I4V-MC-JAIX(2) Clinical Protocol Addendum

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

NCT03559270

Approval Date: 19-Nov-2020

1. Protocol Addendum I4V-MC-JAIX(2) A Multicenter, Open-Label, Phase 3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Moderate to Severe Atopic Dermatitis

BREEZE-AD6

Baricitinib (LY3009104)

This addendum is to be performed in addition to all procedures required by protocol I4V-MC-JAIX(c) or any subsequent amendments to that protocol unless otherwise specified within this addendum.

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Protocol Addendum (2) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 19-Nov-2020 GMT

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3. Rationale for Addendum

The purpose of addendum JAIX(2) is to collect qualitative visual evidence of clinical response to treatment with baricitinib as monotherapy to pair with the clinical assessments and patient self-assessments collected under the main protocol. Sequential photographs of selected lesions or involved areas will be obtained at specific visits before and after treatment with study medication through Week 16.

This addendum will apply to select sites in the United States that have participated in JAIX and its originating study (I4V-MC-JAIW). Eligible patients will enroll directly into JAIX(2).

This addendum is to be performed in addition to all other procedures required by the clinical protocol for Study JAIX(c) unless otherwise specified within this addendum. JAIX(2) applies to JAIX(c) and all subsequent amendments (referred to throughout as the "main protocol").

4. Protocol Additions

4.1. Overview of Protocol Additions

With this addendum, up to approximately 30 patients with moderate to severe atopic dermatitis (AD) will enroll directly into Study JAIX. This group of patients will be in addition to the approximately 450 patients who may enroll after participating in JAIW. Patients entering this addendum cannot have previously enrolled in any other study investigating baricitinib. Patients will complete a screening period (up to 5 weeks in duration). If all inclusion criteria and none of the exclusion criteria of this addendum are met, patients may enroll into JAIX(2) where they will receive open-label baricitinib 2-mg daily as monotherapy until the Week 16 visit. After Week 16, use of background low-potency topical corticosteroids (TCS) is allowed throughout the remaining treatment period. The screening procedures and inclusion/exclusion criteria in this addendum are similar to those of study JAIW.

Patients participating in the addendum will have multiple photographs taken during the first 16 weeks of the treatment period. Study procedures starting at Visit 1 will be similar to those in the main protocol, with the exception of photography and the fact that TCS will not be dispensed or weighed during the first 16 weeks of the study. Atopic dermatitis rescue treatments are not permitted during this study. Due to the monotherapy nature of the first 16 weeks of treatment, patients requiring more than baricitinib prior to Week 16 will be discontinued from the study.

Provisions for managing study activities under exceptional circumstances (such as pandemics or natural disasters) have been added to this addendum (Attachment 4).

4.2. Section 3.3. Benefit/Risk Assessment

The overall benefit risk assessment is consistent with the main protocol. All patients will be assigned to the baricitinib 2-mg dose, which showed efficacy in improving disease signs and symptoms of AD in Phase 2. However, in this addendum, patients will not be allowed to use low-potency TCS as concomitant therapy until after Week 16.

4.3. Section 4. Objectives and Endpoints

The objectives of this addendum are to estimate the clinical response to baricitinib 2-mg. Table JAIX.1 shows the objectives and endpoints of this addendum. Data collected at Visit 1 of JAIX(2) will be used as baseline for efficacy assessments.

Table JAIX.1. Objectives and Endpoints

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

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

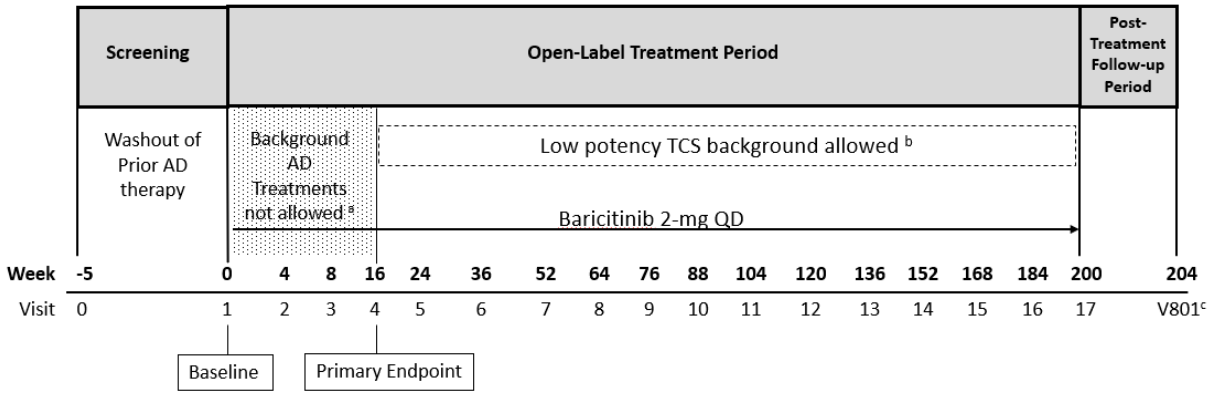
4.4. Section 5. Study Design

4.4.1. Section 5.1. Overall Design

Addendum JAIX(2) allows patients to enter directly into Study JAIX without first completing at least 16 weeks of treatment in an originating study. Patients entering this addendum cannot have previously enrolled in any other study investigating baricitinib. Up to approximately 30 patients are planned to be enrolled in this addendum.

All patients enrolled in JAIX(2) will receive open-label baricitinib 2-mg daily beginning at Visit 1. Patients will use emollient daily throughout the study. Moisturizers with additives such as TCS, antipruritics, or antiseptics are not permitted. Use of other AD treatments including TCS, other topical treatments such as topical calcineurin inhibitors (TCNIs) and phosphodiesterase type 4 (PDE-4) inhibitors, and systemic treatments are either not permitted or are limited to use only after treatment Week 16 (see Section 4.6 of this addendum).

Figure JAIX.1 illustrates the design of this addendum which includes 3 study periods; a 5-week screening period, a 200-week open-label treatment period, and a 4-week posttreatment follow-up (PTFU) period. The full visit schedule for patients enrolled in the addendum is outlined in the Study Schedule of Activities for this addendum (Attachment 1).



Abbreviations: AD = atopic dermatitis; QD = once daily; TCS = topical corticosteroids; V = visit.

a The first 16 weeks of the treatment period are monotherapy. Refer Section 4.4.3 and Section 4.6.1 of this addendum for full details.

b After completion of the Week 16 visit (V4), the patient may begin using low potency TCS as background therapy in addition to daily use of emollients. Other AD treatments are not allowed. Refer to Section 4.4.3 and Section 4.6.1 of this addendum for full details.

c Occurs approximately 28 days after the last dose of investigational product.

Figure JAIX.1. Illustration of study design for Clinical Protocol I4V-MC-JAIX(2).

Throughout the trial, investigators should continue to assess benefit-risk for patients to remain in the trial and should consider discontinuing patients if AD symptoms are unacceptable.

4.4.2. Screening Period

The duration of the screening period for patients enrolled in JAIX(2) is between 8 and 35 days prior to Visit 1 (Week 0). Eligibility of each patient will be reviewed based on all addendum entry criteria described in Section 4.5. At Visit 0, the patient will sign the addendum 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: 2 weeks for systemic treatments and 1 week for topical treatments (not including emollients). Patients will be required to use emollients daily during the 7 days preceding enrollment and throughout the study. Emollients must not contain additives, such as TCS, antiseptics, and antipruritics. If patients have been using emollients daily at the time of screening, then those cumulative days can be utilized to meet inclusion criterion [8]. Site staff should review all washout requirements and prohibited medications with the patient prior to the conclusion of Visit 0 to minimize the risk of patients using these medications inappropriately.

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. Investigators should review the vaccination status of their patients and follow the local guidelines for vaccination of those aged ≥18 years with nonlive vaccines intended to prevent infectious disease before entering patients into the study. Refer to Exclusion Criterion [27] in Section 4.5.2 for additional information regarding herpes zoster vaccinations.

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).

4.4.3. Section 5.1.1. Open-Label Treatment, Weeks 0 to 200

Study activities will be conducted according to the Schedule of Activities (Attachment 1) and as described in Section 4.8 and Section 4.9 of this addendum and Section 9 of the main protocol.

Treatment Weeks 0 to 16

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 Visit 0 (Screening) laboratory test results. Patients who meet all criteria for inclusion and none of the exclusion criteria will proceed to enrollment and begin the open-label treatment period.

During the first 16 weeks of the study, patients will be treated with baricitinib 2-mg as monotherapy (i.e. no TCS, TCNIs, or topical PDE-4 inhibitors or systemic AD treatments are allowed). However, emollients are required to be used daily throughout the treatment period and must not contain additives, such as TCS, antiseptics or antipruritics. There are no rescue therapies available during this open-label study. Additional prohibited therapies are listed in Section 4.6.1.1 of this addendum.

At Visit 1, open-label investigational product (IP) will be allocated by interactive web-response system (IWRS), and the patient will begin treatment with baricitinib 2-mg once daily (QD). The IP will be administered daily. Daily diaries will be utilized during the screening period and through Week 16.

Study procedures and assessments of disease severity will be performed as described in the Schedule of Activities (Attachment 1). At Week 16, all patients should be formally assessed to determine if sufficient clinical benefit has been observed to justify continuing in this study. Clinical benefit is defined as meeting at least 1 of the criteria defined in the main JAIX protocol (Section 5.1.1) during the first 16 weeks of this addendum.

All patients who permanently discontinue IP prior to the primary endpoint will follow the study discontinuation requirements as outlined in the main protocol.

Photographs Weeks 0 to 16

Serial photographs will be taken of select lesions or body regions following guidelines provided by the sponsor. At baseline (Visit 1), the investigator should identify approximately 4 to 6 areas to photograph that are representative of the patient's overall baseline disease severity (Investigator's Global Assessment [IGA] scores 3 or 4). The areas selected should demonstrate the diversity of the body areas impacted and include areas such as the trunk and limbs, hands, feet, neck, and/or face if these areas are affected. The PI should consider the size and visibility of the lesion to determine the most appropriate visual field to be included in the photograph(s). To provide visual context of areas of involvement and perspective of body surface area involved, consideration should be given to collecting both anatomical and target images of lesions/areas. For example, photographing a specific lesion on the abdomen from a distance of a few inches (referred to as targeted) vs a photo of the entire abdominal region (or even entire trunk) taken from a distance of a few feet (referred to as anatomical) or obtaining both targeted and anatomical images of the involved area. No full-body images should be collected.

One to three photos should be taken of each selected area at baseline (Visit 1); no more than 12 total photos. At Visits 2, 3, and 4, the areas photographed at baseline will be photographed again to document changes in disease severity over the first 16 weeks of study treatment. A maximum of 12 photos will be collected at each timepoint.

To enable comparison of the serial photographs for a single patient, the photographs taken at each visit should be obtained under similar lighting conditions, magnification, distance from target, subject preparation and positioning, and per instructions provided by the sponsor or designee. Because masking (deidentification) is required, sites should avoid photographing regions with tattoos that will affect visualization of disease severity after masking is completed.

Standardized photography equipment may be provided by the sponsor. If sites have their own equipment on site, use of this equipment may be permitted instead of sponsor-provided equipment, after agreement with the sponsor. If possible, the same equipment should be used to capture all images collected for a single patient. All images collected under this addendum will be uploaded to a central repository managed by an imaging vendor selected by the sponsor. The imaging vendor will ensure that appropriate masking has been applied to deidentify the image prior to transferring these images to the sponsor.

Treatment Weeks 16 to 200

Patients will continue treatment with 2-mg baricitinib QD.

After Week 16, addendum patients may begin receiving low potency TCS (e.g. Hydrocortisone 2.5% ointment) as background therapy for comfort, if needed.

Study procedures and assessments of disease severity will continue to be performed as described in the Schedule of Activities (Attachment 1). As per the main protocol (Section 5.1.1), a formal assessment of clinical benefit is required at Week 16, and only those patients meeting the protocol-defined Clinical Benefit criteria should continue in the study beyond Week 16.

4.4.4. Section 5.1.2. Post-treatment Follow-up Period

Patients enrolled in the addendum will follow the requirements for early termination visit (ETV) and PTFU as described in the main protocol.

4.4.5. Section 5.2. Number of Participants

Up to approximately 30 participants may be enrolled into Study JAIX via this addendum. This group of patients will be in addition to the approximately 450 patients who may enroll after participating in JAIW.

4.4.6. Section 5.4. Scientific Rationale for Study Design

This open-label addendum will enroll moderate to severe AD patients with a history of inadequate response or intolerance to existing topical therapies for which a systemic treatment such as baricitinib may therefore be appropriate. This addendum study will generate long-term efficacy and safety data in AD and allow for collection of high-quality photographs to highlight the observed efficacy in this study.

During the screening period, a washout of systemic and topical treatments for AD is incorporated to minimize confounding effects of background treatment when establishing baseline disease severity.

During the open-label treatment period, patients will be treated with baricitinib 2-mg, which has been shown to be efficacious as monotherapy in completed Phase 3 AD studies JAHL, JAHM, and JAIW. To ensure that the primary and secondary outcome results represent the effectiveness of baricitinib alone, patients will not be permitted to use background therapies, including TCS, prior to Visit 4 (Week 16). For patient comfort, daily treatment with emollient is required for 7 days prior to treatment initiation and will continue throughout the study. At Week 16, all patients should be formally assessed to determine if sufficient clinical benefit has been observed to justify continuing in the study. The criteria for determining sufficient clinical benefit are discussed in Section 5.1.1. of the main protocol.

Photographs will be obtained at each scheduled visit from baseline through Week 16 to collect visual evidence of time to onset and extent of clinical response.

The PTFU period is for safety monitoring after the patient has been off IP for approximately 28 days. The length of the PTFU period is consistent with other baricitinib AD protocols.

4.5. Section 6. Study Population

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

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. All screening activities must be completed and reviewed before the patient is enrolled. The inclusion/exclusion criteria of this addendum are similar to those of the originating study (JAIW), except for: inclusion of an upper limit for body surface area (BSA) extent during screening, reduction of duration of washout from topical and systemic therapies for AD, and exclusion of sedating antihistaminic therapies from prohibited medications.

4.5.1. Section 6.1 Inclusion Criteria

Informed Consent

[1] are aged ≥18 years 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 before screening, as defined by the American Academy of Dermatology: Criteria for the 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 enrollment (Visit 1)

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

c. 10% to 50% BSA involvement at screening (Visit 0) and enrollment (Visit 1).

[5] have a documented history by a physician and/or investigator of inadequate response to existing topical medications within 6 months of screening (Visit 0), 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 (for example, 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 (for example, 14 days for super-potent TCS), whichever is shorter. Topical corticosteroids may be used with or without TCNIs.

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

c. patients who failed systemic therapies intended to treat AD (such as cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil) within 6 months of screening (Visit 0) will also be considered as surrogates for having inadequate response to topical therapy.

[6] agree to discontinue use of the following excluded medications/treatments for at least 2 weeks before enrollment (Visit 1):

a. oral systemic corticosteroids and leukotriene inhibitors

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 1 week before enrollment (Visit 1):

a. TCS or topical immune modulators (for example, tacrolimus or pimecrolimus)

b. Topical PDE-4 inhibitor (crisaborole).

[8] have applied emollients daily for at least 7 days before enrollment and agree to use emollient daily throughout the treatment period.

[9] Patients who are receiving chronic treatments to improve sleep should be on a stable dose for at least 2 weeks before screening as determined by the investigator.

Patient Characteristics

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

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

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

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

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

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

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

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

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

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

4.5.2. Section 6.2 Exclusion Criteria

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

Medical Conditions Related to Atopic Dermatitis

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

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

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

[14] a history of 2 or more episodes of eczema herpeticum.

[15] 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 screen failure and at least 2 weeks after resolution of the infection.

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

[17] have been treated with the following therapies:

a. monoclonal antibody (for example, ustekinumab, omalizumab, dupilumab) for less than 5 half-lives before enrollment.

b. received prior treatment with any oral Janus kinase (JAK) inhibitor (for example, tofacitinib, ruxolitinib) less than 2 weeks before enrollment.

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

d. have had an intra-articular corticosteroid injection within 6 weeks of 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

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

[19] 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.

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

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

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

[23] have a history of venus thromboembolic event (VTE), or are considered at high risk for VTE as deemed by the investigator, or have 2 or more of the following risk factors for VTE:

a. Aged >65 years.

b. BMI >35 kg/m^2.

c. Oral contraceptive use and current smoker.

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

[25] 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 <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.

[26] 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 of screening.

b. a history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, central nervous system 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 have not received appropriate and documented prophylaxis for TB.

f. evidence of active TB or have previously had evidence of active TB and have not received appropriate and documented treatment.

g. clinically serious infection or received IV antibiotics for an infection, within 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.

[27] have been exposed to a live vaccine within 12 weeks of 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: All patients who are eligible to receive the herpes zoster vaccine (per local guidelines) and who have not received it by screening will be encouraged to do so before enrollment; vaccination must occur >4 weeks before enrollment and first dose of IP. Patients will be excluded if they were exposed to herpes zoster vaccination within 4 weeks of planned enrollment.

[28] have a history of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within 2 years of screening.

[29] 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 within the 2 months before Visit 0:

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.

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.

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

Other Exclusions

[31] are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures, including use of data collection devices and collection of multiple photographs of affected body areas.

[32] 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.

[33] have participated in a clinical study involving an investigational product within the last 30 days. If the previous IP has a long half-life (2 weeks or longer), at least 3 months or 5 half-lives (whichever is longer) must have passed.

[34] have previously been enrolled in this addendum, or any other study investigating baricitinib.

[35] 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.

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

Diagnostic Assessments

[37] 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.

[38] 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 if 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 before 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.

[39] have a positive test for HBV infection, defined as:

a. positive for hepatitis B surface antigen, or

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

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

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

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

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

[42] 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.

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

a. aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN)

b. alkaline phosphatase (ALP) ≥2 × ULN

c. total bilirubin ≥1.5 × ULN

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

e. total white blood cell count <2500 cells/μL (<2.50 × 10^3/μL or <2.50 GI/L)

f. neutropenia (absolute neutrophil count <1200 cells/μL) (<1.20 × 10^3/μL or <1.20 GI/L)

g. lymphopenia (lymphocyte count <750 cells/μL) (<0.75 × 10^3/μL or <0.75 GI/L)

h. thrombocytopenia (platelets <100,000/μL) (<100 × 10^3/μL or <100 GI/L)

i. estimated glomerular filtration rate <60 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 [42] and [43]), 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. Section 6.4. Screen Failures

Patients who are entered into the addendum but do not meet the eligibility criteria for participation in the addendum (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. Section 7. Treatments

Sections 7.1 through 7.6 will follow the main protocol; there are no modifications to these sections with this addendum.

4.6.1. Section 7.7. Concomitant Therapy

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

Rescue therapy is not permitted, see Section 4.6.1.3 of this addendum.

Concomitant therapies permitted/not permitted during the addendum study are described below.

4.6.1.1. Section 7.7.1. Prohibited Medications and Procedures

Prohibited Medications and Procedures Not Requiring Interruption of Investigational Product

The following therapies will not be allowed during the study:

- Medium-potency TCS or higher potency TCS, TCNIs (for example, tacrolimus and pimecrolimus), or topical PDE-4 inhibitor (that is, crisaborole) are not allowed. **Low-potency TCS is not allowed prior to Week 16 (Visit 4)**.
- Allergen immunotherapy.
- Phototherapy including psoralen and ultraviolet A (PUVA), ultraviolet B, tanning booth, and excimer laser.
- Bleach baths.

Prohibited Medications Requiring Temporary Interruption of Investigational Product

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

- Live vaccines (including Bacillus Calmette-Guérin [BCG] or herpes zoster)
  - For BCG vaccination, IP should be temporarily interrupted for 12 weeks.
  - For herpes zoster vaccination, IP should be temporarily interrupted for 4 weeks.

- Probenecid: if a patient is inadvertently started on probenecid, IP should be temporarily interrupted and can be resumed after patient has discontinued probenecid. If a patient is not able to discontinue probenecid, then IP should be permanently discontinued.
- Systemic corticosteroids may be used for the treatment of an adverse event (AE) (for example, worsening of existing condition, such as asthma flare). Investigational product may be restarted if systemic corticosteroids were used for a short duration (<30 days). If used for >30 days, sponsor approval to restart IP is required. Systemic corticosteroids may not be used to treat AD.

Prohibited Medications Requiring Permanent Discontinuation of Investigational Product

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

4.6.1.2. Section 7.7.2. Permitted Medications and Procedures

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

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

Any changes of these concomitant medications must be recorded on the Concomitant Therapy pages of the eCRF.

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

4.6.1.3. Section 7.7.3. Rescue Therapy

No rescue therapy options are available during the study. Background TCS is not permitted prior to Week 16 (Visit 4). After Week 16, patients are allowed to use low-potency TCS as background therapy for comfort if needed. Patients who experience worsening and unacceptable symptoms of AD should consider discontinuing from the study. Patients requiring more than low-potency TCS to manage their symptoms after Week 16 should also be discontinued.

After completing the monotherapy portion of the open-label treatment period, Hydrocortisone 2.5% ointment will be supplied by the sponsor for use for the remainder of the first 2 years of the treatment period (dispensed at Visits 4 to 10 only). In the event that providing this topical formulation during this period is not possible, an alternate, equivalent potency TCS cream and/or ointment may be provided by the sponsor. Use of sponsor-supplied TCS should be recorded via weight of returned tubes as indicated in the Schedule of Activities (Attachment 1). Sponsor will not provide or reimburse the cost of TCS at Visit 11 or after.

In the event that the sponsor is unable to supply TCS as described above, commercially available Hydrocortisone 2.5% ointment or an equivalent-potency TCS cream and/or ointment that is in line with local practices can be supplied by the sponsor or the sites. Refer to Appendix 7 of the main protocol for guidance on potency equivalence.

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

4.7. Section 8. Discontinuation Criteria

4.7.1. Section 8.1.1 Temporary Interruption from Investigational Product

Refer to Section 4.6.1 of this addendum for interruption requirements related to concomitant medications. Otherwise, criteria for temporary interruption of IP due to abnormal laboratory findings and clinical events and C-SSRS findings are the same as those in the main protocol as are the expectations for retesting and resumption of IP.

4.7.2. Section 8.1.2 Permanent Discontinuation from Investigation Product

Refer to Section 4.6.1.1 above for a list of prohibited treatments that require permanent discontinuation of investigation product. Otherwise, the permanent discontinuation requirements of the main protocol (Section 8.1.2) apply to patients enrolled in this addendum.

4.7.3. Section 8.2 Discontinuation from the Study

No rescue therapies are available during this study (Section 4.6.1.3 of this addendum) and patients are not permitted to use low potency TCS prior to Week 16. An investigator may choose to discontinue the patient from the study to allow patient to receive other therapies. Otherwise, the requirements of the main protocol apply.

4.8. Section 9. Study Assessments and Procedures

Attachment 1 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

During the screening period, tests will be conducted to support eligibility assessments. From Visit 1 onward, patients included in the addendum will undergo laboratory testing procedures as defined in the main protocol. Attachment 2 lists the laboratory tests that will be performed for this addendum as part of scheduled study visits. Hepatic monitoring will be completed as defined in Appendix 4 of the main protocol.

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

4.8.1.1. Photography

4.8.1.1.1. Intended Use of Photographs

No formal analyses of the photographs are planned. The photographs may be included in the clinical study report, a regulatory submission package, scientific publications, or other public dissemination of clinical data to demonstrate disease presentation at baseline and clinical response following treatment with baricitinib.

These photographs may also be used in advertising and promotional activities including, but not limited to, communication with health care professionals and payers, patient education, speaker programs, and digital and print media messaging.

These potential uses will be included in the consent form signed by patients participating in this addendum. Patients must agree with the terms for use of their photographs to participate in this study.

4.8.1.2. Section 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 Atopic Dermatitis Sleep Scale (ADSS) and Skin Pain Numeric Rating Scale (NRS), which are currently being developed and validated according to regulatory guidances.

Photographs are commonly obtained in research investigations of atopic dermatitis to document disease presentation at baseline and clinical response following treatment with baricitinib. This study is being conducted with the objective of acquiring images of patients treated with

baricitinib as monotherapy, and therefore patients must agree to have their photos taken to participate in this study.

4.9. Section 9.4. Safety

All safety evaluations and AE reporting requirements described in Section 9.4 of the main protocol are required by this addendum. In addition, the following screening measures will be completed for patients entering addendum JAIX(2).

4.9.1. Section 9.4.2. Physical Exam

For each patient entered in addendum JAIX(2), a complete physical examination (excluding pelvic and rectal examinations) will be performed at screening (Visit 0). Thereafter, symptom-directed physical exams should be performed as described in Section 9.4.2 of the main protocol.

4.9.2. Section 9.4.6. 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. Hepatitis B virus DNA monitoring for these patients will occur as described in Section 9.4.6 of the main protocol.

4.9.3. Electrocardiograms

For patients entered in addendum JAIX(2), a single 12-lead standard ECG will be obtained locally at screening (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.

4.9.4. Chest X-ray and Tuberculosis Testing

For patients entered in addendum JAIX(2), 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 [38], Section 4.5.2 of this addendum.

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.

4.10. Section 10. Statistical Considerations

4.10.1. Section 10.1. Sample Size Determination

This addendum will aim to enroll up to approximately 30 additional patients ≥18 years of age into the JAIX Study. This addendum is descriptive in nature and the sample size is not based on any statistical power calculations.

4.10.2. Section 10.2. Populations for Analyses

The populations for analyses for this addendum are the same as 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):338-351.

Attachment 1. I4V-MC-JAIX(2) Schedule of Activities

	Screening	Period 1: Open-Label Treatment Period																	Period 2: PTFU
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ET[a]**	**801[b]**
Weeks from enrollment		**0**	**4**	**8**	**16**	**24**	**36**	**52**	**64**	**76**	**88**	**104**	**120**	**136**	**152**	**168**	**184**	**200**	**204**
Visit tolerance interval (days)	**-8 to -35**	**0**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28±4 after last dose**
Procedures																			
Inclusion and exclusion review	X	X																	
Informed consent	X																		
Demographics	X																		
Clinical Assessments																			
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
Height	X																		
Body Mass Index	X	X																	
Vital signs (BP and pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X																		
Symptom-directed physical examination[c]		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[d] (posterior—anterior view)	X																		
TB test[e]	X																		
Read PPD if applicable (48 to 72 hrs after PPD)	X[f]																		
Pre-existing Conditions	X																		
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	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															
ePRO (patient diary) returned		X	X	X	X													X[g]	
IWRS	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		
IP returned and compliance assessed			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Screening	Period 1: Open-Label Treatment Period																	Period 2: PTFU
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ET[a]**	**801[b]**
Weeks from enrollment		**0**	**4**	**8**	**16**	**24**	**36**	**52**	**64**	**76**	**88**	**104**	**120**	**136**	**152**	**168**	**184**	**200**	**204**
Visit tolerance interval (days)	**-8 to -35**	**0**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28±4 after last dose**
Dispense TCS[h]					X	X	X	X	X	X	X								
Weigh (tube with cap) and record returned TCS (as needed) [i]						X	X	X	X	X	X	X						X[a]	X
Photography																			
Photographs of representative lesions/body areas [j]		X	X	X	X														
Disease Severity Scales																			
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Outcomes Measures and Other Questionnaires[k]																			
Itch NRS	X	X	X	X	X[g]														
Skin Pain NRS	X	X	X	X	X[g]														
ADSS	X	X	X	X	X[g]														
PGI-S-AD	X	X	X	X	X[g]														
POEM	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
HADS	X	X	X	X	X	X	X	X	X	X	X	X						X[a]	X
EQ-5D-5L		X	X	X	X							X						X[a]	X
WPAI-AD		X	X	X	X							X						X[a]	X
C-SSRS and Self-Harm Supplement[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Self-Harm Follow-Up Form[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments																			
Lipids (fasting) [n]		X			X		X	X		X		X	X	X	X	X	X	X[o]	X
Clinical chemistry [p]	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
Serum pregnancy[q]	X																		
FSH[r]	X																		
TSH	X																		
HIV	X																		
HCV antibody[s]	X																		

	Screening	Period 1: Open-Label Treatment Period																	Period 2: PTFU
Visit Number	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17/ET[a]**	**801[b]**
Weeks from enrollment		**0**	**4**	**8**	**16**	**24**	**36**	**52**	**64**	**76**	**88**	**104**	**120**	**136**	**152**	**168**	**184**	**200**	**204**
Visit tolerance interval (days)	**-8 to -35**	**0**	**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**28±4 after last dose**
HBV testing[t]	X																		
HBV DNA[t]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X						X[u]	X
Urine pregnancy[q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunoglobulin (IgE)		X			X			X				X						X[u]	
Exploratory storage samples (serum and plasma)		X			X			X				X						X[u]	
RNA and biomarkers: blood		X			X			X				X						X[u]	

Abbreviations: AD = atopic dermatitis; ADSS = Atopic Dermatitis Sleep Scale; BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale 11 categories suicidal ideation/suicidal behavior; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ePRO = electronic patient-reported outcomes (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; IgE = immunoglobulin E; IP = investigational product; IWRS = interactive web-response system; NRS = numeric rating scale; PGI-S-AD = Patient Global Impression of Severity–Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PPD = purified protein derivative; PTFU = posttreatment follow-up; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TCS = topical corticosteroids; TSH = thyroid-stimulating hormone; WPAI-AD = Work Productivity and Activity Impairment-Atopic Dermatitis.

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

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

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

[d] A posterior–anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available.

[e] TB test(s) include PPD, QuantiFERON®-TB Gold, and T SPOT®. See Exclusion Criterion [38] for description of TB testing. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally. (Note: Exception: Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing but must have a chest x-ray at

screening.)

[f] If PPD testing was chosen to test for TB, then the patient must return and have her or his PPD test read 48 to 72 hours after Visit 0 (post-PPD).

[g] Applies to ET Visit if conducted prior to Week 16 only.

[h] TCS is not allowed prior to Visit 4 (study Week 16). Low-potency TCS can be used as background therapy from study Week 16 onward. Note, however, that at Visit 11 and after, low potency TCS is allowed but will not be provided by the sponsor or reimbursed by the sponsor.

[i] Returned TCS weight is collected, documented in the source notes and captured in INFORM for sponsor-provided TCS. If non-sponsor provided low potency TCS is dispensed, it is not necessary to collect weight details and if collected, these details should not be reported in INFORM.

[j] Refer to JAIX(2) addendum Section 4.4.3 for photography requirement details.

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

[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 required only if triggered by the Self-Harm Supplement Form.

[n] 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.

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

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

[q] 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 scheduled study visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

[r] For female patients aged ≥40 and <60 years who have had a cessation of menses for ≥12 months, an FSH test will be performed to confirm nonchildbearing potential (FSH ≥40 mIU/mL).

[s] 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.

[t] 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.

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

Attachment 2. JAIX(2) Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Absolute Reticulocyte Count	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin	Alkaline phosphatase
Mean cell hemoglobin concentration	Alanine aminotransferase (ALT)
Leukocytes (WBC)	Aspartate aminotransferase (AST)
Platelets	Blood urea nitrogen (BUN)
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,d]	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[k]
Ketones	Anti-Hepatitis B Surface antibody (HBsAb)[f]
Bilirubin	Human immunodeficiency virus (HIV)[f]
Urobilinogen	Hepatitis C antibody[f,g]
Blood	Thyroid-stimulating hormone (TSH)
Leukocyte esterase	Exploratory storage samples (serum, plasma and mRNA)
Nitrite	Pregnancy Test[h]
	Follicle-stimulating hormone[f,i]
Lipids[a,c]	Serum immunoglobulin (IgE)
Total cholesterol	QuantiFERON®-TB Gold or T-SPOT® TB[j]
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 Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to test. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

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

[e] eGFR for serum creatinine calculated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration Creatinine 2009 equation.

[f] Test required at Visit 0 only to determine eligibility of patient for the study.

[g] A positive hepatitis C antibody result will be confirmed with an alternate hepatitis C method.

[h] For all women of childbearing potential, a serum pregnancy test will be performed at Visit 0 and a local urine pregnancy test will be performed at Visit 1 and at all subsequent scheduled study visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

[i] To confirm postmenopausal status for women ≥40 and <60 years of age who have had a cessation of menses, an FSH test will be performed. Nonchildbearing potential is defined as an FSH ≥40 mIU/mL and a cessation of menses for at least 12 months.

[j] The QuantiFERON®-TB Gold test is the preferred alternative to the PPD test for the evaluation of TB infection, and it may be used instead of the PPD test or T-SPOT® TB test and may be read locally. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed. If the retest is indeterminate, then the patient is excluded from the study.

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

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, 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 atopic dermatitis for research and epidemiologic studies:

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

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

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

Source: Eichenfield et al. 2014.

Attachment 4. Provisions for Changes in Study Conduct During Exceptional Circumstances

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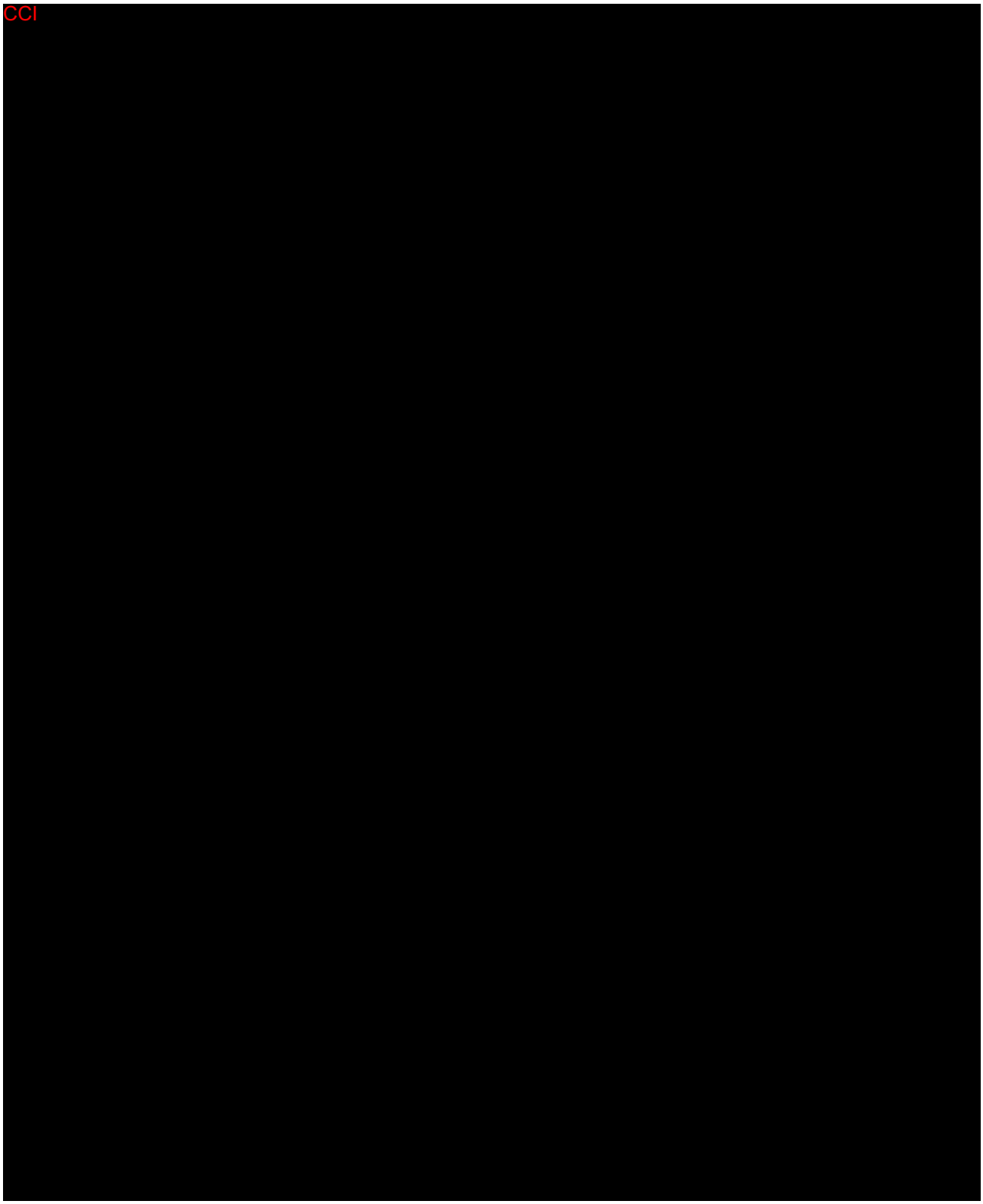

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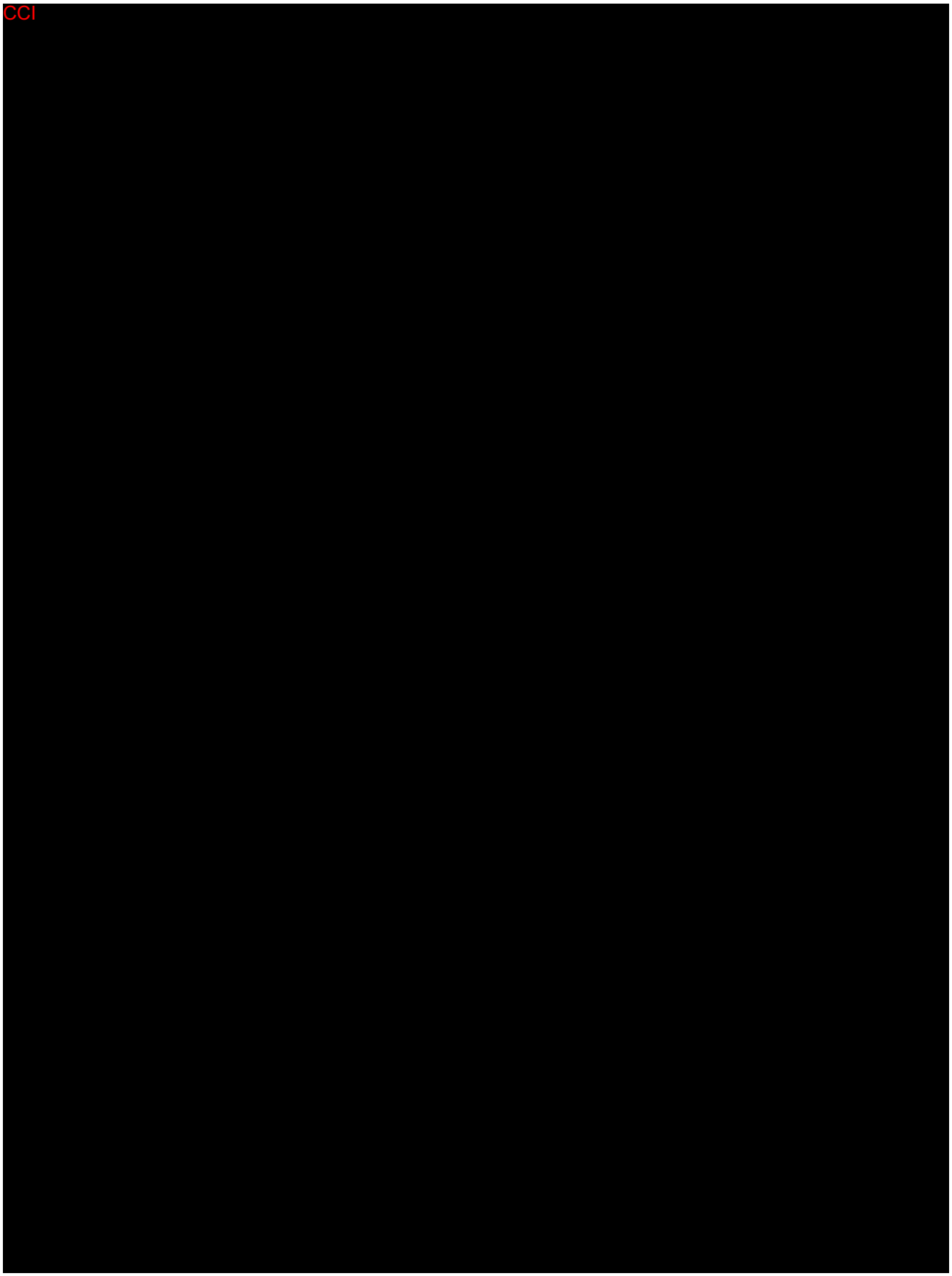

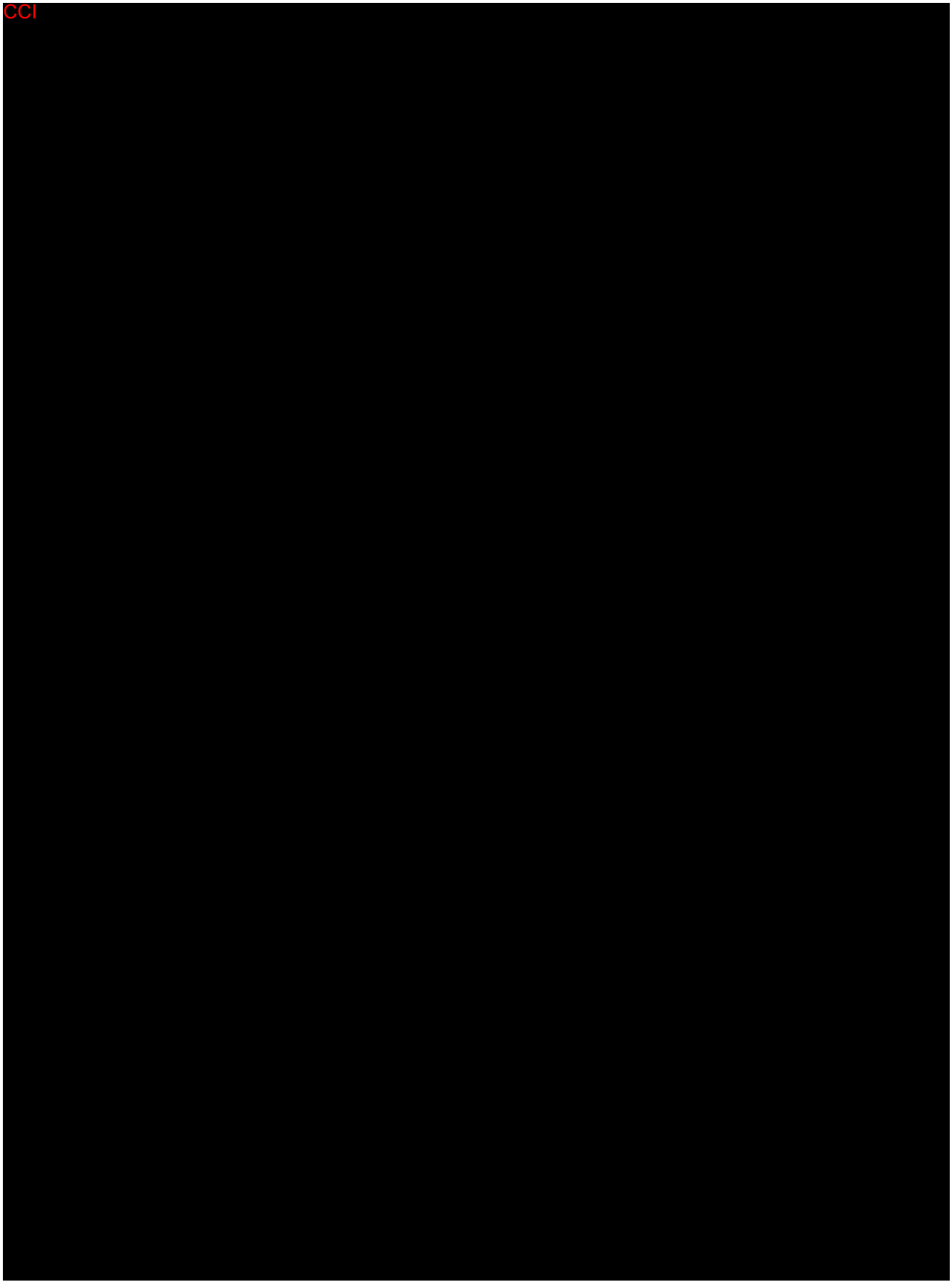
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Signature meaning: Approved