Protocol Addendum: I4V-MC-JAHO (5.1)

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Operationally Seamless, Adaptive Phase 2/3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Severe or Very Severe Alopecia Areata

NCT03570749

Approval Date: 14-Mar-2024

Title Page

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Operationally Seamless, Adaptive Phase 2/3 Study to Evaluate the Efficacy and Safety of Baricitinib in Adult Patients with Severe or Very Severe Alopecia Areata BRAVE-AA1

Protocol Number: I4V-MC-JAHO

Addendum Number: 5.1

Addendum Statement: This addendum is to be performed in place of procedures required by protocol I4V-MC-JAHO or any subsequent amendments to that protocol.

Compound: Baricitinib (LY3009104)

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number:

IND: 112543

Approval Date: Revised Protocol Addendum (5.1) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-074217

Protocol Addendum Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol Addendum	*23-Nov-2022*

Overall Rationale for the Revision [5.1]

The main rationale for the addendum revision is to update the primary objective and the statistical considerations to align with the final enrollment of 20 patients.

Other details are provided in the table below:

Section # and Name	Description of Change	Brief Rationale
1. Rationale for Addendum	Added 'endpoint' in place of 'objective' in brief rationale for Section 2.3.	Editorial correction
	Updated to percent change for the primary endpoint statement in brief rationale for Sections 2.3	To align with the wording used in the description of endpoints in the main protocol amendment, I4V-MC-JAHO(e)
	Revised the brief rationale statement in the table for Section 2.4.2. to state that 20 patients were enrolled into the addendum.	To align with the overall rationale.
	Updated to percent change for the primary endpoint statement in brief rationale for Section 2.9.	To align with the wording used in the description of endpoints in the main protocol amendment, I4V-MC-JAHO(e)
2.3. Objectives and Endpoints	Updated the primary objective and endpoint.	To align with the overall rationale.
	Updated Week 36 to Week 52 in third bullet for endpoints in the table.	To align with the primary endpoint of the study (Week 52).
2.4.1. Overall design	Revised the total number of patients to 20.	To align with the overall rationale.
	Removed the addendum version number 5 (2 instances) in the first paragraph.	Editorial correction.
2.4.2. Number of Participants	Revised the section to state that 20 patients were enrolled into the addendum.	To align with the overall rationale and to indicate that enrollment is completed.
2.6.1. Treatments Administered	Revised that the patients with renal impairment will not receive 4 mg QD in the footnote 'a' for Table JAHO.1. Treatment Regimen.	Updated for clarification.
2.6.7.1. Permitted Medications and Procedures	Removed the instances of Week 36 in the 4th bullet on corticosteroid injections	To align with the primary endpoint of the study (Week 52).
2.6.7.2. Prohibited Medications and Procedures	Revised the period for temporary interruption of BCG vaccination from Week 36 to Week 52.	To align with the primary endpoint of the study (Week 52).

Section # and Name	Description of Change	Brief Rationale
2.9.1. Sample Size Determination	Revised the sample size estimation for approximately 20 patients.	To align with the overall rationale.
2.9.3.1.1. Analysis Methods	The analysis methods were revised to descriptive statistics.	To align with the descriptive nature of the study.
2.9.3.1.2. Missing Data Imputation	Added that no imputation methods will be applied and removed information on non-responder imputation and last observation carried forward.	To substantiate the use of appropriate missing data imputation techniques.
2.9.4.1. Primary Analyses	The primary analyses were revised to descriptive statistics.	To align with the descriptive nature of the study.
	Updated to percent change for the primary endpoint description.	To align with the wording used in the description of endpoints in the main protocol amendment, I4V-MC-JAHO(e)
2.9.4.2. Secondary Analyses	Removed information on missing data imputation in the first paragraph.	To align with the revision made in Section 2.9.3.1.2. Missing Data Imputation.
Throughout the addendum	Minor editorial changes	For clarification

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1. Rationale for Addendum

This addendum is a 52-week subpopulation study to better characterize the effectiveness of baricitinib therapy in Black patients with AA.

AA is a clinically heterogenous, autoimmune mediated, nonscarring hair loss disorder that varies widely in the amount and pattern of hair loss. While AA can affect people of different races and sexes, recent epidemiological studies have suggested that Black or African American patients may have a greater risk of AA (Thompson et al. 2018; Lee et al. 2020). Furthermore, Black or patients of African descent also have a higher prevalence of other comorbid alopecia, including both scarring and nonscarring forms, such as central centrifugal cicatricial alopecia and traction alopecia, which creates further diagnostic challenges in this population (Olsen et al. 2011; Raffi et al. 2019).

In the BRAVE clinical development program for severe AA, baricitinib therapy was demonstrated to be an efficacious therapy compared with placebo. While patients who were Black or African American also showed significantly greater response to baricitinib compared with placebo, the overall response rate was lower in this subgroup compared to other racial subgroups. Potential hypotheses regarding the lower response rate includes the diagnostic challenges within a large clinical trial for ascertaining primary AA in the context of other comorbid alopecia or potential subgroup differences related to hair follicle, including the rate of regrowth (Taylor et al. 2002). Therefore, this knowledge gap indicates a need to study more closely the diagnosis and treatment outcomes of Black or African American patients with severe AA. The present addendum will allow a closer examination and provide additional descriptive outcomes in response to therapy with 4-mg baricitinib in this subpopulation.

The overall changes to this addendum are provided below.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 2.1. Schema for Substudy	Updated the study schema to 52 weeks	The primary study has demonstrated the efficacy of baricitinib versus placebo at 36 weeks. As Black patients were observed to have a slower rate of response, the endpoint for this study was extended to 52 weeks. Long-term efficacy and treatment withdrawal are studied in the JAHO(e) protocol and are not part of the addendum objectives.

Section # and Name	Description of Change	Brief Rationale
Section 2.2. Schedule of Activities	• Removed visits after 52 weeks	• Visits related to long-term extension and substudy are not needed for study objectives
	• Included IWRS visit code	• IWRS visits codes were added to reduce confusion with main protocol visits
	• Added Fitzpatrick scale and Hair Curl Assessment	• Fitzpatrick scale and Hair Curl assessment tools added to better characterize study population
	• Added close-up photography views of scalp at baseline to enhance diagnostic assessment • Added review of screening photographs by external expert to increase diagnostic reliability	• Study procedures were modified including close-up photographs to enhance diagnostic reliability with the inclusion of an independent reviewer who is an expert in severe AA in Black patients.
	• Deleted assessment related to nails	• Measure of nail assessment were removed given the lack of sensitivity to change in the JAHO study.

Section # and Name	Description of Change	Brief Rationale
	• Included Body Hair Symptoms and Impact, Patient Global Impression of Change, Patient Global Impression of Satisfaction • Deleted Alopecia Areata-Investigator Global Assessment, EQ-5D-5L, Short Form-36 Health Survey acute version 2, self-harm supplement, and self-harm follow-up form, and baricitinib plasma concentration (pharmacokinetic sample) • Modified footnotes as per 52-week subpopulation study	• Measures for other body hair areas as well as patient satisfaction and perception of change were included to address treatment response in other body hair areas that were not included in the JAHO study. • Additional measures were deleted as these secondary objectives were identified as not relevant to the addendum. • SOA table and footnotes edited to reflect these changes.
Section 2.3. Objectives and Endpoints	• Modified weeks to Week 36 and Week 52 • Updated the endpoints to	• The primary endpoint of this study was changed to percent change to characterize the degree of

Section # and Name	Description of Change	Brief Rationale
	include 52 weeks • Added secondary objectives related to earlier time points • Deleted secondary objectives related to long-term extension and substudy • Deleted secondary objectives for measures	improvement observed within the subpopulation of Black patients and was based on Week 52 due to the longer regrowth cycle of Black hair. • Earlier time points included to describe early regrowth patterns. • Removed objectives related to design elements and measures that are not relevant to addendum
Section 2.4.1. Overall Design	• Updated as Open-label study, population to be included Black participants, and the total number of participants enrolled in the study • Included 3 study periods	As baricitinib has been demonstrated to be effective, there is no comparison to a placebo arm and outcomes are descriptive in nature
Section 2.4.2. Number of Participants	Included total number of participants to be enrolled in this study	Although the initial target of enrollment was 60 patients, 20 patients were enrolled during the enrollment period.

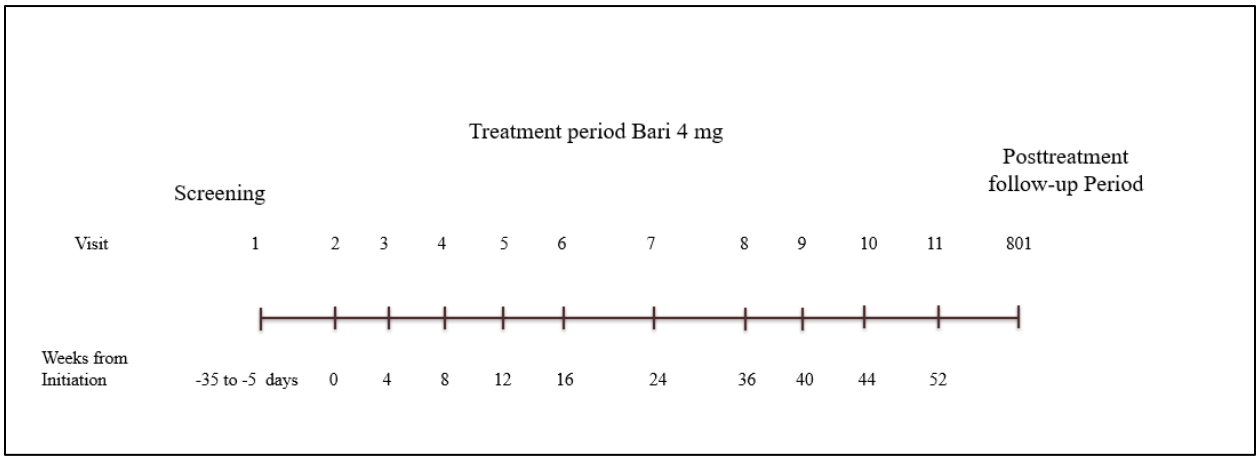
Section # and Name	Description of Change	Brief Rationale
Section 2.4.5. Scientific Rationale for Study Design and Section 2.4.5. Justification for Dose	Modified as per the substudy	Clarification on the objective of this addendum
Section 2.5.1. Inclusion Criteria	Included Black or African American race population	Inclusion to identify the patient subpopulation
Section 2.5.2. Exclusion Criteria	• Included "central centrifugal cicatricial alopecia" in the criterion [8] • Included "baricitinib" in criterion [10]b	• Clarification on potential differential diagnosis • Clarification on prior exposure to JAK inhibitor
Section 2.5.3. Lifestyle Restrictions	Added additional information to clarify the use of extensions and cosmetics	Addressed the use of hair and cosmetic styling relevant to subpopulation to ensure scalp assessment
Section 2.6.1. Treatments Administered	Treatment regimen 4 mg was updated	Open-label therapy was based on 4 mg to provide the dose necessary for patients who have nearly complete or complete scalp hair loss.
Section 2.6.2. Method of Treatment Assignment and Section 2.6.8.1. Continued Access	Modified as per 52-week subpopulation study	Updated as per study design
Section 2.6.7.1. Permitted Medications and Procedures	Included nutraceuticals	Additional clarification on permitted medications
Section 2.7.2. Discontinuation from Study	Deleted that patient should remain in the study after discontinuation of IP	Not needed as study is not for regulatory submission
Section 2.8.1.2. Secondary Efficacy Assessments	• Included as Other Clinician-reported	• For increased clarity

Section # and Name	Description of Change	Brief Rationale
	Outcomes under Section 2.8.1.2.1 and Alopecia Areata Patient-Reported Outcomes under Section 2.8.1.2.2 • Removed eye irritation and nail assessment • Added Body Hair Symptoms and Impact Scale • Added Patient Global Impression of Satisfaction • Added close-up photographs views with normal and polarized light	• Nail and eye irritation measures were not sensitive to change in the JAHO(e) protocol. • Included body hair assessment tool and patient perception of change and satisfaction with treatment related to secondary objectives of the addendum • Added additional photographs views to increase diagnostic reliability and detection of early regrowth
Section 2.9. Statistical considerations	• Revised primary objective • Revised secondary objectives to descriptive within subject changes	• Percent change of SALT score improvement was selected as primary endpoint to characterize the overall regrowth in this population. • Adjusted analyses as needed for secondary objectives relevant to open-label therapy and descriptive statistics

Section # and Name	Description of Change	Brief Rationale
Throughout the document	Updated the treatment as 4-mg baricitinib Changed the word for “randomization” to “initiation” or “enrollment”	Open-label study design without randomization

2. Protocol Additions

2.1. Schema for Substudy



2.2. Schedule of Activities

	Screening Period	Treatment Period											PTFU
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET**	**801º**
Visit Code in IWRS	**501**	**502**	**503**	**504**	**505**	**506**	**507**	**508**	**509**	**510**	**511**		**801**
Weeks from Initiation		**0**	**4**	**8**	**12**	**16**	**24**	**36**	**40**	**44**	**52**		
Visit Tolerance Interval (days)	**-5 to -35**		**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±4**	**±4**	**±7**		**28±4**
Inclusion and Exclusion Review	X	X											
Informed Consent	X												
Treatment Initiation		X											
Clinical Assessments													
Demographics	X												
Fitzpatrick Scale	X												
Preexisting Conditions/Medical History	X												
MPHL/FPHL History	X												
Substance Use (Alcohol, Tobacco)	X												
Previous and Current AA Treatments	X												
Chest x-ray (Posterior and Anterior View)[a]	X												
TB Test[b]	X												
Read PPD if Applicable (48 to 72 hours after V1)[c]	X												
Physical Examination	X												

	Screening Period	Treatment Period											PTFU
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET**	**801[o]**
Visit Code in IWRS	**501**	**502**	**503**	**504**	**505**	**506**	**507**	**508**	**509**	**510**	**511**		**801**
Weeks from Initiation		**0**	**4**	**8**	**12**	**16**	**24**	**36**	**40**	**44**	**52**		
Visit Tolerance Interval (days)	**-5 to -35**		**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±4**	**±4**	**±7**		**28±4**
12-Lead ECG (Single, Local)	X												
Height	X												
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X	X											
Vital Signs (BP and Pulse)	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom-Directed Physical Exam[d]		X	X	X	X	X	X	X	X	X	X	X	X
MPHL/FPHL Assessment[e]								X			X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography Scalp[f]	X	X	X	X	X		X	X			X	X	
Photography Eyebrows/Eyelashes[f]		X	X	X	X		X	X			X	X	
Review by Sponsor Designee	X												
IP Dispensed		X	X	X	X	X	X	X	X	X			

	Screening Period	Treatment Period											PTFU
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET**	**801[o]**
Visit Code in IWRS	**501**	**502**	**503**	**504**	**505**	**506**	**507**	**508**	**509**	**510**	**511**		**801**
Weeks from Initiation		**0**	**4**	**8**	**12**	**16**	**24**	**36**	**40**	**44**	**52**		
Visit Tolerance Interval (days)	**-5 to -35**		**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±4**	**±4**	**±7**		**28±4**
IP Returned and Compliance Assessed			X	X	X	X	X	X	X	X	X	X	
Scales/Questionnaires													
SALT	X	X	X	X	X	X	X	X	X	X	X	X	X
Hamilton-Norwood Scale[e]	X							X			X	X	
ClinRO Measure for Eyebrow Hair Loss™		X	X	X	X	X	X	X	X	X	X	X	X
ClinRO Measure for Eyelash Hair Loss™		X	X	X	X	X	X	X	X	X	X	X	X
PRO for Scalp Hair Assessment™		X	X	X	X	X	X	X	X	X	X	X	X
PRO Measure for Eyebrows™		X	X	X	X	X	X	X	X	X	X	X	X
PRO Measure for Eyelashes™		X	X	X	X	X	X	X	X	X	X	X	X
Body Hair Symptoms and Impact		X	X	X	X	X	X	X	X	X	X	X	
Patient Global Impression of Change				X	X		X	X			X	X	
Patient Global Impression of Satisfaction					X		X	X			X	X	
Skindex-16 for AA		X			X		X	X			X	X	X
HADS		X			X		X	X			X	X	X

	Screening Period	Treatment Period											PTFU
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET**	**801[o]**
Visit Code in IWRS	**501**	**502**	**503**	**504**	**505**	**506**	**507**	**508**	**509**	**510**	**511**		**801**
Weeks from Initiation		**0**	**4**	**8**	**12**	**16**	**24**	**36**	**40**	**44**	**52**		
Visit Tolerance Interval (days)	**-5 to -35**		**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±4**	**±4**	**±7**		**28±4**
C-SSRS[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hair Curl Assessment[h]	X										X	X	
Laboratory Assessment													
Lipids (Fasting Visit)[i]		X			X		X	X			X	X	X
Clinical Chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test[k]	X												
FSH[l]	X												
TSH	X												
HIV	X												
HCV antibody testing[m]	X												
HBV Testing[n]	X												
HBV DNA[n]	X				X		X	X			X	X	X
Urinalysis	X	X	X	X	X	X	X	X			X	X	X

	Screening Period	Treatment Period											PTFU
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ET**	**801[o]**
Visit Code in IWRS	**501**	**502**	**503**	**504**	**505**	**506**	**507**	**508**	**509**	**510**	**511**		**801**
Weeks from Initiation		**0**	**4**	**8**	**12**	**16**	**24**	**36**	**40**	**44**	**52**		
Visit Tolerance Interval (days)	**-5 to -35**		**±4**	**±4**	**±4**	**±4**	**±7**	**±7**	**±4**	**±4**	**±7**		**28±4**
Urine Pregnancy Test[k]		X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics Blood		X											
Serum Immunoglobulin (IgE)		X			X			X			X		
Exploratory Storage Samples (serum, plasma)		X			X		X	X			X	X	X
RNA and Biomarkers: Blood		X			X		X	X			X	X	X

Abbreviations: AA = alopecia areata; AGA = androgenetic alopecia; BMI = body mass index; BP = blood pressure; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ClinRO = clinician-reported outcome; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FPHL = female pattern hair loss; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety and Depression Scale; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IP = investigational product; IWRS = investigator web-response system; MPHL = male pattern hair loss; PPD = purified protein derivative; PRO = patient-reported outcome; PTFU = posttreatment follow-up; SALT = Severity of Alopecia Tool; TSH = thyroid-stimulating hormone; TB = tuberculosis.

[a] A posterior-anterior view chest x-ray will be obtained locally at Screening (Visit 1), unless one has been performed in the past 6 months and the x-ray and/or the report is available.

[b] TB test(s) including PPD, QuantiFERON®-TB Gold, and T SPOT®. See exclusion criterion [28] 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. It is preferred that the QuantiFERON-TB Gold test be performed centrally; the T-SPOT must be performed locally. Note: 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.

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

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

[e] Presence of MPHL (AGA) will be assessed at screening using the Hamilton-Norwood Scales for male patients, through examination, and via patient interview; these will be re-evaluated at Weeks 36 and 52/ET. The presence of FPHL (AGA) will be assessed at Weeks 36 and 52/ET for female patients whose history of AGA is "no history" or unknown at screening.

[f] All sites/patients will obtain photographs of the scalp at Screening and Baseline. All sites/patients will obtain photographs of the scalp at Weeks 4, 8, 12, 24, 36, and 52, and at Early Termination. Photographs of the eyelash/eyebrows will be captured at Baseline and repeated at Weeks 4, 8, 12, 24, 36, and 52, and at early termination only from patients with AA involvement of those areas (ClinRO ≥1) at Baseline (Visit 2). See Section 2.8.1.4 Photography for details.

[g] A "Baseline/Screening" form is used at Visit 1. A "Since Last Visit" form used for all remaining visits. A suicidal ideation and behavior subscales excerpt is adapted for the assessment of 11 preferred ideation and behavior categories.

[h] Information will be collected from patients who require Spanish once the translation is available.

[i] Fasting lipid profile: patients should not eat or drink anything except water for 8 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. For ET visits, collect fasting lipids when possible.

[j] Clinical chemistry will include the following value calculated from serum creatinine: eGFR (calculated using the CKD-EPI creatinine 2009 equation).

[k] For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 and at all subsequent study visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period.

[l] 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).

[m] 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.

[n] 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

[o] Visit 801 (posttreatment follow-up period) occurs approximately 28 days after the last dose of IP. Patients who have completed Week 52 and will continue on marketed product beyond Week 52 do not need to complete V801.

2.3. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
To describe the effectiveness of 4-mg baricitinib in achieving scalp hair regrowth in patients with severe AA	Percent change from baseline in SALT score at Week 52
Key Secondary Objectives (Treatment Period 2)	
To describe the effectiveness of 4-mg baricitinib in achieving regrowth as assessed by physician assessed signs and symptoms of AA	• Proportion of patients achieving SALT ≤20 from baseline through Week 52 • Proportion of patients achieving a $SALT_{50}$, $SALT_{75}$, and $SALT_{90}$ from baseline through Week 52 • Percent change from baseline in SALT score at Week 52 • Mean change from baseline in SALT through Week 52 • Proportion of patients achieving ClinRO Measure for EB Hair Loss 0 or 1 with ≥2-point improvement from Baseline through Week 52 (among patients with ClinRO Measure for EB Hair Loss ≥2 at Baseline) • Proportion of patients achieving ClinRO Measure for EL Hair Loss 0 or 1 with ≥2-point improvement from Baseline through Week 52 (among patients with ClinRO Measure for EL Hair Loss ≥2 at Baseline)
To describe the effectiveness of 4-mg baricitinib during open-label treatment as assessed by PRO measures	• Proportion of patients with PRO for Scalp Hair Assessment score of 0 or 1 with ≥2-point improvement from Baseline through Week 52 among patients with a score ≥3 at Baseline • Proportion of patients with PRO for Eyebrow Hair Loss score of 0 or 1 with ≥2-point improvement from baseline through Week 52 among patients with a score of ≥2 at Baseline • Proportion of patients with PRO for Eyelash Hair Loss score of 0 or 1 with ≥2-point improvement from baseline through Week 52 among patients with a score of ≥2 at baseline • Proportion of patients with ≥1-point improvement in body hair areas (nose, beard, genital) as measured by the Body Hair Symptoms and Impact scale at Week 52 • Mean change in bothersome score on each area of hair loss (nose, beard, genital) as

Objectives	Endpoints
	measured by the Body Hair Symptoms and Impact scale at Week 52 • Proportion of patients who rate their AA as much improved or very much improved on the Patient Global Impression of Change scale at Week 52
To describe the effectiveness of 4-mg baricitinib during open-label treatment on emotional symptoms and quality of life	• Mean change in HADS anxiety and depression scale scores from baseline at Week 36 and Week 52 • Mean change in Skindex-16 AA emotions, functioning, and symptom scores from baseline at Week 36 and Week 52
To describe treatment satisfaction after therapy with 4-mg baricitinib for severe AA	• Distribution of scores on the Patient Global Impression of Satisfaction at Week 52
Exploratory Objectives may include evaluating the response to baricitinib treatment on clinical measures and patient-reported outcomes. These endpoints may include dichotomous endpoints or change from baseline for the following measures: SALT, ClinROs for Eyebrows, and/or Eyelash Hair Loss™, PROs for Scalp Hair Assessment, Eyebrows, and Eyelashes™, Body Hair Symptoms and Impact, Skindex-16 AA, PGI-Change, HADS, and PGI - Satisfaction, and baseline Hair Curl Assessment.	

Abbreviations: AA = alopecia areata; ClinRO = clinician-reported outcome; EB = eyebrow; EL = eyelash; HADS = Hospital Anxiety and Depression Scale; PGI = Patient Global Impression; PRO = patient-reported outcome; SALT = Severity of Alopecia Tool; Skindex-16 AA = Skindex-16 for Alopecia Areata.

2.4. Study Design

2.4.1. Overall Design

Study I4V-MC-JAHO (JAHO) addendum is an open-label therapy in a subpopulation of Black patients with severe AA. Approximately 20 adult patients will be enrolled into Study JAHO addendum.

Patients must self-identify as Black or African American for race. Patients must have a current AA episode of more than 6 months' duration prior to screening (Visit 1), with at least 50% scalp involvement at screening AND Baseline (Visits 1 and 2) with no spontaneous improvement (no more than a 10-point reduction in SALT) over the past 6 months. Patients with a current episode of severe or very severe AA of more than 8 years will not be eligible for inclusion in the study unless episodes of regrowth, spontaneous or under treatment, have been observed on the affected areas of the scalp over the past 8 years. Photographs at screening must be submitted to Sponsor's designee for the confirmation of severe AA prior to enrollment.

All procedures to be conducted during the study, including the timing of all procedures, are indicated in the SOA (Section 2.2). Section 9.4.4 of the JAHO(e) protocol describes the collection of laboratory samples; Appendix 2, Appendix 4, and Appendix 5 list the specific laboratory tests that will be performed for this study. Study governance considerations are described in detail in Appendix 3.

2.4.1.1. Period 1: Screening (-35 to -5 days)

The duration of the Screening Period is between 5 and 35 days prior to Visit 2 (Week 0). Therapies that must be washed out or discontinued before initiation of therapy (Visit 2) are listed in exclusion criterion [10]. Patients who receive a PPD skin test at Visit 1 will return 48 to 72 hours later to read the skin test. Patients who are eligible for herpes zoster vaccine (per local guidelines) and have not previously received the vaccine will be encouraged to do so prior to initiation. Vaccination with the live herpes zoster vaccination (single injection) must occur at least 28 days (4 weeks) prior to enrollment. Vaccination with the nonlive herpes zoster vaccine requires 2 injections administered at least 8 weeks apart. It is recommended that patients who have initiated vaccination with the non-live herpes zoster vaccine receive the second dose at least 4 weeks prior to enrollment. For both vaccines, completion of the vaccination may require rescreening the patients to comply with the maximum allowed duration of the screening period. In addition, 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.

At Screening (Visit 1), photographs of the scalp will be obtained from all patients. Views will include the right lateral, frontal, left lateral, forward tilt, and posterior. Up to 4 additional close-up views will be taken with and without cross-polarization lens of the left and right temporal area, the crown, and a representative patch selected by the physician, when applicable. Medical history and photographic data obtained at screening will be sent to the Sponsor's designee who will confirm the diagnosis of AA prior to initiation of therapy at Visit 2. Patients who meet all of the inclusion criteria (Section 2.5.1) and none of the exclusion criteria (Section 2.5.2) will continue to Visit 2.

2.4.1.2. Period 2: Open-Label Treatment (Weeks 0-52)

At Visit 2 (Week 0, Baseline), study eligibility for each patient will be reviewed on the basis of all inclusion (Section 2.5.1) and exclusion (Section 2.5.2) criteria and laboratory test results. Patients who meet all eligibility criteria will proceed to initiation of therapy and begin the 52 weeks open-label treatment (Study Period 2).

At Visit 2, after laboratory samples are collected and all assessments are completed, patients will take the first dose of IP in the clinic.

During Study Period 2, procedures and medications will be prohibited as listed in Section 2.6.7.2

At Baseline (Visit 2), photographs of the scalp and eyebrows/eyelashes will be obtained from all patients. Additional close-up views of the left and right temporal area, the crown, and the same representative patch selected at screening by the physician will be taken. Close-up photographs will be taken with and without a cross-polarization lens. After baseline, photographs of the scalp and close-up photographs will be repeated at Week 4, 8, 12, 24, 36, 44, 52 visits and in case of ET visit. Photographs of the eyebrows/eyelashes will be captured at these visits only from patients who have AA involvement (ClinRO ≥1) of those areas at Baseline, as assessed by investigator (see SOA [Section 2.2] and Section 2.8.1.4). Missed photographs after screening

will not be considered a protocol violation. Detailed requirements for photography are located in the Photography Manual.

The primary efficacy endpoint will be at Week 52 (Visit 11).

2.4.1.3. Period 3: Posttreatment Follow-Up

Patients who complete the study through Visit 11 (Week 52) will have a posttreatment follow-up visit (Visit 801) approximately 28 days after the last dose of IP. Patients who have completed Week 52 and who will continue on marketed product beyond Week 52 do not need to complete Period 3 (Visit 801).

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

Patients who have discontinued IP product but remain in the study for more than 28 days without IP will have an ET if they choose to discontinue early. However, a separate follow-up visit (V801) is not required.

2.4.2. Number of Participants

Twenty patients were enrolled into the addendum.

2.4.3. End of Study Definition

End of study is the date of the last visit or last scheduled procedure shown in the SOA (Section 2.2) for the last patient.

2.4.4. Scientific Rationale for Study Design

Baricitinib has been evaluated in the JAHO and JAIR studies and shown to be efficacious in the treatment of severe AA. Therefore, the subpopulation addendum does not require a comparator arm.

2.4.5. Justification for Dose

Based on the JAHO study primary outcomes, 4-mg baricitinib resulted in a greater proportion of patients achieving a SALT≤20 compared with 2-mg baricitinib. Therefore, 4-mg baricitinib dose was selected as the treatment for this addendum.

2.5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waiver or exemption) is not permitted.

Study investigator(s) will review patient history and screening test results at Visit 1 and Visit 2 to determine if the patient meets all inclusion criteria and none of the exclusion criteria to qualify for initiation in the study. All screening activities must be completed and reviewed before the patient is enrolled. Photographs taken at Screening must be submitted to the Sponsor or designee for the verification of SALT score ≥50 and hair loss due to AA. Subjects must not be enrolled until verification has been confirmed.

2.5.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria at screening:

Informed Consent

[1] Are at least 18 years and ≤60 years for males (≤70 years of age for females) at the time of informed consent.

Note: Use local requirements to provide consent if the age of adulthood is defined as >18 years. Different upper age limits have been included for male and female patients based on difference in the prevalence of concomitant androgenetic alopecia.

[2] Self-identify as Black or African American race.

[3] Are able to read, understand, and give documented (electronic or paper signature) informed consent.

Type of Patient and Disease Characteristics

[4] Have severe or very severe AA, as determined by all of the following:

a. Current AA episode of more than 6 months' duration and hair loss encompassing ≥50% of the scalp as measured by SALT at Visit 1 AND Visit 2.

b. No spontaneous improvement (that is, no more than 10-point spontaneous reduction in SALT) over the past 6 months.

c. Current episode of severe or very severe AA of less than 8 years.

Note: patients who have severe or very severe AA for ≥8 years may be enrolled if episodes of regrowth, spontaneous or under treatment, have been observed on the affected areas of the scalp over the past 8 years.

[5] Agree not to use any AA treatments during the study, including, but not limited to

a. systemic therapies (for example, methotrexate, cyclosporine, corticosteroids, JAK inhibitors, apremilast, dimethyl fumarate derivatives, hydroxychloroquine, mycophenolate-mofetil, IFNγ, azathioprine) and biologics (for example, monoclonal antibodies)

b. intralesional corticosteroid injections

c. topical therapies, including irritants and immunotherapies (for example, diphenylcyclopropenone)

d. phototherapy, including lasers

e. platelet-rich plasma injection

f. HMG-CoA reductase inhibitors or "Statins" (for example, simvastatin, simvastatin + ezetimibe) for treatment of AA, and

g. Cryotherapy.

Note: Treatment with bimatoprost ophthalmic solution for eyelashes may be continued if the patient has been on a stable dose for 8 weeks prior to enrollment. Treatment with finasteride (or other 5 alpha reductase inhibitors) or oral or topical minoxidil may be continued if the patient has been on a stable dose for 12 months and is anticipated to continue on a stable dose up until Week 36.

[6] Are male or nonpregnant, nonbreastfeeding female patients

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 and agree to not father a child while enrolled in the study and for at least 4 weeks after 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 child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and vaginal 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 male partners while enrolled in the study and for at least 4 weeks after the last dose of IP.

   The following birth control methods are considered acceptable (the patient should choose 2 to be used with their male partners, 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 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.

c. Females of nonchildbearing potential are not required to use birth control. 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 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).

2.5.2. Exclusion Criteria

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

Medical Conditions Related to AA

[7] primarily "diffuse" type of AA (characterized by diffuse hair shedding)

[8] are currently experiencing other forms of alopecia, including but not limited to: androgenetic alopecia (male pattern Grade IV or greater using Hamilton-Norwood classification, or female pattern), central centrifugal cicatricial alopecia traction, trichotillomania, telogen effluvium, chemotherapy-induced hair loss or any other concomitant conditions (for example, tinea capitis, psoriasis, lupus erythematosus, or secondary syphilis) that would interfere with evaluations of the effect of study medication on AA.

[9] Patients who, in the opinion of the investigator, are currently experiencing or have a history of unstable concomitant disease that requires frequent hospitalizations and/or frequent use of systemic immunosuppressants that may interfere with participation in the study.

[10] Have been treated with the following therapies:

a. Corticosteroids

i. Topical corticosteroids applied to the scalp or eyebrows within 1 week prior to enrollment.

ii. Systemic corticosteroids within 8 weeks prior to enrollment.

iii. Intralesional corticosteroid injections for treatment of AA within 8 weeks prior to enrollment.

iv. Have had an intraarticular corticosteroid injection within 8 weeks prior to enrollment.

Note: Intranasal, ophthalmic, or inhaled steroid use is allowed during screening and throughout the study.

b. JAK inhibitors

i. Topical JAK inhibitor applied to the scalp (for example, tofacitinib, ruxolitinib) within 4 weeks prior to enrollment.

ii. Oral JAK inhibitor within 8 weeks prior to enrollment.

iii. Previously treated with an oral JAK inhibitor (for example, baricitinib, tofacitinib, ruxolitinib) and had an inadequate response (for example, absence of significant terminal hair growth after at least 12 weeks of treatment).

c. Other topical therapies (for example, anthralin, diphenylcyclopropenone, or other topical immunotherapies) for the treatment of AA within 4 weeks prior to enrollment.

d. Monoclonal antibody (for example, ustekinumab, secukinumab, adalimumab, dupilumab) less than 5 half-lives prior to enrollment.

e. Probenecid at the time of the enrollment (Visit 2) that cannot be discontinued for the duration of the study (probenecid may increase baricitinib exposures).

f. Platelet-rich plasma within 8 weeks prior to enrollment.

g. Phototherapy (Ultra Violet therapy and laser on scalp lesions) within 4 weeks prior to enrollment.

h. HMG-CoA reductase inhibitors or "statins" (for example, simvastatin, simvastatin + ezetimibe) for treatment of AA within 4 weeks prior to enrollment.

i. Cryotherapy for treatment of AA within 4 weeks prior to enrollment.

j. Finasteride (or other 5 alpha reductase inhibitors) or minoxidil (topical or oral) within 8 weeks prior to enrollment, unless the subject has been on a stable dose for at least 12 months AND is anticipated to continue on a stable dose up until Week 36

k. Immunosuppressants (for example, methotrexate, cyclosporine, dimethyl fumarate derivatives, mycophenolate-mofetil, IFNγ, azathioprine) within 8 weeks of enrollment.

l. Apremilast or hydroxychloroquine within 4 weeks prior to enrollment.

Medical Conditions in General

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

[12] 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.

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

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

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

[16] Have a history of 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) body mass index >35 kg/m^2

c) Oral contraceptive use and current smoker status

[17] 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.

[18] 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 successfully 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 cell skin cancers that have been successfully treated with no evidence of recurrence for at least 3 years may participate in the study.

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

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

b. A history of disseminated/complicated herpes zoster (for example, multidermatomal involvement, ophthalmic zoster, central nervous system involvement, or postherpetic neuralgia).

c. Symptomatic herpes simplex at the time of enrollment.

d. Active or chronic viral infection from HBV, HCV, or HIV.

e. Household contact with a person with active 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 4 weeks prior to 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.

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

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

[21] A history of 2 or more episodes of eczema herpeticum in the past.

[22] 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 (for example, atopic dermatitis, unstable chronic asthma).

[23] Have been exposed to a live vaccine within 12 weeks prior to 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 with the live herpes zoster vaccine can occur during the screening period but must take place >4 weeks prior to enrollment and start of IP. Vaccination with the nonlive herpes zoster vaccine requires at least 2 injections administered 8 weeks apart. It is recommended that patients who have initiated vaccination with the nonlive herpes zoster vaccine receive the second dose at least 4 weeks prior to enrollment. For both vaccines, completion of the vaccination may require rescreening the patients to comply with the maximum allowed duration of the screening period. Patients will be excluded if they were exposed to herpes zoster vaccination within 4 weeks of planned enrollment.

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

[25] 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 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 of Visit 1.

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

[26] 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.

Diagnostic Assessments

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

[28] Have evidence of active TB or latent TB

a. Have evidence of active TB, defined in this study as the following:

i. Documented by a positive PPD test (≥5 mm of induration between approximately 48 and 72 hours after application, regardless of vaccination history), medical history, clinical features, and abnormal chest x-ray at screening.

ii. 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:

i. Documented to have a positive PPD test (≥5 mm of 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

ii. 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

iii. 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 indeterminate, 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 they complete at least 4 weeks of appropriate treatment prior to enrollment and agree 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.

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

a. Positive for hepatitis B surface antigen, or

b. Positive for 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 will need to be monitored during the study.

[30] 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.

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

[32] Have screening laboratory test values, including 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.

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

a. AST or ALT ≥2 × ULN

b. ALP ≥2 × ULN

c. TBL ≥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. eGFR <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 [32] and [33]), 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.

Other Exclusion Criteria

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

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

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

[37] Have previously been randomized in this study or any other study investigating baricitinib.

[38] 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.

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

2.5.3. Lifestyle Restrictions

Study participants should be instructed not to donate blood or blood products during the study. It is highly recommended that patients remain consistent with hairstyle and hair coloring during the study to facilitate scalp hair assessments. Patients who prefer to shave their scalp must refrain from shaving the scalp within 2 weeks prior to a study visit. For patients who prefer to wear a wig, it is recommended that the wig should not be taped at more than 2 places on the periphery of the scalp to avoid pulling the hair. Patients with hair extensions are allowed to be enrolled in the trial as long as the entire scalp (and regrowth when applicable) can be assessed at every visit. Hair styling gel or other hair products must not be used on the day of scheduled visits.

Patients with eyebrows and/or eyelashes extensions, and/or tattoos are allowed to be enrolled in the trial as long as the degree of eyebrows and eyelashes involvement (and regrowth when applicable) can be assessed at every visit.

2.5.4. Screen Failures

Patients who are entered into the study but do not meet the enrollment criteria for participation in this study (screen failure) may be rescreened a maximum of 2 times. The interval between screen failure and rescreenings should be at least 4 weeks. At the time of rescreening, the individual

must sign a new ICF, repeat all necessary screening procedures, and will be assigned a new identification number.

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

2.6. Treatments

2.6.1. Treatments Administered

Patients will receive 4-mg baricitinib dispensed as study drug. Table JAHO.1 shows the treatment regimen and the IP supplied. 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 IP dispensing and collection, and
- at the end of the study, returning all unused medication to Lilly or its designee, unless the Sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

Table JAHO.1. Treatment Regimen

Treatment Regimen	Investigational Product Supplied	Dose
4-mg Baricitinib QD[a]	4-mg Baricitinib tablets	1 tablet per day

Abbreviation: QD = once daily; eGFR = estimated glomerular filtration rate.

[a]The baricitinib dose for patients who have renal impairment (defined as eGFR <60 mL/min/1.73 m^2) will be 2-mg QD.

2.6.1.1. Packaging and Labelling

The sponsor (or its designee) will provide the following IPs: tablets containing 4-mg of baricitinib. Storage and handling instructions are provided in the IP packaging.

2.6.2. Method of Treatment Assignment

The interactive web-response system will be used to assign bottles, each containing 4-mg baricitinib IP tablets (2-mg IP tablets for patients with eGFR <60 mL/min/1.73 m^2), to each patient, starting at Visit 2 (Week 0), and at each visit up to and including Visit 10 (Week 44). Site personnel will confirm that they have located the correct bottles by entering a confirmation number found on the bottle into the interactive web-response system.

2.6.2.1. Selection and Timing of Doses

The IP should be taken QD 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. All patients will take 1 tablet QD.

2.6.2.2. Dose Adjustment for Renal Impairment

Based on pharmacokinetic simulations of baricitinib exposures for the mild and moderate categories of renal function (stratified as eGFR 60 to <90 mL/min/1.73 m^2 and eGFR 30 to <60 mL/min/1.73 m^2, respectively), dose adjustment is not required for patients with eGFR ≥60 mL/min/1.73 m^2. Patients with eGFR <60 mL/min/1.73 m^2 will receive a dose of 2-mg QD, which will ensure that exposures do not exceed those of the 4 mg QD dose in patients with eGFR ≥60 mL/min/1.73 m^2.

2.6.3. Blinding

Not applicable

2.6.4. Dosage Modification

No other dose adjustments will be made other than for renal impairment as described in Section 2.6.2.2

2.6.5. Preparation/Handling/Storage/Accountability

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

Follow storage and handling instructions on the IP packaging.

2.6.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit during the treatment period (Visit 3 through Visit 11) by counting returned tablets. A patient will be considered significantly noncompliant if he/she misses more than 20% of the prescribed doses of IP during the study unless the patient's IP is withheld by the investigator for safety reasons. Similarly, a patient will be considered significantly noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken 20% more than the prescribed amount of medication during the study.

2.6.7. 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 eCRF. Patients will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study. For AA therapies permitted, see Section 2.6.7.1.

2.6.7.1. Permitted Medications and Procedures

The following medications are permitted during the study:

- Topical corticosteroids except on the scalp, eyebrows, and eyelids.
- Topical calcineurin inhibitors except on the scalp, eyebrows and eyelids.
- Intranasal, ophthalmic, or inhaled steroid use.

- A maximum of 2 intra-articular or soft tissue (bursa, tendon, and/or ligament) corticosteroid injections are allowed.
- Nonlive vaccinations such as seasonal vaccination, nonlive herpes zoster (for subjects who become eligible during the trial), and/or all emergency vaccinations, such as rabies or tetanus vaccinations.
- Bimatoprost ophthalmic solution (if on stable dose for 8 weeks prior to enrollment).
- Finasteride (or other 5 alpha reductase inhibitors) or oral or topical minoxidil, if on a stable dose for 12 months prior to enrollment.
- HMG-CoA reductase inhibitors or "statins" (for example, simvastatin, simvastatin + ezetimibe) for treatment of hypercholesterolemia and the prevention of cardiovascular disease.

Nutraceuticals (for example, Viviscal, Nutrafol) and other over-the-counter hair products may be used if patients are currently using them at baseline. They should be encouraged to continue with the same amount and frequency during the study. Oil on the scalp should be avoided at scheduled visits to reduce potential glare for photographs.

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

2.6.7.2. Prohibited Medications and Procedures

Any investigational or commercial topical, intralesional or systemic therapies (except those listed in Section 2.6.7.1) or phototherapy to treat AA are not allowed during the trial.

In addition, the following medications and procedures are prohibited during the study:

Prohibited Medications and Procedures Requiring Temporary Interruption of Investigational Product

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

- Live vaccines, including BCG or herpes zoster, (see exclusion criterion [23]).
    - For BCG vaccination, IP should be temporarily interrupted for 12 weeks. If BCG vaccine is given prior to Week 52, IP should be permanently discontinued.
    - For live herpes zoster vaccination, IP should be temporarily interrupted for 4 weeks after the injection.
- 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 AE (for example, worsening of an existing condition, such as an asthma flare). IP 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.
- Phototherapy: Full body Ultra Violet therapy.

Prohibited Medications Requiring Permanent Discontinuation of Investigational Product

- Corticosteroids (systemic, intralesional, or topical on the scalp, eyebrows, and/or eyelids) for the treatment of AA.
- Topical JAK inhibitors applied to the scalp, eyebrows, and eyelids.
- Other oral JAK inhibitors (for example, tofacitinib and ruxolitinib).
- Any systemic treatment with an immunosuppressive/immunomodulating substance, including, but not limited to, cyclosporine, mycophenolate-mofetil, IFNγ, azathioprine, methotrexate, dimethyl fumarate derivatives, hydroxychloroquine, or biologics (for example, monoclonal antibodies).
- Any other AA treatment which has been inadvertently initiated and cannot be discontinued will lead to permanent discontinuation of IP.

2.6.8. Treatment after the End of the Study

2.6.8.1. Continued Access

After the conclusion of the study, continued access to baricitinib will not be provided. Patients will be referred to their local treatment centers for AA therapy, as clinically indicated.

2.7. Discontinuation Criteria

2.7.1. Discontinuation from Study Treatment

2.7.1.1. Permanent Discontinuation from Investigational Product

IP should be permanently discontinued if the patient or the patient's designee requests to discontinue IP.

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

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

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

IP should be permanently discontinued if any of the following are observed:

- white blood cell count <1000 cells/µL (1.00 × 10^3/µL or 1.00 GI/L)
- absolute neutrophil count <500 cells/µL (0.50 × 10^3/µL or 0.50 GI/L)
- lymphocyte count <200 cells/µL (0.20 × 10^3/µL or 0.20 GI/L), and
- hemoglobin <6.5 g/dL (<65.0 g/L).

NOTE: Temporary interruption rules (see Section 2.7.1.2) must be followed, where applicable. For laboratory values that meet permanent discontinuation thresholds, IP should be discontinued. However, if, in the opinion of the investigator, the laboratory abnormality is due to intercurrent illness, such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when the laboratory value meets resumption thresholds (Table JAHO.2) following the resolution of the intercurrent illness or other identified factor, may the investigator restart IP, after consultation with the Lilly-designated medical monitor.

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

- pregnancy
- malignancy (except for successfully treated basal or squamous cell skin carcinoma)
- HBV DNA is detected with a value above limit of quantitation (see Section 9.4.8 of the JAHO(e) protocol).
- certain prohibited medications are taken per Section 2.6.7.2 (Prohibited Medications and Procedures)
- development of a VTE

Note: Patients who develop a VTE may have additional follow-up and testing recommended (see Section 9.4.9 and Appendix 7 of JAHO(e)).

If a patient develops multiple risk factors for a VTE during the conduct of the study, as described in exclusion criterion [16], the investigator may consider study discontinuation if he/she believes the risk outweighs the benefits of continuing therapy. It is recommended that the investigator consult with Lilly (or its designee) before discontinuing therapy for this reason.

Patients discontinuing from the IP prematurely for any reason should complete AE and other follow-up procedures per Section 2.2 (SOA), Section 2.8.2 (Adverse Events) of this addendum, and Section 9.4 (Safety) of the JAHO(e) protocol.

2.7.1.2. Temporary Interruption of Investigational Product

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to IP. For example, IP should be temporarily interrupted if the patient experiences a cardiovascular AE considered to be related to study treatment, is graded as moderate (Grade 2 according to Common Terminology Criteria for Adverse Events Version 3.0), and that does not resolve promptly with supportive

care. Except in cases of emergency, it is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting therapy for reasons other than those defined in Table JAHO.2.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table JAHO.2, specific guidance is provided for temporarily interrupting treatment and when treatment may be restarted. Retest frequency and timing of follow-up laboratory tests to monitor the abnormal finding are at the discretion of the investigator. IP that was temporarily interrupted because of an AE or abnormal laboratory value not specifically covered in Table JAHO.2 may be restarted at the discretion of the investigator.

Table JAHO.2. Criteria for Temporary Interruption of Investigational Product

Hold Investigational Product if the Following Laboratory Test Results or Clinical Events Occur:	Investigational Product May Be Resumed When:
WBC count <2000 cells/µL (<2.00 × 10^3/µL or <2.00 GI/L)	WBC count ≥2500 cells/µL (≥2.50 × 10^3/µL or ≥2.50 GI/L)
ANC <1000 cells/µL (<1.00 × 10^3/µL or <1.00 GI/L)	ANC ≥1200 cells/µL (≥1.20 × 10^3/µL or ≥1.20 GI/L)
Lymphocyte count <500 cells/µL (<0.50 × 10^3/µL or <0.50 GI/L)	Lymphocyte count ≥750 cells/µL (≥0.75 × 10^3/µL or ≥0.75 GI/L)
Platelet count <75,000/µL (<75 × 10^3/µL or <75 GI/L)	Platelet count ≥100,000/µL (≥100 × 10^3/µL or ≥100 GI/L)
eGFR <40 mL/min/1.73 m^2 (from serum creatinine) for patients with screening eGFR ≥60 mL/min/1.73 m^2	eGFR ≥50 mL/min/1.73 m^2
eGFR <30 mL/min/1.73 m^2 (from serum creatinine) for patients with screening eGFR ≥40 to <60 mL/min/1.73 m^2	eGFR ≥40 mL/min/1.73 m^2
ALT or AST >5 × ULN	ALT and AST return to <2 × ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥10 g/dL (≥100.0 g/L)
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection
Clinical features of VTE (such as deep vein thrombosis or pulmonary embolism) are present[a]	VTE ruled out

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

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

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

For specific guidance on temporary interruption of IP after the use of a prohibited medication, please refer to Section 2.6.7.2 (Prohibited Medications and Procedures).

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

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

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

2.7.1.3. Discontinuation of Inadvertently Enrolled Patients

If the Sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the Sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with IP. Safety follow-up is as outlined in Section 2.2 (SOA), Section 2.8.2 (Adverse Events) of this addendum, and Section 9.4 (Safety) of the JAHO(e) protocol.

2.7.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational medicinal product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent for AA (not allowed per protocol [Section 2.6.7.2]) that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- subject decision
    - the patient or the patient's designee (for example, parents or legal guardian) requests the patient to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2.2 (SOA), Section 2.8.2 (Adverse Events) of this addendum, and Section 9.4 (Safety) of the JAHO(e) protocol.

2.7.3. Lost to Follow-Up

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

2.8. Study Assessments and Procedures

Section 2.2 lists the SOA, with the study procedures and their timing (including tolerance limits for timing).

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

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

2.8.1. Efficacy Assessments

2.8.1.1. Primary Efficacy Assessments

2.8.1.1.1. Severity of Alopecia Tool Score

The SALT uses a visual aid showing the division of the scalp hair into 4 areas with the top constituting 40% of total surface, the posterior/back 24%, right side and left side of scalp 18% each. The percentage of hair loss in each area is determined and is multiplied by the percentage of scalp covered by that area. The total sum of the 4 products of each area will give the SALT score, as developed by the National Alopecia Areata Foundation Working Committee (Oslen et al. 2004). Only terminal hair is included in the SALT; vellus hair or any fine downy hair is not taken into account in the SALT scoring process (Oslen et al. 1999, 2004).

2.8.1.2. Secondary Efficacy Assessments

2.8.1.2.1. Other Clinician-Reported Outcomes

2.8.1.2.1.1. Eyebrow Hair Loss and Eyelash Hair Loss

Lilly has developed 2 single-item ClinRO assessments: ClinRO Measure for Eyebrow Hair Loss™ and ClinRO Measure for Eyelash Hair Loss™. Each of these ClinRO assessments uses a 4-point response scale, ranging from 0 = no hair loss to 3 = severe hair loss (Wyrwich et al. 2020a.

2.8.1.2.2. Alopecia Areata Patient-Reported Outcomes

2.8.1.2.2.1. Patient-Reported Outcomes for Scalp Hair Assessment™

Lilly has developed a novel single-item PRO assessment of the patient's current extent of scalp involvement. It is comprised of 5 category response options: 0 = no missing hair (0% of my

scalp is missing hair; I have a full head of hair); 1 = a limited area (1% to 20% of my scalp is missing hair); 2 = a moderate area (21% to 49% of my scalp is missing hair); 3 = a large area (50% to 94% of my scalp is missing hair); and 4 = Nearly all or all (95% to 100% of my scalp is missing hair) (Wyrwich et al. 2020b).

2.8.1.2.2.2. Patient-Reported Outcomes for Appearance of Eyebrows, Appearance of Eyelashes

Lilly has developed single-item PRO assessments measuring AA signs and symptoms. The PRO Measure for Eyebrows™ and PRO Measure for Eyelashes™ are single-item instruments which use a 4-point response scale, ranging from 0 = no problem to 3 = severe problem (Wyrwich et al. 2020a).

2.8.1.2.2.3. Patient-Reported Outcomes for Body Hair

The Body Hair Symptoms and Impact Questionnaire asks patients about current nasal, beard (male only), and genital hair loss. For each of these areas, patients are asked to assess the amount of hair loss using the categories of "no missing hair," "a limited amount of hair loss," "a large amount of hair loss," or "complete or nearly complete hair loss." Patients are also asked to rate how bothered they are by the hair loss using a 11-point Numeric Rating Scale of 0 to 10 where 0 is "not at all bothered" and 10 is "worst imaginable for being bothered."

2.8.1.2.2.4. Patient-Reported Outcomes for Change

Patients will assess their overall impression of change (PGI-C) during the course of therapy. This single-item question assesses their perception of change relative to their baseline status using a 7 Likert-point scale where 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse, and 7 = very much worse.

2.8.1.2.2.5. Patient-Reported Outcomes for Satisfaction

Treatment satisfaction will be assessed using the single item Patient Global Impression of Satisfaction (PGI-Satisfaction in which they assess their current satisfaction with the treatment outcome using a 7-point Likert scale where 1 = completely satisfied, 2 = mostly satisfied, 3 = somewhat satisfied, 4 = neither satisfied or dissatisfied, 5 = dissatisfied, 6 = mostly dissatisfied, and 7 = completely dissatisfied.

2.8.1.3. Health Outcomes and Quality-of-Life Measures

The following patient self-reported questionnaires will be administered via an electronic tablet.

2.8.1.3.1. Skindex-16 A for Alopecia Areata

The Skindex-16 has been used to assess the health-related quality of life in patients with skin diseases. The Skindex-16 items' wordings were adapted for use among adults with AA. It is composed of 16 items grouped under 3 domains: Symptoms (4 items), Emotions (7 items), and Functioning (5 items).

2.8.1.3.2. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale is a 14-item self-assessment scale that determines the levels of anxiety (7 items) and depression (7 items) that a patient is experiencing over the past week. The Hospital Anxiety and Depression Scale utilizes a 4-point Likert response scale (for example, 0 to 3) for each item, and is intended for ages 12 to 65 years (Zigmond and Snaith 1983; White et al. 1999). Scores for each domain (anxiety and depression) can range from 0 to

21, with higher scores indicating greater anxiety or depression (Zigmond and Snaith 1983; Snaith 2003).

2.8.1.4. Photography

At Screening (Visit 1), photographs of the scalp will be obtained from all patients. Views will include the right lateral, frontal, left lateral, forward tilt, and posterior. Up to 4 additional close-up views will be taken with and without cross-polarization lens of the left and right temporal area, the crown, and a representative patch (when applicable) selected by the physician. At Baseline (Visit 2), photographs of the scalp will be repeated as at the screening visit. All patients will also have photograph of the eyebrows/eyelashes. After baseline, photographs of the scalp and close-up will be repeated as per the SOA. After Baseline, photographs of the eyebrows/ eyelashes will be captured only from patients who have AA involvement (ClinRO ≥1) of those areas at Baseline, as assessed by investigator (see SOA [Section 2.2] and Section 2.8.1.4). Missed photographs after screening will not be considered a protocol violation. Detailed requirements for photography are located in the Photography Manual.

Camera equipment, necessary ancillary materials, and a study-specific photography manual will be provided to all sites by the Sponsor or designee. The photographs will be obtained by trained site personnel under similar lighting conditions and magnifications, and per instructions provided during training and as outlined in the photographic procedure manual.

Photographs are commonly obtained in research investigations of AA and are effective in demonstrating disease presentation at Baseline and clinical response after treatment with baricitinib.

The photographs may be included in the CSR, a regulatory submission package, scientific publications, or in other public dissemination of clinical data to demonstrate disease presentation at Baseline and clinical response after treatment with baricitinib.

Photographs from consenting patients may also be used in advertising and promotional activities including, but not limited to, communication with healthcare professionals/payers, as well as in patient education, speaker programs, and digital/print media messaging.

Patient anonymity will be protected in photographs included in patient education, speaker programs, print media, or any form available to the public. To protect the patient’s anonymity, identifiable characteristics of the skin, such as facial birthmarks, or tattoos will be redacted from the final photographs and will not appear in any published version of the photograph. No formal analyses of photographs are planned.

2.8.1.5. Appropriateness of Assessments

The primary clinical and safety assessments in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

2.8.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The Investigator will record all relevant AE/SAE information in the CRF. The Investigator remains responsible for following, through an appropriate health care option, AEs that are: serious or, otherwise, medically important; considered related to the IP or the study; or that caused the patient to discontinue the IP before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

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

The investigator will interpret and document whether an AE has a reasonable possibility of being related to study treatment, to a study device, or to a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the IP, study device, and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

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

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

2.8.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect

- important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for seriousness criteria. The SAE reporting to the Sponsor begins after the patient has signed the ICF and has received IP. However, if an SAE occurs after signing the ICF, but prior to receiving IP, the SAE should be reported to the Sponsor, as per SAE-reporting requirements and timelines (see Section 2.8.2) if it is considered reasonably possibly related to study procedure.

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

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

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

2.8.2.1.1. Suspected Unexpected Serious Adverse Reactions

SUSARs are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

2.8.2.2. Adverse Events of Special Interest

Adverse events of special interest will include the following:

- infections (including TB, herpes zoster, or opportunistic infections)
- malignancies
- hepatic events (see Section 9.4.10.1 of the JAHO(e) protocol)
- major adverse cardiovascular events (see Section 9.4.10 of the JAHO(e) protocol), and

- thrombotic events (such as deep vein thrombosis and pulmonary embolism and arterial thrombotic event (see Section 9.4.9 of the JAHO(e) protocol).

Sites will provide details on these AEs, as instructed on the eCRF, and may be asked for additional description by Lilly.

2.8.2.3. Complaint Handling

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

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

2.8.3. Treatment of Overdose

Refer to the IB.

2.8.4. Safety

Refer to JAHO(e) protocol for electrocardiogram, vital signs, physical examination, laboratory tests, C-SSRS, chest x-ray and TB testing, HBV DNA monitoring, venous thromboembolism assessment, and safety monitoring.

2.8.5. Pharmacogenomics

2.8.5.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis, as specified in the SOA (Section 2.2), where local regulations allow.

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

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards impose shorter time limits. This retention period enables the use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of baricitinib or after baricitinib becomes commercially available.

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

2.8.6. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Blood samples for biomarker research will be collected at the times specified in the SOA (Section 2.2), where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to baricitinib, pathways associated with AA, mechanism of action of baricitinib, and/or research method or in validating diagnostic tools or assay(s) related to AA.

All samples will be coded with the patient number. These samples, and any data generated, can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables the use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of baricitinib or after baricitinib becomes commercially available.

2.9. Statistical Considerations

2.9.1. Sample Size Determination

Study JAHO addendum initially intended to screen approximately 80 patients to enroll 60 patients, as a sample size considered sufficient for subject improvement in hair growth. Subsequent enrollment resulted in a sample size of 20 patients. The sample size of approximately 20 patients is sufficient to provide descriptive information on subject improvement in hair regrowth. As the addendum objectives were designed as descriptive in nature, it did not rely on power calculations and therefore, a sample size of approximately 20 patients is sufficient for further description of treatment outcomes with this population.

2.9.2. Populations for Analyses

For the purpose of analyses, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	All patients enrolled will be included in the FAS.
Safety Population	The safety population is defined as all enrolled patients who receive at least 1 dose of IP and who did not discontinue from the study for the reason ‘Lost to Follow-up’ at the first postbaseline visit.

Abbreviations: AGA = androgenetic alopecia; IP = investigational product.

[a] Some male patients with Grade IV AGA and female patients with patterned baldness may only be identified after hair regrowth on the scalp.

Any additional analysis populations may be defined in the SAP.

2.9.3. Statistical Analyses

2.9.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly.

The efficacy analysis of the primary and key secondary endpoints will be conducted in the full analysis set population. All other efficacy analyses will be conducted in the full analysis set population or other populations described in the SAP. Safety analyses will be conducted using the safety population.

Any change to the data analysis methods described in this addendum will require an amendment ONLY if it changes a principal feature of the addendum. Any other change to the data analysis methods described in this addendum (and the justification for making the change) will be described in the CSR. Additional exploratory analyses of the data will be conducted, as deemed appropriate. Complete details of the planned analyses will be documented in the SAP.

2.9.3.1.1. Analysis Methods

The primary and secondary efficacy objective/endpoints for the study are descriptive in nature and will be analyzed in a descriptive way using observed data, unless otherwise stated.

For all discrete efficacy outcome variables, frequency and counts with percentages and 100(1-alpha) % CI of the percentages using the Wilson method, without continuity correction method will be reported. Continuous safety outcome variables vital signs, body weight, and other continuous safety variables, including laboratory variables, will be descriptively summarized in terms of number of patients, mean, standard deviation, median, minimum, and maximum. Shift tables for categorical safety analyses (for example, “high” or “low” laboratory results) will also be produced, as appropriate.

2.9.3.1.2. Missing Data Imputation

No imputation methods will be applied. Data will be analyzed as observed case analysis. If deemed necessary imputation method for handling of missing data will be included in the SAP as appropriate.

2.9.3.1.3. Descriptive Population Analyses Patient Disposition

A detailed description of patient disposition will be summarized with reasons for discontinuation. Frequency counts and percentages will be presented for, all patients who discontinue from the study or the study treatment will be identified, along with their reason for discontinuation. Patient Characteristics Demographic and Baseline characteristics will be summarized descriptively. Descriptive statistics including number of patients, mean, standard deviation, median, minimum, and maximum will be provided for continuous measures, and

frequency counts and percentages will be tabulated for categorical measures. A complete list of patient characteristics and Baseline clinical measures will be provided in the SAP.

2.9.3.1.4. Concomitant Therapy

Concomitant medications will be descriptively summarized in terms of frequencies and percentages using the safety population. Additional summaries may be produced by prior treatment received.

2.9.3.1.5. Treatment Compliance

Treatment compliance with the study medication will be evaluated at every clinic visit through the counts of returned IP tablets. A patient will be considered significantly noncompliant if he/she misses more than 20% of the prescribed doses during the study, unless the patient's IP is withheld by the investigator for safety reasons (that is, compliance <80%). Similarly, a patient will be considered significantly noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication (that is, compliance ≥120%).

2.9.4. Efficacy Analyses

2.9.4.1. Primary Analyses

The primary efficacy measure is the continuous endpoint defined as the percent change in SALT Score from baseline at Week 52. The mean percent change from baseline, standard error, and 95% confidence interval (CI) for mean percent change will be reported with all other descriptive statistics such as number of patients, standard deviation, median, minimum, and maximum. Additional analysis of the primary efficacy outcome may be conducted and include analyzing all available data up to the permanent treatment discontinuation.

2.9.4.2. Secondary Analyses

Proportion of patients achieving a binary response and 100(1-alpha) % CI of the percentages using Wilson method, without continuity correction method will be reported.

Additional analysis of the secondary efficacy outcome may be conducted and include analyzing all available data up to the permanent treatment discontinuation.

2.9.4.3. Exploratory Analyses

Analyses will be conducted for the other exploratory objectives defined in Section 2.3. Specific details of analyses will be specified in the SAP.

2.9.5. Safety Analyses

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

Treatment-emergent adverse events are defined as AEs that first occurred or worsened in severity after the first dose of study treatment. The number of TEAEs, as well as the number and percentage of patients who experienced at least 1 TEAE, will be summarized using the Medical Dictionary for Regulatory Activities for each system organ class (or a body system) and each

preferred term. Serious adverse events and AEs that lead to discontinuation of IP will also be summarized.

All clinical laboratory results will be descriptively summarized. Individual results that are outside of normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables obtained at the Baseline to postbaseline visits will be summarized as changes from Baseline Categorical variables, including the incidence of abnormal values and incidence of AEs of special interest, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures.

Observed values and changes from Baseline for vital signs and physical characteristics will be descriptively summarized by timepoint. Change from Baseline in vital signs and body weight will be descriptively summarized.

Summary tables or listings for the C-SSRS will be produced, as needed.

The incidence and average duration of IP interruptions will be summarized descriptively (if necessary). Further analyses may be performed and will be planned in the SAP.

Full details of the safety analyses and any derivations of AEs of special interest will be documented in the program safety analysis plan and study SAP, if needed.

2.9.6. Other Analyses

Additional subgroup analyses may be conducted to characterize the treatment response. These subgroup characteristics may include gender (male vs female), baseline severity (SALT score 50-94 vs SALT score 95-100), and duration of current episode (<4 years vs ≥4 years) and disease (<10 years vs ≥10 years). All subgroup analyses will be descriptive in nature, as appropriate.

3. References

Lee H, Jung SJ, Patel AB, et al. Racial characteristics of alopecia areata in the United States. *J Am Acad Dermatol*. 2020;83(4):1064-1070. https://doi.org/10.1016/j.jaad.2019.06.1300

Olsen EA, Callender V, McMichael A, et al. Central hair loss in African American women: incidence and potential risk factors. *J Am Acad Dermatol*. 2011;64(2):245-252. https://doi.org/10.1016/j.jaad.2009.11.693

Oslen EA, Bettencourt MS, Cote NL. The presence of loose anagen hairs obtained by hair pull in the normal population. *J Investig Dermatol Symp Proc*. 1999;4(3);258-260. https://doi.org/10.1038/sj.jidsp.5640225

Oslen EA, Hprdinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines – Part II. National Alopecia Areata Foundation. *J Am Acad Dermatol*. 2004;51(3);440-447. https://doi.org/10.1016/j.jaad.2003.09.032

Raffi J, Suresh R, Agbai O. Clinical recognition and management of alopecia in women of color. *Int J Womens Dermatol*. 2019;5(5):314-319. https://doi.org/10.1016/j.ijwd.2019.08.005

Snaith RP. The Hospital Anxiety and Depression Scale. *Health Qual Life Outcomes*. 2003;1:29. https://doi.org/10.1186/1477-7525-1-29

Taylor SC. Skin of color: biology, structure, function, and implications for dermatologic disease. *J Am Acad Dermatol.* 2002;46(2 Suppl Understanding):S41-S62. https://doi.org/10.1067/mjd.2002.120790

Thompson JM, Park MK, Qureshi AA, Cho E. Race and Alopecia Areata amongst US Women. *J Investig Dermatol Symp Proc*. 2018;19(1):S47-S50. https://doi.org/10.1016/j.jisp.2017.10.007

White D, Leach C, Sims R, et al. Validation of the Hospital Anxiety and Depression Scale for use with adolescents. *Br J Psychiatry*. 1999;175:452-454. https://doi.org/10.1192/bjp.175.5.452

Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*.1983;67(6):361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Wyrwich KW, Kitchen H, Knight S, et al. Development of clinician-reported outcome (ClinRO) and patient-reported outcome (PRO) measures for eyebrow, eyelash and nail assessment in Alopecia Areata. *Am J Clin Dermatol*. 2020a;21(5):725-732. https://doi.org/10.1007/s40257-020-00545-9

Wyrwich KW, Kitchen H, Knight S, et al. The Alopecia Areata Investigator Global Assessment scale: a measure for evaluating clinically meaningful success in clinical trials. *Br J Dermatol*. 2020b;183(4):702-709. https://doi.org/10.1111/bjd.18883

4. Supporting Documentation

4.1. Appendix 1. Abbreviations and Definitions

Term	Definition
AA	alopecia areata
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin vaccine
CI	confidence interval
ClinRO	clinician-reported outcome
CRF	case report form
CRP	clinical research physician
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ePRO	electronic patient-reported outcome
ERB	ethical review board
ET	early termination
GCP	good clinical practice
HADS	Hospital Anxiety and Depression Scale
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus

Term	Definition
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
IAS	interim analysis set
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFNγ	interferon gamma
IP	investigational product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
JAK	Janus kinase
NRI	nonresponder imputation
PPD	purified protein derivative
PRO	patient-reported outcome
QD	once daily administration
SAE	serious adverse event
SALT	Severity of Alopecia Tool
SAP	statistical analysis plan
SOA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which does not necessarily have to have a causal relationship with this treatment.
TSH	thyroid-stimulating hormone

Term	Definition
ULN	upper limit of normal
VTE	venous thromboembolic event

4.2. Appendix 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]
	Creatine phosphokinase (CPK)
Urinalysis[a,b,d]	
Color	**Other Tests**[a]
Specific gravity	Hepatitis B Surface antigen (HBsAg)[f]
pH	Anti-Hepatitis B Core antibody (HBcAb)[f]
Protein	Hepatitis B virus (HBV) DNA[l]
Glucose	Anti-Hepatitis B Surface antibody (HBsAb)[f]
Ketones	Human immunodeficiency virus (HIV)[f]
Bilirubin	Hepatitis C antibody[f,g]
Urobilinogen	Thyroid-stimulating hormone (TSH)[f]
Blood	Exploratory storage samples (serum, plasma and mRNA)
Leukocyte esterase	Pregnancy Test[h]
Nitrite	Follicle-stimulating hormone[f,i]
	QuantiFERON-TB Gold[j] (central testing preferred) or T-SPOT.*TB*[k] (local testing)
Lipids[a,c]	PPD (local testing/reading)
Total cholesterol	Serum immunoglobulin (IgE)
Low-density lipoprotein	
High-density lipoprotein	
Triglycerides	

Abbreviations: mRNA = messenger ribonucleic acid; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; IgE = immunoglobulin E; 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 8 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] Estimated glomerular filtration rate for serum creatinine calculated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration creatinine 2009 equation.

[f] Test required at Visit 1 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 1 and a local urine pregnancy test will be performed at Visit 2 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.

[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 (central testing) 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. If the QuantiFERON-TB Gold test is indeterminate, 1 retest is allowed.

[k] T-SPOT.*TB* must be read locally.

[l] HBV DNA testing will be done in those patients who are HBcAb+ at screening, regardless of hepatitis B surface antibody status.

4.3. Appendix 3. Study Governance Considerations

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

4.3.1.1. Appendix 3.1.1. Informed Consent

The investigator is responsible for:

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

4.3.1.2. Appendix 3.1.2. Recruitment

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

4.3.1.3. Appendix 3.1.3. Ethical Review

The investigator must give assurance that the ERB was properly constituted and convened, as required by ICH guidelines and other applicable laws and regulations.

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

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

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

4.3.1.4. Appendix 3.1.4. Regulatory Considerations

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

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

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

4.3.1.5. Appendix 3.1.5. Investigator Information

Physicians with expertise in the diagnosis and treatment of alopecia areata will participate as investigators in this clinical trial.

4.3.1.6. Appendix 3.1.6. Protocol Signatures

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

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

4.3.1.7. Appendix 3.1.7. Final Report Signature

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

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

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

4.3.2. Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.

- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

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

4.3.2.1. Appendix 3.2.1. Data Capture System

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

ePRO measures (for example, a rating scale) and eCOAs are entered into an ePRO/eCOA instrument at the time that the information is obtained. In those instances where there is no prior written or electronic source data at the site, the ePRO/eCOA instrument record will serve as the source.

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

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

CRF data will be encoded and stored in the electronic data capture system.

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

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

4.3.3. Appendix 3.3. Study and Site Closure

4.3.3.1. Appendix 3.3.1. Discontinuation of Study Sites

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

4.3.3.2. Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. Study termination may occur in a specific country or region when baricitinib is approved for the treatment of AA and becomes reimbursed or commercially available in that country or region, or a negative regulatory action or opinion is received in that country or region.

4.3.4. Appendix 3.4. Publication Policy

The publication policy for Study JAHO is described in the Clinical Trial Agreement.

4.4. Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Erythrocyte count (RBC)	Prothrombin Time
Leukocytes (WBC)	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

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

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

4.5. Appendix 5. Liver Function Testing and Hepatic Safety Monitoring

Liver Function Testing and Hepatic Safety Monitoring

Analyte	Exclusion Criteria	Additional Hepatic Testing	Hepatic eCRF Reporting	Temporary Interruption of IP	Permanent Discontinuation of IP after Consultation with the Lilly-Designated Medical Monitor
Protocol Section	Section 6.2	Section 9.4.10.1	Section 9.4.10.1	Section 8.1.1	Section 8.1.1
ALT/AST	≥2 × ULN	As per protocol only ALT >3 × ULN	As per protocol only ALT ≥5 × ULN on ≥2 consecutive tests	≥5 × ULN	• >8 × ULN • >5 × ULN for >2 weeks • >3 × ULN **AND** TBL >2 × ULN or INR >1.5 • >3 × ULN with symptoms[a]
ALP	≥2 × ULN	≥2 × ULN	≥2 × ULN on ≥2 consecutive tests	No applicable criteria	• >3 × ULN • >2.5 × ULN **AND** TBL >2 × ULN • >2.5 × ULN with symptoms[a]
TBL	≥1.5 × ULN	≥2 × ULN	≥2 × ULN (excluding Gilbert's syndrome)	No applicable criteria	• ALT or AST (as per protocol) >3 × ULN **AND** TBL >2 × ULN • ALP >2.5 × ULN **AND** TBL >2 × ULN

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form; INR = international normalized ratio; IP = investigational product; TBL = total bilirubin level; ULN = upper level of normal.

[a] Fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

4.6. Appendix 6. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local ERBs, regulatory bodies and any other relevant local authorities, the implementation of these exceptional circumstances changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

In the event written approval is granted by the sponsor for changes in study conduct, additional written guidance, if needed, will be provided by the sponsor.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

The site should document the participant's verbal consent for having remote visits and remote dispensing of IP, ancillaries, prior to the implementation of these activities.

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits"
- a change in the method, location, or both, of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

1. **Remote visits**

   Visit 11 (Week 52) requires a live clinical assessment because it is the primary outcome visit. To facilitate an onsite visit, the visit window may be extended (see below in Adjustment to Visit Windows of this appendix).

   All other visits may be conducted remotely if the visit could not otherwise be conducted due to local or national restrictions.

In source documents and the CRF, the study site should capture the visit location and method, with a specific explanation for any data missing because of missed in-person site visits.

Telemedicine: Live, onsite clinical efficacy assessments are preferred for ALL visits. However, if a remote visit is the only option, telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments (with the exception of Visit 11). Assessments to be completed in this manner include:

- PRO Scalp, SALT Score, and ClinROs for Eyebrows/Eyelashes if Visual Assessment by telemedicine is possible. If NO visual assessment AND ONLY verbal assessment by phone is possible. SALT, ClinROs for Eyelash/Eyelash should not be assessed.
- AEs and product complaints
- concomitant medications
- C-SSRS (Since Last Visit Version)
- Photos should be captured at next onsite visit after a remote V8 or V11/ET

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

2. **Local laboratory testing option**

   Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

   - Obtain local labs for safety (hematology, chemistry) and urine pregnancy when applicable, as per the study protocol schedule of activities.
   - A urine pregnancy test should be sent to female patients of child bearing potential. The patient should conduct the test and provide the verification of results to the site per a method agreed to between the patient and the site. Investigational product must be temporarily held until site can review photo of pregnancy test results.

- All labs will be reviewed by the investigators. Lilly Medical should be informed of any labs that meet criteria for temporary or permanent study drug discontinuation.
- Sign and date review of local labs per normal process and follow-up with the patient as needed. Results will not be recorded in the eCRF.
- Safety labs should be obtained at a minimum of every 12 weeks and IP should not be dispensed until these can be collected and reviewed.

3. Study intervention and ancillary supplies

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Sponsor approves the alternative method of delivery, taking local regulatory requirements into consideration.
- Participant consents verbally to alternate method of delivery.
- Site confirms the participant's receipt of the trial supplies.
- Site/sponsor confirms appropriate ethics review board notification.
- Alternate delivery of IP should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including the verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

4. Screening period guidance

Not Applicable

5. Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted,

upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visits 11	Visits 11 (Week 52) may be conducted within 7 days before the intended date, or up to 28 days after the intended date
All other Visits	All other visits should be conducted as per the visit window the stated in the Schedule of Activities in Section 2.2

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Signature Page for VV-CLIN-074217 v3.0

Approval	PPD 14-Mar-2024 15:17:39 GMT+0000

Approval	PPD 14-Mar-2024 15:23:11 GMT+0000

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