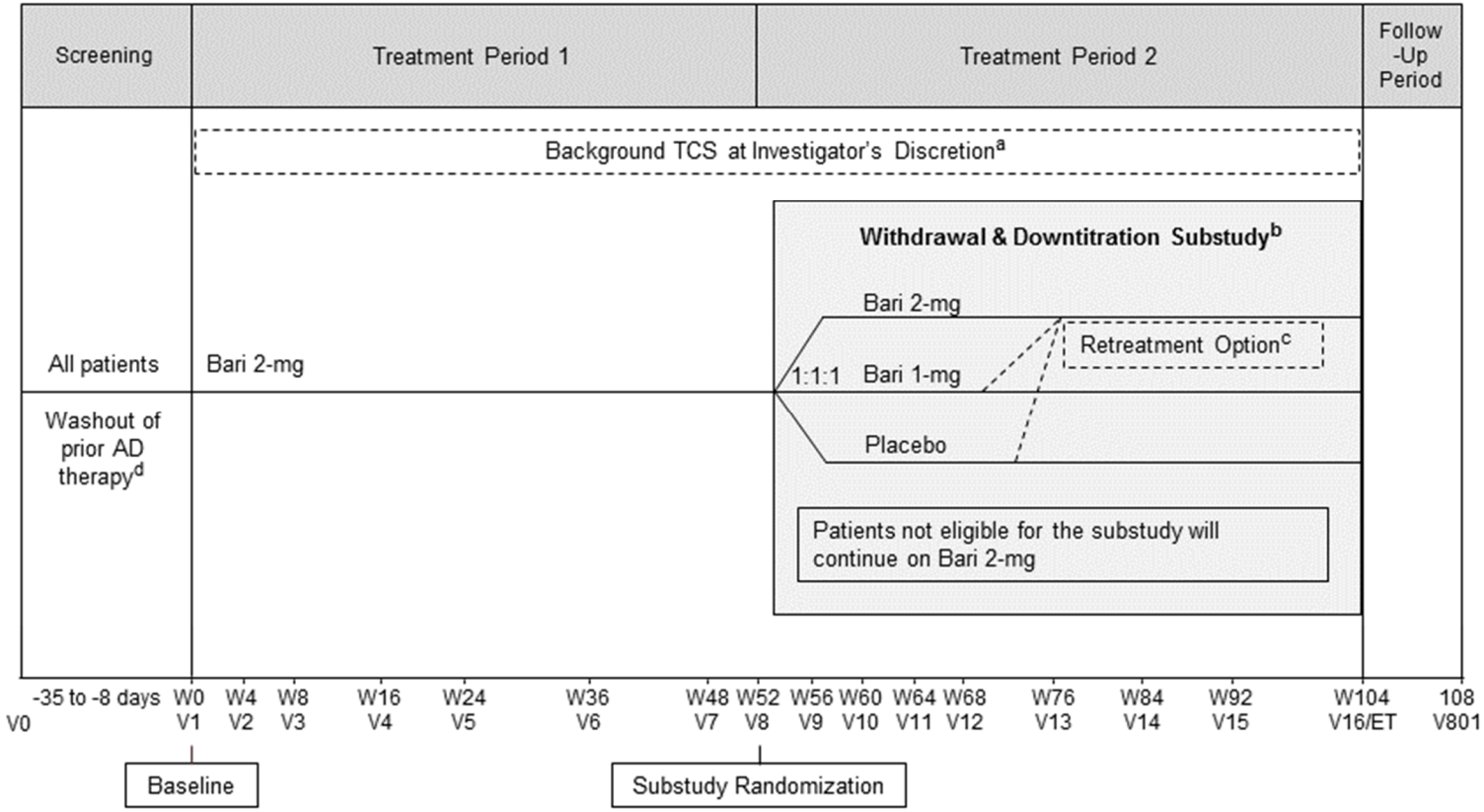
4.3.1. Overall Design

This addendum allows patients to enter directly into Study JAHN without first completing a feeder study. Approximately 250 patients are anticipated to be enrolled. This option has been included in the main protocol Section 10.1. Sample Size Determination, "Additional patients may enroll from addenda or other studies".

Figure JAHN.1 illustrates the study design. Patients can participate in JAHN(7) if all the criteria are met during the screening period (up to 5 weeks in duration). All patients enrolled in JAHN(7) will receive open-label baricitinib 2-mg for 52 weeks (Treatment Period 1). During Treatment Period 2 (Weeks 52 to 104), patients may participate in the randomized withdrawal and downtitration substudy if all eligibility criteria are met, otherwise patients will continue to be treated with open-label baricitinib 2-mg. Patients will use emollients daily throughout the study. Topical corticosteroids and other topical treatments can be used at the investigator's discretion to help control unacceptable and worsening symptoms of AD if necessary (see Section 7.7.1 of the main protocol).

After the screening period, all safety and efficacy assessments will be collected at identical time points as in the main JAHN protocol. The full visit schedule for patients enrolled in the addendum is outlined in the Study Schedule of Activities (Attachment 1).

Throughout the trial, including at the start of the substudy (Week 52), investigators should continue to assess benefit-risk for patients to remain in the trial and should consider discontinuing patients if AD symptoms are unacceptable.



Abbreviations: AD = atopic dermatitis; Bari = baricitinib; ET = early termination; IGA = Investigator's Global Assessment; TCS = topical corticosteroids; V = visit; W = week.

[a] Background TCS may be initiated or reinitiated at any time during the study, however, we recommend waiting at least 1 week after initial treatment assignment since everyone will be on active, open-label treatment. For those eligible for the substudy, TCS will also be provided as part of retreatment any time a patient's IGA score becomes ≥3. Please refer to additional TCS guidelines in Section 7.7.1 of the main protocol.

[b] Eligible patients will be randomized in the withdrawal and down-titration substudy as described in Section 5.1.3.1 of the main protocol. Patients who do not enroll in the substudy will remain on their treatment as described in Section 5.1.3.2 of the main protocol.

[c] Patients enrolled in the substudy will automatically be retreated if their IGA score becomes ≥3 as described in Section 5.1.3.1 of the main protocol.

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

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

4.3.1.1. Screening Period

The duration of the screening period for patients enrolled in JAHN(7) is between 8 and 35 days prior to Visit 1 (Week 0). At Visit 0, the patient will sign the informed consent form (ICF) prior to any study assessments, examinations, or procedures being performed. All screening procedures will be performed according to the Schedule of Activities (Attachment 1).

Patients who receive a purified protein derivative (PPD) skin test at Visit 0 will need to return within 48 to 72 hours later to read the skin test. Prior to enrollment, treatments for AD will be washed out: 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 enrollment and throughout the study. If patients have been using emollients daily at the time of screening, then those cumulative days can be utilized to meet inclusion criterion [8]. Additionally, collection of data through daily diaries will be required throughout the screening period. The baseline for the daily electronic patient reported outcome (ePRO) will be the average score of the 7 days prior to enrollment; thus, the minimum screening window was set at 8 days.

All patients who have not previously received the herpes zoster vaccine by screening will be encouraged (per local guidelines) to do so prior to enrollment. Refer to the exclusion criterion [26] for additional information regarding herpes zoster vaccination.

Patients who meet all of the inclusion and none of the exclusion criteria for this addendum (Section 4.5) will continue to Visit 1 and follow all study procedures described in the Schedule of Activities (Attachment 1) and Section 9 of the main protocol.

4.3.1.2. Treatment Periods

Study activities will be conducted according to the Schedule of Activities (Attachment 1) and as described in Section 9 of the main protocol.

Treatment Period 1: Weeks 0 to 52

At Visit 1 (Week 0, baseline), study eligibility for each patient will be reviewed, based on all inclusion and exclusion criteria (Section 4.5), and laboratory test results. Patients who meet all criteria will proceed to enrollment and begin the 52-week open-label, treatment period. All activities starting at Visit 2 are identical for patients enrolled in JAHN(7) and patients enrolled in the main protocol.

All patients will be assigned to open label baricitinib 2-mg once daily at Visit 1 (Week 0). All patients will be required to use emollients daily. Topical corticosteroids can be initiated at investigator's discretion during treatment to control worsening and unacceptable symptoms of AD; however, since treatment is open-label it is strongly encouraged not to dispense topical corticosteroids (TCS) until at least 1 week after baricitinib treatment has been started, and only if the patient requires TCS therapy. If possible, monotherapy treatment with baricitinib is preferred if tolerated. Initiation of TCS may occur at either a scheduled or unscheduled visit and investigators should make every attempt to conduct disease severity and safety assessments immediately before administering initial treatment with TCS or other topical/systemic AD

treatments. For management of TCS and other topical therapies, follow the guidelines in Section 7.7.1 of the main protocol.

Treatment Period 2: Weeks 52 to 104
At Week 52, all patients participating in JAHN(7) may be eligible to participate in the randomized withdrawal and down-titration substudy as described in Section 5.1.3.1 of the main protocol. To be eligible, a patient in JAHN(7) must meet all of the following criteria:

- Investigator's Global Assessment (IGA) 0, 1, or 2 at Week 52
- has not used high-potency TCS in the last 14 days (potency classification in Appendix 6 of the main protocol)
- does not currently have study drug interrupted

Patients participating in JAHN(7) who are not eligible for the substudy will continue to receive open-label baricitinib 2-mg. Topical corticosteroids can be initiated at investigator's discretion during treatment to control worsening and unacceptable symptoms of AD. For management of TCS, follow the guidelines in Section 7.7.1 of the main protocol.

4.4. Number of Participants

Approximately 250 patients may be enrolled in JAHN(7). It is estimated that there will be approximately 60 patients enrolled into the randomized withdrawal and down-titration substudy. Given that this addendum was planned, these patients are included in the anticipated number of participants in Study JAHN described in Section 5.2 of the main protocol.

4.5. Study Population

At participating centers, patients may be eligible to enroll in this addendum if they meet all of the addendum inclusion criteria and none of the addendum exclusion criteria. The inclusion/ exclusion criteria are all the same as those utilized in the feeder studies to ensure inclusion of the same patient population.

4.5.1. Inclusion Criteria

Patients may be included in this addendum if they meet all of the following 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 Attachment 3).

[4] have moderate to severe AD, including all of the following:

a. Eczema Area and Severity Index (EASI) score ≥16 at screening (Visit 0) and at enrollment (Visit 1)

b. IGA score of ≥3 at screening (Visit 0) and at enrollment (Visit 1)

c. ≥10% of body surface area involvement at screening (Visit 0) and at enrollment (Visit 1).

[5] have a documented history by a physician and/or investigator of inadequate response to existing topical medications within 6 months preceding screening, or history of intolerance to topical therapy as defined by at least 1 of the following:

a. inability to achieve good disease control defined as mild disease or better (e.g., IGA ≤2) after use of at least a medium potency TCS for at least 4 weeks, or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter. Topical corticosteroids may be used with or without topical calcineurin inhibitors.

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

c. documented history of clinically significant adverse reactions with the use of TCS such as skin atrophy, allergic reactions, systemic effects that in the opinion of the investigator outweigh the benefits of retreatment.

[6] agree to discontinue use of the following excluded medications/treatments for at least 4 weeks prior to enrollment (Visit 1) and throughout the study:

a. oral systemic corticosteroids

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

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

d. phototherapy, includes therapeutic phototherapy (psoralen plus ultraviolet-A, ultraviolet-B), excimer laser as well as self-treatment with tanning beds.

[7] agree to discontinue use of the following excluded medications for at least 2 weeks prior to enrollment (Visit 1) and throughout the study:

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

b. Topical phosphodiesterase type 4 inhibitor (crisaborole)

[8] have applied emollients daily for at least 14 days prior to enrollment and agree to use emollient daily throughout the treatment period.

Note: If patients have been using emollients daily prior to screening, then those cumulative days can be utilized to meet the criterion above.

Patient Characteristics

[9] Male or nonpregnant, nonbreastfeeding female patients

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 the opposite sex.

Total abstinence is defined as refraining from intercourse during the entirety of the study and for at least 1 week following the last dose of investigational product. Periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods and withdrawal are not acceptable methods of contraception.

Otherwise, patients and their partners of child-bearing potential must agree to use 2 effective methods of contraception, where at least 1 form is highly effective for the entirety of the study and for at least 1 week following the last dose of investigational product.

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

- Highly effective birth control methods:
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or implantable
  - Intrauterine device/intrauterine hormone-releasing system
  - Vasectomized partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Effective birth control methods:

- Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide
- Oral contraceptives that do not inhibit ovulation

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

a. Females of non–child-bearing 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).

4.5.2. Exclusion Criteria

Patients will be excluded from participation in this addendum if they meet any of the following criteria:

Medical Conditions Related to Atopic Dermatitis

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

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

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

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

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

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

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

[16] have been treated with the following therapies:

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

b. received prior treatment with any oral Janus kinase inhibitor (e.g., tofacitinib, ruxolitinib) less than 4 weeks prior to enrollment

c. received any parenteral corticosteroid administered by intramuscular or intravenous injection within 6 weeks prior to planned enrollment (Visit 1) or are anticipated to require parenteral injection of corticosteroids during the first 16 weeks of the study.

d. have had an intra-articular corticosteroid injection within 6 weeks prior to planned enrollment (Visit 1).

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

e. probenecid at the time of enrollment (Visit 1) that cannot be discontinued for the duration of the study

Medical Conditions in General

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

[18] have uncontrolled arterial hypertension characterized by a repeated systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg in a seated position.

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

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

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

[22] have a history of recurrent (≥2) VTE or are considered at high risk of VTE as deemed by the investigator.

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

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

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.

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

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

a. symptomatic herpes zoster infection within 12 weeks prior to screening.

b. a history of disseminated/complicated herpes zoster (e.g., multidermatomal involvement, ophthalmic zoster, CNS involvement, or post-herpetic neuralgia).

c. symptomatic herpes simplex at the time of enrollment.

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 intravenous antibiotics for an infection, within the past 4 weeks of enrollment.

h. any other active or recent infection within 4 weeks of enrollment that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

[26] have been exposed to a live vaccine within 12 weeks prior to planned enrollment 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, who have not received it prior to screening will be encouraged (per local guidelines) to do so prior to enrollment; vaccination must occur >4 weeks prior to enrollment and start of investigational product. Patients will be excluded if they were exposed to herpes zoster vaccination within 4 weeks of planned enrollment. 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.

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

[28] 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:

a. 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

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

c. Any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS;

and the ideation or behavior occurred within 2 months prior to Visit 0.

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

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

Other Exclusions

[30] are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.

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

[32] 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.

[33] have previously been enrolled in this study or any other study investigating baricitinib or who have experienced hypersensitivity to the active substance or to any of the excipients.

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

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

Diagnostic Assessments

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

[37] 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 enrollment 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.

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

a. positive for hepatitis B surface antigen, or

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

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

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

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

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

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

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

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

a. aspartate aminotransferance or Alanine aminotransferase ≥2x upper limit of normal (ULN)

b. alkaline phosphatase ≥2x ULN

c. total bilirubin ≥1.5x ULN

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

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

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

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

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

i. estimated glomerular filtration rate <40 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration equation Creatinine 2009 equation).

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

4.5.3. Screen Failures

Patients who are entered into the addendum but do not meet the eligibility criteria for participation (screen failure) may be rescreened a maximum of 2 times. If patients are rescreened, rescreening cannot occur until at least 4 weeks after the date of their previous screen failure. When rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number. Additionally, all necessary screening procedures must be conducted at rescreen to ensure all eligibility criteria are met.

4.6. Treatments

4.6.1. Treatments Administered

Patients in JAHN(7) will receive open-label baricitinib 2-mg, administered orally once a day.

At Week 52 patients who qualify for the randomized withdrawal and down-titration substudy will receive double-blind treatment.

Table JAHN.1 shows the treatment regimens.

Table JAHN.1. Treatment Regimen

Assigned Treatment	**IP Supplied in JAHN(7)**	**Dose**
Open-label baricitinib 2-mg QD	Open-label baricitinib 2-mg tablets	1 tablet per day
Assigned Substudy Treatment[a]	**IP Supplied in JAHN(7)**	**Dose**
Blinded baricitinib 2-mg QD	Baricitinib 2-mg tablets Placebo to match 4-mg tablets Placebo to match 1-mg tablets	3 tablets per day
Blinded baricitinib 1-mg QD	Baricitinib 1-mg tablets Placebo to match 4-mg tablets Placebo to match 2-mg tablets	3 tablets per day
Blinded placebo QD	Placebo to match 4-mg tablets Placebo to match 2-mg tablets Placebo to match 1-mg tablets	3 tablets per day

Abbreviations: IP = investigational product; QD = once daily.

[a] The blinded materials provided for JAHN(7) addendum patients who enter substudy treatment at Week 52 will match the material dispensed to eligible substudy patients in the JAHN main protocol. Thus, the reason for the placebo to match 4-mg tablets.

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 that all unused medications are to be destroyed by the site, as allowed by local law.

For Weeks 0 to 52, all patients will be instructed to take 1 tablet daily at the same time each day.

For Weeks 52 to 104, patients enrolled in the substudy will be instructed to take 3 tablets together daily at the same time each day and patients not enrolled in the substudy will be instructed to continue taking 1 tablet daily at the same time each day. The blinded materials provided in the JAHN main protocol will be dispensed to JAHN(7) addendum patients who enter substudy treatment at Week 52. This means that all JAHN(7) addendum patients entered into the substudy will receive 3 tablets daily (see Table JAHN.1). All 3 tablets should be taken together, at the same time each day.

4.6.2. Packaging and Labeling

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

- tablets containing 2-mg baricitinib
- tablets containing 1-mg baricitinib
- placebo tablets to match baricitinib 4-mg, 2-mg, and 1-mg tablets.

Packaging for the open-label dosing will include 1 tablet per day in bottles.

Packaging for each double-blind dose will include 3 tablets per day in blister-packs, and matches the dispensing in the JAHN main protocol. Each tablet (4-mg, 2-mg, and 1-mg) has a distinctive shape and color, and each strength tablet has a matching placebo. All blinded packages used for JAHN(7) patients participating in the substudy will contain placebo to match 4-mg in order to maintain consistency in the substudy dispensing between the main protocol for JAHN and JAHN(7). Each active dose package will contain the appropriate active strength tablet, and corresponding placebo tablets for the other strength.

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

4.6.3. Method of Treatment Assignment

At entry into JAHN(7), patients who meet all criteria for enrollment will be assigned treatment at Visit 1 (Week 0). The interactive web response system will assign open-label bottles starting at Visit 1 (Week 0), and at each visit up to and including Visit 7 (Week 48) for all patients.

At Week 52, patients eligible for the withdrawal and down-titration substudy will be assigned to treatment as described in Section 7.2 of the main protocol.

Patients who do not qualify for the substudy will continue to be assigned open-label bottles from Visit 8 (Week 52) until Visit 15 (Week 92).

4.6.4. Selection and Timing of Doses

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

4.6.5. Blinding

Week 0 to Week 52 of JAHN(7) is open label for all patients. Beginning at Week 52 to Week 104, some patients will enter double-blind treatment as described in Section 7.3 of the main protocol.

4.7. Safety

All safety evaluations described in Section 9.4 of the main protocol will be performed. In addition, the following measures will be completed for patients entered in JAHN(7).

4.7.1. Physical Exam

For each patient entered in JAHN(7), a complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 0 (Screening). Thereafter, physical exams should be performed as described in Section 9.4.2 of the main protocol.

4.7.2. Hepatitis B Virus DNA Monitoring

Hepatitis B virus DNA testing will be performed in enrolled patients who tested positive for anti-HBcAb during screening of this addendum. HBV DNA monitoring for these patients will occur as described in in Section 9.4.7 of the main protocol.

4.7.3. Electrocardiograms

For patients entered in JAHN(7), a single 12-lead standard ECG will be obtained locally at Visit 0 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.

4.7.4. Chest X-ray and Tuberculosis Testing

For patients entered in JAHN(7), a posterior-anterior view chest x-ray will be obtained locally at screening (Visit 0), 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 0) for evidence of active or latent TB as described in the exclusion criterion [37], Section 4.5.2.

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.

4.8. Statistical Considerations

4.8.1. Sample Size Determination

This addendum will aim to enroll approximately 250 additional patients ≥18 years of age into the JAHN Study. It is anticipated that approximately 80% of enrolled patients will complete the first 52 weeks (treatment period 1). Of those, it is expected 30% will enroll into the JAHN randomized withdrawal and down-titration substudy. This addendum is descriptive in nature and the sample size is not based on any statistical power calculations.

4.8.2. Populations for Analyses

Unless otherwise specified, the efficacy and health outcome analyses for treatment period 1 will be conducted on the intent-to-treat population, defined as all enrolled patients.

Unless otherwise specified, safety analyses will be conducted on the safety population defined as all enrolled patients who receive at least 1 dose of investigational product and who did not discontinue from the study for the reason “Lost to Follow-up” at the first postbaseline visit. The safety population of this addendum may be combined with the corresponding safety population of the main protocol.

4.8.3. Statistical Analyses

4.8.3.1. General Statistical Considerations

Statistical considerations described below apply to patients enrolled in JAHN(7). For treatment period 1, efficacy outcomes will be analyzed separately and using different methods from the main protocol. Since the safety population may be combined with corresponding safety population in the main protocol, analysis of safety outcomes will be analyzed using methods in the main protocol. These analysis methods are described below. Patient data from treatment period 2 of JAHN(7) will be analyzed as described in Section 10 of the main protocol.

Treatment Period 1: Weeks 0-52

All analyses of efficacy data from patients enrolled in JAHN(7) during treatment period 1 are descriptive. Patients enrolled in this addendum do not contribute efficacy data to the analysis described in the main protocol for this treatment period. However, results from the analysis may compared to other related cohorts in the JAHN study.

For patients enrolled in JAHN(7) treatment period 1 'baseline' refers to data collected during screening or at Visit 1.

Analyses of discrete efficacy variables in treatment period 1 will be descriptively summarized in terms of frequencies and percentages. The percentages and the 95% confidence interval (CI) of the percentages will be reported.

Continuous efficacy variables in treatment period 1 will be descriptively summarized in terms of number of patients, mean, standard deviation, median, minimum, and maximum. When evaluating continuous measures over time, a restricted maximum likelihood-based mixed-effects model of repeated measures will be used. The model will include visit as a fixed categorical effect and baseline score and baseline score-by-visit interaction as fixed continuous effects. 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. Least squares (LS) means along with its 95% CI will be reported.

Continuous efficacy and health outcome variables may also be descriptively summarized using analysis of covariance (ANCOVA) with baseline value in the model for treatment period 1. The LS means and 95% CIs will be reported. Missing data imputation method for the ANCOVA model will be specified in the SAP.

Overall strategy for imputing missing data are described in the JAHN protocol.

Treatment Period 2: Weeks 52-104

As patients from JAHN(7) will have been treated with open-label baricitinib for 52 weeks, similar to patients enrolled in the main protocol who were on placebo at the time of entry, and since patients are randomized at the start of treatment period 2, data from patients in JAHN(7) who participate in the substudy during treatment period 2 may be combined with the corresponding population from the main protocol and will be analyzed as described in Section 10 of the main protocol.

5. References

Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, Berger TG, Bergman JN, Cohen DE, Cooper KD, Cordoro KM, Davis DM, Krol A, Margolis DJ, Paller AS, Schwarzenberger K, Silverman RA, Williams HC, Elmets CA, Block J, Harrod CG, Smith Begolka W, Sidbury R. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338-3351.

Attachment 1. I4V-MC-JAHN(7) Schedule of Activities

	Screening Period	Treatment Period 1							Treatment Period 2									PTFU Period
Visit number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ET**	**801[a]**
Weeks from entry into JAHN		**0**	**4**	**8**	**16**	**24**	**36**	**48**	**52**	**56**	**60**	**64**	**68**	**76**	**84**	**92**	**104**	**108**
Visit tolerance interval (days) from entry into JAHN	**-8 to -35**		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	28 ± 4 after last dose
Procedures																		
Inclusion and exclusion review	X	X																
Informed consent	X																	
Clinical Assessments																		
Demographics	X																	
Medical history	X																	
Substance use (alcohol, tobacco use)	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
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
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
12-lead ECG (single)	X																	
Chest x-ray (posterior-anterior view)[c]	X																	
TB test[d]	X																	
Read PPD if applicable (48-72 hours post PPD)	X[e]																	
Preexisting conditions	X																	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ePRO (patient diary) dispensed	X	X	X	X				X	X[g]	X[g]	X[g]	X[g]						
ePRO (patient diary) returned[f]		X	X	X	X				X	X[g]	X[g]	X[g]	X[g]				X[h]	
Treatment assignment[i]		X																
Randomization[i]									X									

	Screening Period	Treatment Period 1							Treatment Period 2									PTFU Period
Visit number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ET**	**801[a]**
Weeks from entry into JAHN		**0**	**4**	**8**	**16**	**24**	**36**	**48**	**52**	**56**	**60**	**64**	**68**	**76**	**84**	**92**	**104**	**108**
Visit tolerance interval (days) from entry into JAHN	**-8 to -35**		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	28 ± 4 after last dose
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP dispensed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IP returned and compliance assessed			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense TCS (as needed)		X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weigh (tube with cap) and record returned TCS (as needed)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician-Assessed Efficacy Measures																		
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Outcomes Measures and Other Questionnaires[j]																		
POEM	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WPAI-AD		X	X		X	X	X	X	X	X			X	X	X	X	X	X
EQ-5D-5L		X	X		X	X	X	X	X	X			X	X	X	X	X	X
Itch NRS	X	X	X	X	X			X	X	X	X	X	X				X[k]	
Skin Pain NRS	X	X	X	X	X			X	X	X	X	X	X				X[k]	
ADSS	X	X	X	X	X			X	X	X	X	X	X				X[k]	
PGI-S-AD	X	X	X	X	X			X	X	X	X	X	X				X[k]	
HADS	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
C-SSRS[l] and Self-Harm Supplement Form	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-up Form[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																		
Clinical chemistry[n]	X	X	X	X	X	X	X		X			X		X		X	X	X
Hematology	X	X	X	X	X	X	X		X			X		X		X	X	X
Lipids (fasting)[o]		X			X		X		X			X		X			X	
FSH[p]	X																	
TSH	X																	

	Screening Period	Treatment Period 1							Treatment Period 2									PTFU Period
Visit number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16/ET**	**801[a]**
Weeks from entry into JAHN		**0**	**4**	**8**	**16**	**24**	**36**	**48**	**52**	**56**	**60**	**64**	**68**	**76**	**84**	**92**	**104**	**108**
Visit tolerance interval (days) from entry into JAHN	**-8 to -35**		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	28 ± 4 after last dose
HIV	X																	
HCV antibody[q]	X																	
HBV testing	X																	
HBV DNA[r]	X				X		X		X			X		X		X	X	X
Urinalysis	X	X	X		X		X		X			X		X		X	X	X
Serum pregnancy[s]	X																	
Urine pregnancy[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics: blood		X																
Serum immunoglobulin (IgE)		X			X		X		X								X	
Stored serum and plasma samples for exploratory analysis		X			X		X		X								X	
Stored blood for RNA analysis		X			X		X		X								X	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia–Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ePRO = electronic patient-reported outcome (device); EQ-5D-5L = the European Quality of Life–5 Dimensions–5 Levels; ET = early termination; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety Depression Scale; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; 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 = posttreatment follow-up; RNA = ribonucleic acid; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TCS = topical corticosteroids; TSH = thyroid stimulating hormone; WPAI-AD = Work Productivity and Activity Impairment Questionnaire – Atopic Dermatitis.

a Patients who have discontinued IP but remain in the study for more than 28 days without IP can combine their Visit 16/ET with Visit 801 (follow-up 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 reports are available.
d TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. See Exclusion Criterion [37] 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 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 0 (post-PPD)
f Patient ePRO devices will need to be collected from screen fail patients
g Patient diaries are not required for patients known by the investigator to not meet substudy eligibility criteria (IGA score ≥3, patients receiving high-potency TCS and/or on a study drug interruption at Week 52 [Section 5.1.3.1 of the main protocol]). Thus, patient diaries will not need to be dispensed/returned for visits indicated.
h Applies only if ET visit occurs while patient has diary.
i At Week 1 treatment assignment is to open label baricitinib 2-mg and at Week 52 those deemed eligible to participate in the substudy will be randomized to either placebo, baricitinib 1-mg, or baricitinib 2-mg.
j Investigators are strongly encouraged not to dispense TCS until after 1 week of baricitinib treatment since treatment will be open-label; however, in the case of worsening and unacceptable symptoms this is allowed.
k The following measures (POEM, DLQI, HADS, EQ-5D-5L, and WPAI-AD) should be completed prior to any clinical assessments being performed on days when study visits occur.
l Suicidal ideation and behavior subscales excerpt – adapted for the assessment of 11 preferred ideation and behavior categories.
m The Self-Harm Follow-up Form is only required if triggered by the Self-Harm Supplement Form.
n Clinical chemistry will include the following value calculated from serum creatinine: eGFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine 2009 equation).
o 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.
p 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).
q 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.
r Patients who are positive for HBcAb and negative for HBV DNA may be enrolled. Any enrolled patient who is HBcAb positive, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule (see Section 9.4.7 of the main protocol).
s For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 0. Urine pregnancy tests (local laboratory) will be performed at Visit 1 and at all subsequent study visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

Attachment 2. I4V-MC-JAHN(7) Clinical Laboratory Tests

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

Abbreviations: 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] Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis
[d] 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.
[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] HBV DNA testing will be done in those patients who are HBcAb positive at screening.
[h] A positive hepatitis C antibody (Hep C antibody) result will be confirmed with an alternate hepatitis C method.
[i] 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.
[j] To confirm postmenopausal status for women ≥40 and <60 years of age who have had a cessation of menses, an FSH test will be performed. Non-childbearing potential is defined as an FSH ≥40 mIU/mL and a cessation of menses for at least 12 months.
[k] 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.

Attachment 3. American Academy of Dermatology: Criteria for the Diagnosis and Assessment of Atopic Dermatitis

Features to be considered in diagnosis of patients with AD:

Essential Features—must be present:

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

*Patterns include:

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

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

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

Associated Features—these clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used for defining or detecting AD 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. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70(2):338-3351.

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