Protocol I4V-MC-JAHW(e)

Open-label, Active-Controlled, Safety, and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Active Juvenile Idiopathic Arthritis-Associated Uveitis or Chronic Anterior Antinuclear Antibody-Positive Uveitis

NCT04088409

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EudraCT: 2019-000119-10

EU trial number: 2023-505811-18-00

Confidential Information

Baricitinib (LY3009104)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Approval Date: Protocol Amendment (e) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-080417

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (d)	*07-Nov-2020*
Amendment (c)	*14-Aug-2020*
Amendment (b)	*31-May-2019*
Amendment (a)	*05-Apr-2019*
Original Protocol	*05-Mar-2019*

Amendment [e]
This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or rights of the study participants
- reliability and robustness of the data generated in the clinical study, and
- the quality or safety of any investigational medicinal product used in the trial.

Overall Rationale for the Amendment:
The primary purpose of this amendment is to update the protocol to reflect recent modifications to the EU Paediatric Investigation Plan (PIP) endorsed by the European Medicines Agency Paediatric Committee EMEA-001220-PIP01-11-M08. Because of the agreement to the original PIP, the standard of care for the treatment of patients with JIA-associated uveitis (JIAU) has changed substantially. For contemporary management of JIAU, adalimumab has emerged as the preferred treatment for patients developing inadequate response with methotrexate (Constantin et al. 2018; Quartier 2021). During a recent consensus meeting, an expert panel of international pediatric rheumatologists and ophthalmologists unanimously recommended adalimumab as the first-line therapy in children with JIAU and idiopathic chronic anterior uveitis (CAU) who are methotrexate-inadequate responders (MTX-IR) (Foeldvari et al. 2022). The need to minimize unnecessary delays in the initiation of alternative therapy following the failure of conventional systemic treatments, such as methotrexate, is important as persistent uveitis predisposes patients to higher risk of ocular complications and blindness (Cassidy et al. 2006; Foeldvari et al. 2022).

As a result of this approved PIP modification, the secondary outcomes for Part A and Part B have been updated, and exploratory objectives have been removed to be consistent with the PIP. This amendment also updates the number of participants involved in the study. Patients currently assigned to baricitinib who have completed the primary endpoint as a responder will continue receiving baricitinib until the end of study or discontinuation from the study, as stated in the Paediatric Committee acceptance of a modification of an agreed PIP. The number of participants in the adalimumab arm has been updated.

A secondary purpose of this amendment is to harmonize trial procedures across EU countries, as described by the Clinical Trial Facilitation Group “Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/2014.”

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis Objective(s)/Endpoints	Deleted time to treatment response in the Endpoints column in the Secondary objectives for Part A Removed time to inactive anterior uveitis disease in each affected eye in the Endpoints column in the Secondary objectives for Part B Modified "proportion" to "number" in the Endpoints column in the Secondary objectives for Part B, description of inactive anterior uveitis including time to inactive anterior uveitis disease (using SUN definition) PediACR 30/50/70/90/100 response rate statement removed from the endpoint in secondary for Part B objectives	As per PIP
Section 1. Synopsis Title of Study	Regulatory Agency Identifier numbers added	Elaboration of information needed according to CTR
Section 1. Synopsis Study Population	Added a summary of study population	Added as a subsection of the synopsis, as needed according to CTR
Section 1. Synopsis Number of Patients	Updated the total number of participants to be enrolled	As per PIP
Section 1. Synopsis Statistical Analysis	Updated the number of patients	As per PIP
Section 1. Synopsis Ethical Consideration of Benefit/Risk	Information about ethical considerations of benefit/risk added	To add the benefit/risk information to the synopsis, as needed according to CTR
Section 2. Schedule of Activities	Included measurements of external tibial length at specific weeks X-rays have been updated to imaging. Visits for imaging of wrist, hand, finger, and knee updated Questionnaires for CHAQ, CHQ PF 50, morning stiffness duration, SPARCC enthesitis index, clinical sacroiliitis, black mobility, and PASI removed from Part B Occipital frontal circumference measurement and joint assessment removed from Part B Footnotes updated for external tibial length and modified the footnote for imaging	As per Protocol Addendum 3.1 to harmonize trial procedures and as per PIP

	Footnotes added for procedures specific to Germany sites Abbreviations updated to reflect the current changes for tanner scale and external tibial length Tanner stage scale description updated for Part A, footnote updated for the same for both Parts A and B	For robust safety assessment
Section 4. Objectives and Endpoints	Deleted Exploratory objectives Updated Endpoints column for Part A and Part B Deleted time to response statement in endpoint of secondary objectives for Part A Proportion updated to the number of responders in the endpoints for Part B secondary objectives. The week number has been specified for the responders in Part B secondary objectives. Added description of inactive anterior uveitis including time to inactive anterior uveitis disease (using SUN definition) Deleted proportion of patients with inactive anterior uveitis and time to inactive anterior uveitis disease (using SUN definition) from endpoints under part B secondary objectives Deleted exploratory objectives	As per PIP and to maintain consistency across all the sections of protocol
Section 5.1. Overall Design	Updated the total number of participants for baricitinib and adalimumab arms Study design updated figure added with number of participants and duration Information about overall design added for better clarity Statement added about the current amendment following the updated study design and a footnote added to reference to Section 5.1.3	As per PIP and for maintaining consistency across all the sections of the protocol
Section 5.1.3. Open-Label Treatment Period-Part B	Information about patient randomization to adalimumab arm updated Information added about patients on baricitinib and continuation of treatment in Part B	As per PIP
Section 5.2. Number of Participants	Updated the number of participants to be evaluated for the primary endpoint	As per PIP
Section 7.1. Treatments Administered	Updated the note for oral suspension dose for participants with hereditary fructose tolerance	Incorporated from Protocol Addendum 2.1 for consolidation

	Table on treatment regimens updated with authorization status of medications information added	To comply with CTR requirement
Section 7.1.1. Packaging and Labelling	Statement added about sponsor (or its designee) will supply the investigational products as per Good Manufacturing Practice and study interventions will be labelled according to country requirements	To comply with CTR requirement
Section 7.2. Method of Treatment Assignment	Updated the number of participants to be randomly assigned to baricitinib and adalimumab arms	As per PIP
Section 7.4 Dosage Modification	Statement about dose increase for Part B patients in adalimumab removed	As per PIP
Section 7.8.2. Special Treatment Considerations	Statement about rescue therapy removed	As per PIP
Section 8.1.3. Discontinuation of Inadvertently Enrolled Patients	Clarified discontinuation rules for sites in France	Incorporated from Protocol Addendum 2.1 for consolidation
Section 9.1.2. Secondary Efficacy Assessments	Updated statement for time to treatment response	For clarification
Section 9.1.4. Exploratory Efficacy Assessments	Deleted section	Removed exploratory assessments
Section 9.2.1.1. Suspected Unexpected Serious Adverse Reactions	European regulation added Information added about sponsor having the legal responsibility to notify regulatory agencies	Elaboration of information needed according to CTR
Section 9.4.6.2. Growth Monitoring	Included details related to the MRI of the knee and external tibial length measurement	For consistency across all the sections of the protocol
Section 10.1. Sample Size Determination	Updated number of participants for sample size determination	As per PIP
Section 10.3.1. General Statistical Considerations	Statement about handling of missing, unused, and spurious data added. Changed the method to impute missing data in Part A. Information about Nonresponder Imputation (NRI) added.	As per PIP
Section 10.3.3.2. Secondary Analyses	Modified table of secondary endpoint analyses for Part A	For consistency across all the sections of the protocol
Section 10.3.3.3. Exploratory Analyses	Deleted the description of exploratory analyses	For consistency across all the sections of the protocol
Section 10.3.6. Health Outcomes	Section removed and subsequent sections renumbered	As per PIP
Section 10.3.7. Interim Analyses	Information about the study continuing for baricitinib treated patients removed Information about additional analyses and	As per PIP

	snapshots of study data added	
Section 11. References	Included reference for European Medicines Agency Included references for PIP modification	Incorporated from Protocol Addendum 2.1 for consolidation As per PIP
Appendix 3. Study Governance Considerations Appendix 3.1.1. Informed Consent Appendix 3.2.1. Data Protection and Data Capture System Appendix 3.4 Publication Policy and Dissemination of Clinical Study Data	Statement added about reporting to sponsor or designee about significant issues related to participant Information about participants being provided a unique identifier, personal study-related data, informed consent, information security, and transfer of personal data information added Information about sponsor's disclosure of summary of study information added	Elaboration of information needed according to CTR
Appendix 10. Protocol Amendment History	Changes for amendment (d) added	As per harmonized protocol template
Throughout the document	Minor edits	For clarity

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1. Synopsis

Title of Study
An Open-label, Active-Controlled, Safety, and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Active Juvenile Idiopathic Arthritis-Associated Uveitis or Chronic Anterior Antinuclear Antibody-Positive Uveitis.

Regulatory Agency Identifier Numbers:

EudraCT: 2019-000119-10
EU trial number: 2023-505811-18-00

Rationale
Juvenile idiopathic arthritis (JIA)-associated uveitis (JIA-U) is the most common extra-articular manifestation of JIA. It involves chronic inflammation of the uveal components of the eye, that is, the iris, choroid, and retina. If inadequately treated, patients with JIA-U can develop glaucoma, cataracts, visual impairment, and blindness (Sen and Ramanan 2017).

Uveitis usually occurs within 3 years following the onset of arthritis in patients with JIA (Verazza et al. 2008). However, in a small proportion of patients, CAU may occur in the absence of any detectable systemic manifestations of JIA (Sen and Ramanan 2017). Owing to the similarity of the conditions, it is recommended that patients with anterior antinuclear antibody (ANA)-positive CAU, in the absence of systemic symptoms, should be treated in the same manner as patients with JIA-U (Heiligenhaus et al. 2012).

The etiology and pathogenesis of JIA-U and ANA-positive uveitis are still poorly understood; however, the aqueous humor of these patients contains elevated levels of a number of cytokines, including interleukin (IL)-2, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α (Agrawal et al. 2014; Sijssens et al. 2007). Therefore, pharmacologic interventions that reduce the activity of such cytokines may prove to be novel therapies for these conditions.

Baricitinib belongs to the pharmacological class of Janus kinase (JAK) inhibitors. Janus kinases are a family of 4 protein tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) that play an important role in cytokine signal transduction. Baricitinib is a JAK1/JAK2 inhibitor demonstrating selectivity for and inhibition of JAK1 and JAK2 with lower potency towards inhibition of JAK3 or TYK2 (Fridman et al. 2010).

In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2, and JAK3 with half-maximal inhibitory concentration values of 5.9, 5.7, 53, and >400 nM, respectively (Fridman et al. 2010). Janus kinases are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation, and immune function (e.g., IL-2, IL-6, IL-12, IL-15, IL-23, INFs, and granulocyte-macrophage colony-stimulating factor signal through the JAK family) (O'Shea et al. 2015). Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signaling pathways by partially inhibiting JAK1 and JAK2

enzymatic activity, then reducing the phosphorylation and activation of STATs and thereby reducing inflammation, cellular activation, and proliferation of key immune cells (O'Shea et al. 2013).

This activity profile suggests that baricitinib may inhibit cytokines implicated in JIA and JIA-U, including IL-6 and IFN-γ (O'Shea et al. 2013), as well as other cytokines that may have a role in JIA-U including IL-2 and TNF-α. Therefore, there is a compelling rationale to evaluate baricitinib for the treatment of these autoimmune diseases.

The aim of this study is to evaluate the efficacy and safety of oral baricitinib when administered once daily (QD) to pediatric patients with JIA-U or ANA-positive uveitis without systemic features despite prior treatment with adequate doses of topical steroids and methotrexate (MTX). The safety and tolerability data from this study will establish an understanding of the benefit/risk relationship for baricitinib in these patients.

Adalimumab, an injectable TNF inhibitor therapy, was recently shown to be an effective treatment for JIA-U (Ramanan et al. 2017), and is now approved for this indication. As adalimumab is the only approved therapy for JIA-U, adalimumab is included in this study to provide an active comparator arm.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To evaluate the efficacy of baricitinib in children with juvenile idiopathic arthritis-associated uveitis (JIA-U) or anterior antinuclear antibody (ANA)-positive uveitis	• Proportion of responders at Week 24. Response is defined according to the Standardization of Uveitis Nomenclature (SUN) criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through Week 24, in the eye most severely affected at baseline.
Secondary for Part A • To evaluate the efficacy of baricitinib in children with JIA-U or ANA-positive uveitis in the most severely affected eye and less affected eye • To evaluate the efficacy of adalimumab in children with JIA-U or ANA-positive uveitis in the most severely affected eye and less affected eye	• Change in SUN grade of cells in the anterior chamber through Week 24 in the most severely affected eye. • Change in SUN grade of cells in the anterior chamber through Week 24 in the less severely affected eye (if applicable). • In patients with bilateral uveitis disease at baseline: Proportion of responders at Week 24, defined according to the SUN criteria as a 2-step decrease in the level of anterior chamber cells in the most severely affected eye at baseline (or both eyes if the inflammation grade is the same in both eyes) and a 1-step decrease in the level of anterior chamber cells in the less severely affected eye at baseline[a]. • Change in visual acuity measured by age-appropriate LogMAR test through Week 24. • Change in vitreous haze through Week 24 in each affected eye. • Change in grade of flare in the anterior chamber through Week 24 in each affected eye. • Change in overall uveitis-related disability: o Change in Patient Uveitis-related Disease Activity through Week 24. o Change in Patient Uveitis-related Improvement at Week 12 and Week 24. o Change in Patient Arthritis Disease Activity through Week 24. o Change in Patient Arthritis Improvement at Week 12 and Week 24. o Change in Ophthalmologist Uveitis-related Disease Activity through Week 24. o Change in Ophthalmologist Uveitis-related Improvement at Week 12 and Week 24.

Objectives	Endpoints
	• Proportion of patients with inactive anterior uveitis (using SUN definition) in each affected eye through Week 24. • Time to inactive anterior uveitis disease (using SUN definition) in each affected eye. • Proportion of patients who are able to taper concomitant topical corticosteroids to <2 drops per day and to 0 drops per day. • PediACR30/50/70/90/100 response rates (for patients with JIA-U).
• To evaluate the safety of baricitinib in children with JIA-U or ANA-positive uveitis	• Adverse events (AEs) including serious adverse events. • Permanent discontinuation of investigational product due to AE. • Temporary interruption of investigational product.
Secondary for Part B (open-label extension) • To describe the efficacy of baricitinib in children with JIA-U or ANA-positive uveitis in the most severely affected eye and less affected eye (among the responders at Week 24)	• Number of responders through Week 284. Response is defined according to the SUN criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through Week 284, in the eye most severely affected at baseline. • Change in SUN grade of cells in the anterior chamber through Week 284 in the most severely affected eye. • Change in SUN grade of cells in the anterior chamber through Week 284 in the less severely affected eye (if applicable). • In patients with bilateral uveitis disease at baseline: Number of responders through Week 284, defined according to the SUN criteria as a 2-step decrease in the level of anterior chamber cells in the most severely affected eye at baseline (or both eyes if the inflammation grade is the same in both eyes) and a 1-step decrease in the level of anterior chamber cells in the less severely affected eye at baseline. • Change in grade of flare in the anterior chamber through Week 284 in each affected eye. • Description of inactive anterior uveitis including time to inactive anterior uveitis disease (using SUN definition) in each affected eye through Week 284. • Number of patients who are able to taper concomitant topical corticosteroids to <2 drops per day and to 0 drops per day. Number of patients who are able to taper concomitant oral corticosteroids to <5 mg per day and to 0 mg per day.

Objectives	Endpoints
• To evaluate the safety of baricitinib in children with JIA-U or ANA-positive uveitis	• Adverse events including serious adverse events. • Permanent discontinuation of investigational product due to AE. • Temporary interruption of investigational product.

Abbreviations: AE = adverse event; LogMAR = logarithm of the minimum angle of resolution; PediACR = Pediatric American College of Rheumatology; SUN = Standardization of Uveitis Nomenclature.

a Response is defined according to the SUN criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to 0 through Week 24 in the eye most severely affected at baseline.

Summary of Study Design

Study I4V-MC-JAHW (JAHW) is a multicenter, open-label, active-controlled Phase 3 study in patients with active JIA-U or chronic ANA-positive uveitis without systemic features despite prior treatment with adequate doses of topical steroid therapy and MTX.

Treatment Arms and Duration

The study consists of 2 arms. Patients in the baricitinib arm will receive oral baricitinib at least QD at a fixed dose by age group. Patients in the adalimumab (active control) arm will receive adalimumab as a subcutaneous injection every 2 weeks. The dose will be based on body weight (adalimumab Summary of Product Characteristics [SmPC]).

Study JAHW will be conducted in 2 parts:

- Treatment Period Part A: 24 weeks
- Treatment Period Part B: 260 weeks.

Patients who complete Part A may be eligible to continue to Part B, the open-label extension (OLE) period of the study. Patients on adalimumab will be discontinued after Week 24. Patients who do not continue in the OLE will have a follow-up visit (Visit 801) approximately 28 days after the last dose of the investigational product.

Study Population

This study includes patients from 2 years to less than 18 years old with active JIA-U or chronic ANA-positive uveitis without systemic features despite prior treatment with adequate doses of topical steroid therapy and MTX.

Number of Patients

- Baricitinib arm: At least 20 patients (MTX-IR and/or bDMARD-IR) evaluable for primary endpoint.
- Adalimumab arm: At least 4 patients evaluable for the primary endpoint.

Statistical Analysis

A Bayesian analysis will determine if the study should be considered a positive study or a negative study. The study will be considered positive if the posterior probability is at least 80%

that the baricitinib treatment response is greater than 57%, otherwise the study will be considered negative.

Efficacy and health outcome endpoints will be summarized using descriptive statistics. The last-observation-carried-forward approach will be used to impute missing data.

Categorical data will be summarized as frequency counts and percentages. The proportions and 95% confidence interval will be reported. Missing data will be imputed using the modified nonresponder imputation method.

Two interim analyses will be performed to determine if the study should be stopped for futility when 10 and 20 baricitinib-treated patients have completed 24 weeks of treatment. At each interim analysis, the posterior probability of the treatment response rate being lower than 40% will be calculated, and the study will be stopped if this probability is greater than 75% (otherwise the study will continue).

Descriptive response rates will be evaluated in adalimumab-treated patients.

An analysis will evaluate response rates in MTX-IR adalimumab-treated patients and MTX-IR baricitinib-treated patients.

All safety data will be descriptively summarized using corresponding populations.

Ethical Considerations of Benefit/Risk

Based on the efficacy of baricitinib demonstrated in the Phase 3 RA program and the observed safety profile, the probability of a positive benefit/risk warrants this study to be conducted, given the unmet need in patients with JIA-U and ANA-positive uveitis.

2. Schedule of Activities

The Schedule of Activities described below should be followed for all participants enrolled in Study JAHW. In the event participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Appendix 9 and consult with the sponsor's representative for additional guidance.

Table JAHW.1. Schedule of Activities

	Screening		Treatment Period Part A							Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1[a]**	**V2[a] Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**ETV[b]**	**V801[c]**
Study Week			**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**0**	**28**	**56**	**84**	**112**	**140**	**168**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±4**							
Informed consent and assent[d]	X										
Complete medical history	X										
Immunization record	X		X	X	X	X	X	X	X		
Demographics	X										
Physical examination[e]	X										
Tanner Stage Scale[z]			X								
Symptom-directed physical examination[e]			X	X	X	X	X	X	X	X	X
Habits: tobacco and caffeine			X								
Height	X		X			X			X	X	
Weight	X		X	X	X	X	X	X	X	X	X
Imaging of wrist, hand, finger, and knee[f]			X[f]								
Occipital frontal circumference measurement in children up to 3 years of age			X	X[g]						X	X
Vital signs (blood pressure, pulse, temperature)			X	X	X	X	X	X	X	X	X

	Screening		Treatment Period Part A							Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1[a]**	**V2[a] Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**ETV[b]**	**V801[c]**
Study Week			**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**0**	**28**	**56**	**84**	**112**	**140**	**168**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±4**							
Inclusion/exclusion criteria review	X		X								
Preexisting conditions	X										
JIA diagnosis (ILAR criteria)	X										
Previous JIA and uveitis therapy	X										
Visual acuity (LogMAR)			X	X	X	X	X	X	X	X	X
Slit-lamp examination of the retina and optic disc			X	X	X	X	X	X	X	X	X
Optical coherence tomography			X	X	X	X	X	X	X	X	X
Slit-lamp examination for anterior chamber cells and flare assessment	X		X	X	X	X	X	X	X	X	X
Slit-lamp examination for assessment of vitritis and vitreous haze	X		X	X	X	X	X	X	X	X	X
Cataract scoring[h]			X	X	X	X	X	X	X	X	X
IOP using I-Care tonometry, Goldmann tonometry, or Tono-Pen			X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X
Adverse events	X		X	X	X	X	X	X	X	X	X
Log in IWRS	X		X	X	X	X	X	X	X	X	X
Randomization			X								
Dispense study drug			X	X	X	X	X	X	X		

	Screening		Treatment Period Part A							Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1[a]**	**V2[a] Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**ETV[b]**	**V801[c]**
Study Week			**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**0**	**28**	**56**	**84**	**112**	**140**	**168**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±4**							
Investigational product returned and compliance assessed[i]				X	X	X	X	X	X	X	
Joint assessment	X		X	X	X	X	X	X	X	X	X
External tibial length measurement[y]			X			X			X		
Physician's Global Assessment of Disease Activity	X		X	X	X	X	X	X	X	X	X
Patient Uveitis-related Disease Activity[j]	X		X	X	X	X	X	X	X	X	X
Patient Uveitis-related Improvement[j]						X			X	X	X
Patient Arthritis Disease Activity[j]	X		X	X	X	X	X	X	X	X	X
Patient Arthritis Improvement[j]						X			X	X	X
Ophthalmologist Uveitis-related Disease Activity	X		X	X	X	X	X	X	X	X	X
Ophthalmologist Uveitis-related Improvement						X			X	X	X
CHAQ[k]			X	X	X	X	X	X	X	X	X
CHQ-PF50[k]			X			X			X	X	X
Morning stiffness duration[j]			X	X	X	X	X	X	X	X	X
SPARCC Enthesitis Index[l]			X	X	X	X	X	X	X	X	X
Clinical sacroiliitis[l]			X	X	X	X	X	X	X	X	X
Back mobility			X	X	X	X	X	X	X	X	X

	Screening		Treatment Period Part A							Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1[a]**	**V2[a] Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**ETV[b]**	**V801[c]**
Study Week			**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**0**	**28**	**56**	**84**	**112**	**140**	**168**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±4**							
(Schober's test)[l]											
PASI[m]			X	X	X	X	X	X	X	X	X
Chest x-ray[n]	X										
Administer PPD/ QuantiFERON®-TB Gold/T-SPOT® TB[o]	X										
Read PPD[o]		X									
ECG[p]	X										
hsCRP	X		X	X	X	X	X	X	X	X	X
ESR[q]			X	X	X	X	X	X	X	X	X
HLA-B27					X						
RF and ACPA	X										
Antinuclear antibodies			X						X	X	
TSH	X										
HIV/HCV[r]	X										
HBV (HBsAg, HBcAb, HBsAb)	X										
HBV DNA[s]	X		X			X			X	X	X
Serum pregnancy test[t]	X										
Urine pregnancy test[t]			X	X	X	X	X	X	X	X	X
Clinical chemistry[u]	X		X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X	X	X
Urinalysis	X		X			X			X	X	X
Iron studies (iron, TIBC, and ferritin)			X			X			X	X	X

	Screening		Treatment Period Part A							Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1[a]**	**V2[a] Baseline**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**ETV[b]**	**V801[c]**
Study Week			**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**0**	**28**	**56**	**84**	**112**	**140**	**168**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±4**							
Fasting lipid panel[v]			X			X			X	X	X
IgA, IgG, IgM			X			X			X	X	X
Lymphocyte subsets (T, B, NK, and T-cell subsets)			X			X			X	X	X
Antipneumococcal IgG multianalyte Ab assay[w]				At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks postvaccination based on the vaccination schedule of each patient							
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay[w]				At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks postvaccination based on the vaccination schedule of each patient							
IGF-1 and IGFBP-3			X			X			X	X	X
Gonadal hormone[x]			X			X			X	X	X
Exploratory storage samples (RNA, serum, and plasma)			X			X			X		
Pharmacogenetic (DNA) collection					X						

Abbreviations: Ab = antibody; ACPA = anti-citrullinated protein antibodies; CHAQ = Childhood Health Assessment Questionnaire; CHQ-PF50 = Child Health Questionnaire-Parent Form 50; CRP = C-reactive protein; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; ETV = early termination visit; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hsCRP = high-sensitivity C-reactive protein; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor-binding protein-3; ILAR = International League of Associations for Rheumatology; IOP = intraocular pressure; IWRS = interactive web-response system; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; LogMAR = logarithm of the minimum angle of resolution; NK = natural killer; PASI = Psoriasis Area and Severity Index; PPD = purified protein derivative; RF = rheumatoid factor; RNA = ribonucleic acid; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; TIBC = total iron-binding capacity; TSH = thyroid-stimulating hormone; V = visit.

[a] Baseline laboratory samples should be taken **before** administration of investigational product.

[b] Early termination visit (ETV) occurs if the patient terminates participation early. If the ETV occurs on the same day as the scheduled visit, any assessments/procedures conducted during the scheduled visit should not be repeated for a separate ETV.

[c] Patients who complete the study or discontinue early from the study will have a post-treatment safety follow-up visit (V801) approximately 28 days after the last dose of investigational product.

[d] The parent or legal guardian will sign the informed consent form (ICF) and the patient will sign the assent form (as appropriate) per local requirements prior to any study assessments, examinations, or procedures being performed.

[e] One complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1. All subsequent physical examinations may be symptom-directed. A complete physical examination may be repeated at the investigator's discretion at any time. Must include an assessment of serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA.

[f] Semiannual wrist, hand, finger, and knee radiographs to monitor bone age and long bone growth. Imaging will be required until skeletal maturity is attained and this should be determined by a qualified physician at the site. For patients already enrolled in JAHW at the time of Amendment (d), the x-ray procedures will be optional. For these ongoing patients that consent to the x-ray procedures, x-rays must be completed within 30 days from time of consent/assent and every 6 months ±30 days thereafter. For patients from Germany, MRI should be utilized for knee imaging. If MRI is not available, X-rays can be used as an alternative.

[g] Occipital frontal circumference measurement is required every 3 months for patients under 3 years of age, but is no longer required once the patient reaches 3 years of age.

[h] Only for patients with cataracts at baseline, or who develop cataracts during the study.

[i] Patients will return all investigational products for drug accountability.

[j] Patient-reported and caregiver-reported questionnaires will be administered on paper at the site and are recommended to be completed prior to any clinical examinations.

[k] Caregiver-reported questionnaires (CHAQ and CHQ-PF50) will be administered via an on-site eCOA device and are recommended to be completed prior to any clinical assessments.

[l] Only for patients with enthesitis-related juvenile idiopathic arthritis (ERA) or juvenile psoriatic arthritis (JPsA).

[m] Only for patients with JPsA.

[n] Only for patients with a history of active or latent TB with documented evidence of appropriate treatment and patients with a positive or repeated not-negative TB test(s) (either PPD, QuantiFERON®-TB Gold, and/or T-SPOT®). A chest x-ray (posterior-anterior view) will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available for review.

[o] TB tests include PPD, QuantiFERON®-TB Gold, and T SPOT®. In countries where the QuantiFERON-TB Gold test or T-SPOT is available, either test may be used instead of the PPD TB test. The QuantiFERON-TB Gold test may be performed locally or centrally; the T-SPOT must be performed locally. PPD tests must be read 48 to 72 hours after screening. (Exception: Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing but must have a chest x-ray at screening.)

[p] The ECG will be collected and read locally (no central over read). An ECG performed within 1 year prior to screening may be used.

[q] Performed locally. To be drawn prior to dosing early in the visit.

[r] For patients who are positive for HCV antibody, a follow-up test for HCV RNA is required. Patients with a positive HCV antibody will return to the site and have an HCV RNA sample drawn, which will be processed centrally. Results must be known prior to enrollment. Patients who are positive for HCV antibody and negative for HCV RNA may be enrolled.

[s] For patients who are positive for HBcAb, a follow-up test for HBV DNA is required. Patients with a positive HBcAb will return to the site and have an HBV DNA sample drawn, which will be processed centrally. Results must be known prior to enrollment. Any enrolled patient who is HBcAb positive, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule of activities.

[t] Pregnancy tests prior to first dose of investigational product for females ≥10 years of age (<10 years at investigator discretion) if menarche reached or if there is reason to believe the patient is sexually active. Pregnancy test results from baseline must be known prior to first dose of investigational product.

[u] Clinical chemistry will include eGFR (calculated by Bedside Schwartz 2009 formula).

[v] Fasting lipid profile: Patients should not eat or drink anything except water for 4-12 hours depending on weight and age as specified below. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Recommended fasting times by age and weight are as follows:

- Patients ≥12 years: fast for 12 hours prior to laboratory test
- Patients 8 to <12 years and weighing >50 kg: fast for 12 hours prior to laboratory test
- Patients 8 to <12 years and weighing ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 25 to ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 10 to <25 kg: fast for 6 hours prior to laboratory test
- Children <8 years and weighing <10 kg: fast for 4 hours prior to laboratory test

[w] If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks postvaccination, and 12 weeks post vaccination.

[x] Estradiol (for females) or testosterone (for males) will be collected for the assessment of pubertal development in patients aged 8 to <18 years.

[y] For sites in Germany only. This will be collected at baseline and every 3 months during study participation. Guidance on measuring external tibial length will be provided by the sponsor.

[z] Participants 8 years and older will be assessing their sexual maturity. Once the participant reaches the score 5 in the scale, no further assessments are needed.

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart (Appendix 7).

Table JAHW.2. Schedule of Activities for Patients Participating in Long-Term Extension Period

	Treatment Period Part B																						Early Termination	Post-Treatment Follow-Up
Visit #	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**ETV[a]**	**V801[b]**
Study Week	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**	**W120**	**W132**	**W144**	**W156**	**W168**	**W180**	**W192**	**W204**	**W216**	**W228**	**W240**	**W252**	**W264**	**W276**	**W284**	**Any Week**	
Study Day (Approximately)	**252**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092**	**1176**	**1260**	**1344**	**1428**	**1512**	**1596**	**1680**	**1764**	**1848**	**1932**	**1988**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)	**±7**																							
Symptom-directed physical examination[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging of wrist, hand, finger, and knee[d]	X		X		X		X		X		X		X		X		X		X		X			
Vital signs (blood pressure, pulse, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual acuity (LogMAR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination of the retina and optic disc	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optical coherence tomography	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination for anterior chamber cells and flare assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Treatment Period Part B																						Early Termination	Post-Treatment Follow-Up
Visit #	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**ETV[a]**	**V801[b]**
Study Week	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**	**W120**	**W132**	**W144**	**W156**	**W168**	**W180**	**W192**	**W204**	**W216**	**W228**	**W240**	**W252**	**W264**	**W276**	**W284**	**Any Week**	
Study Day (Approximately)	**252**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092**	**1176**	**1260**	**1344**	**1428**	**1512**	**1596**	**1680**	**1764**	**1848**	**1932**	**1988**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)	**±7**																							
Slit-lamp examination for assessment of vitritis and vitreous haze	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cataract scoring[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP using I-Care tonometry, Goldmann tonometry, or Tono-Pen	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Log in IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

	Treatment Period Part B																						Early Termination	Post-Treatment Follow-Up
Visit #	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**ETV[a]**	**V801[b]**
Study Week	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**	**W120**	**W132**	**W144**	**W156**	**W168**	**W180**	**W192**	**W204**	**W216**	**W228**	**W240**	**W252**	**W264**	**W276**	**W284**	**Any Week**	
Study Day (Approximately)	**252**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092**	**1176**	**1260**	**1344**	**1428**	**1512**	**1596**	**1680**	**1764**	**1848**	**1932**	**1988**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)	**±7**																							
Investigational product returned and compliance assessed[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
External tibial length measurement[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physician's Global Assessment of Disease Activity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tanner Stage Scale[r]	X			X			X			X			X			X				X				
hsCRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antinuclear antibodies		X				X				X				X				X				X		
RF and ACPA		X				X				X				X				X				X		
HBV DNA[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Treatment Period Part B																						Early Termination	Post-Treatment Follow-Up
Visit #	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**ETV[a]**	**V801[b]**
Study Week	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**	**W108**	**W120**	**W132**	**W144**	**W156**	**W168**	**W180**	**W192**	**W204**	**W216**	**W228**	**W240**	**W252**	**W264**	**W276**	**W284**	**Any Week**	
Study Day (Approximately)	**252**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092**	**1176**	**1260**	**1344**	**1428**	**1512**	**1596**	**1680**	**1764**	**1848**	**1932**	**1988**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)	**±7**																							
Urinalysis		X				X				X				X				X				X	X	X
Iron studies (iron, TIBC and ferritin)		X				X				X				X				X				X	X	X
Fasting lipid panel[o]		X				X				X				X				X				X	X	X
IgA, IgG, IgM		X				X				X				X				X				X	X	X
Lymphocyte subsets (T, B, NK, and T-cell subsets)		X				X				X				X				X				X	X	X
Antipneumococcal IgG multianalyte Ab assay[p]	At relevant visits for prevaccination, 4 weeks postvaccination, and 12 weeks postvaccination based on the vaccination schedule of each patient																							
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay[p]	At relevant visits for prevaccination, 4 weeks postvaccination, and 12 weeks postvaccination based on the vaccination schedule of each patient																							
IGF-1 and IGFBP-3	X			X				X				X				X				X			X	X
Gonadal hormone[q]	X			X				X				X				X				X			X	X
Exploratory storage samples (RNA, serum, and plasma)												X										X		

Abbreviations: Ab = antibody; ACPA = anti-citrullinated protein antibodies; DNA = deoxyribonucleic acid; eCOA = electronic Clinical Outcome Assessment; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; ETV = early termination visit; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; hsCRP = high-sensitivity C-reactive protein; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor-binding protein-3; IOP = intraocular pressure; IWRS = interactive web-response system; JIA = juvenile idiopathic arthritis; LogMAR = logarithm of the minimum angle of resolution; NK = natural killer; RF = rheumatoid factor; RNA = ribonucleic acid; TB = tuberculosis; TIBC = total iron-binding capacity; V = visit.

[a] Early termination visit occurs if the patient terminates participation early. If the ETV occurs on the same day as the scheduled visit, any assessments/procedures conducted during the scheduled visit should not be repeated for a separate ETV.

[b] Patients who complete the study or discontinue early from the study will have a post-treatment safety follow-up visit (V801) approximately 28 days after the last dose of investigational product.

[c] All physical examinations in Part B may be symptom-directed; however, a complete physical examination may be repeated at the investigator's discretion at any time. Must include an assessment of serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA.

[d] Semiannual wrist, hand, finger, and knee radiographs to monitor bone age and long-bone growth. These x-rays are mandatory for all patients enrolled in this study. Imaging will be required until skeletal maturity is attained as determined by a qualified physician (either study investigator or as noted in radiology report). X-rays will be completed approximately every 6 months. If a patient had imaging conducted ≤4 months previously in the Schedule of Activities Part A, the patient should not undergo imaging until next defined imaging visit. For patients from Germany, MRI should be utilized for knee imaging. If MRI is not available, x-rays can be used as an alternative.

[f] Only for patients with cataracts at baseline, or who develop cataracts during the study.

[g] Patients will return all investigational products for drug accountability.

[h] Applicable for sites in Germany only.

[k] Performed locally. To be drawn prior to dosing early in the visit.

[l] For patients who are positive for HBcAb, a follow-up test for HBV DNA is required. Patients with a positive HBcAb will return to the site and have an HBV DNA sample drawn, which will be processed centrally. Results must be known prior to enrollment. Any enrolled patient who is HBcAb positive, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule of activities.

[m] Urine pregnancy tests are required for females ≥10 years of age (<10 years at investigator discretion) if menarche reached or if there is reason to believe the patient is sexually active.

[n] Clinical chemistry will include eGFR (calculated by Bedside Schwartz 2009 formula).

[o] Fasting lipid profile: Patients should not eat or drink anything except water for 4-12 hours depending on weight and age as specified below. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Recommended fasting times by age and weight are as follows:

- Patients ≥12 years: fast for 12 hours prior to laboratory test
- Patients 8 to <12 years and weighing >50 kg: fast for 12 hours prior to laboratory test
- Patients 8 to <12 years and weighing ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 25 to ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 10 to <25 kg: fast for 6 hours prior to laboratory test
- Children <8 years and weighing <10 kg: fast for 4 hours prior to laboratory test

[p] If patients are eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal conjugate vaccine according to local recommended schedule of vaccination, IgG titers for eligible vaccine will be evaluated at prevaccination, 4 weeks postvaccination, and 12 weeks postvaccination.

[q] Estradiol (for females) or testosterone (for males) will be collected for the assessment of pubertal development in patients aged 8 to <18 years.

[r] Participants 8 years and older will be assessing their sexual maturity. Once the participant reaches the score 5 in the scale, no further assessments are needed.

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in the sponsor-provided weight-based prioritization chart (Appendix 7).

3. Introduction

3.1. Study Rationale

Baricitinib belongs to the pharmacological class of Janus kinase (JAK) inhibitors. Janus kinases are a family of 4 protein tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) that play an important role in cytokine signal transduction. Baricitinib is a JAK1/JAK2 inhibitor demonstrating selectivity for and inhibition of JAK1 and JAK2 with lower potency towards inhibition of JAK3 or TYK2 (Fridman et al. 2010).

In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2, and JAK3 with half-maximal inhibitory concentration values of 5.9, 5.7, 53, and >400 nM, respectively (Fridman et al. 2010). Janus kinases are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation, and immune function (e.g., interleukin [IL]-2, IL-6, IL-12, IL-15, IL-23, interferons, and granulocyte-macrophage colony-stimulating factor signal through the JAK family) (O'Shea et al. 2015). Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signaling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, then reducing the phosphorylation and activation of STATs and thereby reducing inflammation, cellular activation, and proliferation of key immune cells (O'Shea et al. 2013).

The etiology and pathogenesis of juvenile idiopathic arthritis (JIA), JIA-associated uveitis (JIA-U) and antinuclear antibody (ANA)-positive uveitis are still poorly understood, but the diseases share several immunological abnormalities identified in rheumatoid arthritis (RA) (Ravelli and Martini 2007). The inflammatory synovitis in JIA is similar to that observed in RA. The synovium in JIA shows pronounced hyperplasia of the lining layer and an infiltration of the sublining layer with mononuclear cells, including T cells, B cells, macrophages, dendritic cells, and plasma cells, as observed in RA. Similarly, B- and T-lymphocytes appear to be involved in the pathogenesis of JIA-U; eye biopsies from patients with JIA-U were found to contain a predominance of CD4+ T cells and plasma cells, along with B cells (Kalinina Ayuso et al. 2014).

Some studies have shown that levels of inflammatory cytokines elevated in adults with RA, such as IL-6 and tumor necrosis factor-alpha (TNF-α), are also elevated in the synovial fluid and serum of patients with JIA, as well as the aqueous humor of patients with JIA-U (Sijssens et al. 2007). Inflammatory cytokines, such as IL-6, which transduces cell signaling through the JAK/STAT pathway (Rawlings et al. 2004), and TNF, whose expression is reduced by inhibition of JAK1 and JAK2, are considered to be associated with the pathology of JIA-U and ANA-positive uveitis (Sijssens et al. 2007; Agrawal et al. 2014). Therefore, inhibition of JAK-STAT signaling by baricitinib can target multiple cytokine pathways associated with JIA-U and ANA-positive uveitis, and may provide novel therapeutic approaches to disease management.

Biologic DMARDs, in particular the recently approved anti–TNF-α monoclonal antibody adalimumab, have led to significant improvements in JIA-U treatment. However, many patients

fail to respond to or do not achieve long-lasting remission with these medications. For example, during a 2-year treatment period, 40% of JIA-U patients receiving adalimumab and 79.7% receiving infliximab did not achieve clinical remission (Cecchin et al. 2018).

Baricitinib has demonstrated clinical safety and efficacy in adult patients with moderately to severely active RA in 4 completed Phase 3 studies (Genovese et al. 2016; Dougados et al. 2017; Fleischmann et al. 2017; Taylor et al. 2017). These studies are summarized in Table JAHW.3.

Table JAHW.3. Summary of Baricitinib Phase 3 Clinical Studies in Rheumatoid Arthritis

Se	I4V-MC-JADZ (RA-BEGIN)	I4V-MC-JADV (RA-BEAM)	I4V-MC-JADX (RA-BUILD)	I4V-MC-JADW (RA-BEACON)
Length of Study	52 weeks	52 weeks	24 weeks	24 weeks
Patient Population	Limited or no prior DMARD exposure	Inadequate response to MTX and bDMARD-naive	csDMARD-IR and bDMARD-naive	IR to ≥1 TNF-α inhibitor; No limit on number or nature of other prior bDMARDs.
Treatment Arms (N)	• MTX QW (210) • BARI 4-mg QD (159) • BARI 4-mg QD plus MTX QW (215)	• Placebo QD for 24 weeks, followed by switch to BARI 4-mg QD from Week 24 to Week 52 (488) • BARI 4-mg QD (487) • Adalimumab 40-mg Q2W (330)	• Placebo QD (228) • BARI 2-mg (229) • BARI 4-mg (227)	• Placebo QD (176) • BARI 2-mg (174) • BARI 4-mg (177)
Primary Endpoint	ACR20 at W24	ACR20 at W12	ACR20 at W12	ACR20 at W12
Response Rate	• BARI: 77% • MTX: 62% (p≤0.01)	• BARI: 70% • Placebo: 40% (p≤0.001)[a] • Adalimumab: 61% (p = 0.014)[a]	• BARI: 62% • Placebo: 39% (p≤0.001)	• BARI: 55% • Placebo: 27% (p≤0.001)
Reference	Fleischman et al. 2017	Taylor et al. 2017	Dougados et al. 2017	Genovese et al. 2016

Abbreviations: ACR = American College of Rheumatology; BARI = baricitinib; bDMARD = biologic disease-modifying antirheumatic drug; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; IR = inadequate response or intolerance; MTX = methotrexate; N = number of patients; QD = once daily; QW = once weekly; Q2W = every 2 weeks; TNF-α = tumor necrosis factor-alpha; W = week.

[a] p-value from comparison with baricitinib.

Table JAHW.4 summarizes the efficacy findings from the Phase 3 studies in adult RA by displaying the results of the primary and secondary endpoints, which were controlled for multiplicity. Baricitinib 4 mg was efficacious across domains of efficacy that included signs and symptoms, physical function, reduction of radiographic progression, and other patient-reported outcomes, such as pain and morning joint stiffness.

Table JAHW.4. Summary of Primary and Major (Gated) Secondary Endpoints for Baricitinib Phase 3 Rheumatoid Arthritis Studies

Endpoint[a]	JADZ[a]		JADV		JADX		JADW	
	BARI 4-mg vs. MTX	BARI 4-mg + MTX vs. MTX	BARI 4-mg vs. PBO	BARI 4-mg vs. ADA	BARI 4-mg vs. PBO	BARI 2-mg vs. PBO	BARI 4-mg vs. PBO	BARI 2-mg vs. PBO
ACR20 at primary time point[a]	≤0.01[b]	≤0.001	≤0.001	≤0.05[b]	≤0.001	≤0.001	≤0.001	≤0.001
ΔHAQ-DI at W12	≤0.001	≤0.001	≤0.001	ng	≤0.001	≤0.001	≤0.001	≤0.001
ΔmTSS at W24	NS	≤0.05	≤0.001	ng	ng	ng	n/a	n/a
ΔDAS28-hsCRP at W12	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001
SDAI remission (≤3.3) at W12	≤0.01	≤0.001	≤0.001	ng	≤0.001	≤0.001	NS	NS[c]
MJS Duration at W12	n/a	n/a	≤0.001	ng	≤0.001	ng	n/a	n/a
MJS Severity at W12	n/a	n/a	≤0.001	ng	≤0.001	ng	n/a	n/a
Worst Tiredness at W12	n/a	n/a	≤0.001	ng	≤0.05	ng	n/a	n/a
Worst Joint Pain at W12	n/a	n/a	≤0.001	ng	≤0.001	ng	n/a	n/a

Abbreviations: Δ = change from baseline; ACR20 = American College of Rheumatology 20% response rate; ADA = adalimumab; BARI = baricitinib; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; HAQ-DI = Health Assessment Questionnaire–Disability Index; MJS = morning joint stiffness; mTSS = van der Heijde modified Total Sharp Score; MTX = methotrexate; n/a = not applicable; ng = not gated (i.e., not a gated secondary objective); NS = not statistically significant; PBO = placebo; SDAI = Simplified Disease Activity Index; vs. = versus; W = week.

Note: $\leq 0.05 = p \leq 0.05$; $\leq 0.01 = p \leq 0.01$; $\leq 0.001 = p \leq 0.001$.

[a] The primary time point was 24 weeks in Study JADZ, and 12 weeks in Studies JADV, JADX, and JADW.

[b] The primary evaluation in Study JADZ was for noninferiority; the gated comparison of baricitinib 4-mg vs. ADA in Study JADV was for noninferiority. Once noninferiority was shown, superiority was tested; p-values shown are for superiority.

[c] Baricitinib 4-mg was not statistically significantly superior to placebo in the proportion of patients who achieved an SDAI score ≤3.3 at Week 12; therefore, progression through the gated endpoints stopped with this hypothesis, and hypotheses regarding baricitinib 2-mg versus placebo were not evaluated within the context of this method of strong control for multiplicity.

Baricitinib is now approved in the European Union, the United States, Japan, and other regions for the treatment of adult patients with moderate-to-severe RA. Given the promising results already observed with baricitinib in patients with RA, benefits in efficacy are expected for pediatric patients with JIA-U and ANA-positive uveitis.

The aim of the current study is to evaluate the efficacy and safety of baricitinib when administered once daily (QD) to pediatric patients with JIA-U or ANA-positive uveitis who have had an inadequate response to topical steroids and methotrexate (MTX) or biologic disease-modifying antirheumatic drugs (bDMARDs). The inclusion of patients with an inadequate response or intolerance to MTX treatment (MTX-IR patients) was driven by physician and patient preference for an alternative oral therapeutic option for pediatric patients with JIA-U who are MTX-IR (Batchelor and Marriott 2015). The currently approved therapy for JIA-U, adalimumab, is only available in injectable form. An orally ingested product such as baricitinib may be preferable to injectable bDMARDs for both patients and caregivers/legal guardians. The inclusion of bDMARD-IR patients was driven by the unmet need in patients who have tried and had inadequate response to such therapies, including adalimumab.

3.2. Background

Juvenile idiopathic arthritis is a disease distinct from RA and is defined as arthritis that has an onset in patients prior to 16 years of age, persisting for more than 6 weeks, and of unknown etiology. Juvenile idiopathic arthritis belongs to a heterogeneous group of autoimmune diseases that represent the most common rheumatic condition of childhood and is estimated to affect 1 in 1000 children (Ravelli and Martini 2007). The International League of Associations for Rheumatology (ILAR) classification of JIA identifies the following 7 mutually exclusive categories (Petty et al. 2004):

- systemic arthritis
- oligoarthritis (persistent or extended)
- rheumatoid factor (RF) negative polyarthritis
- RF positive polyarthritis

- juvenile psoriatic arthritis (JPsA)
- enthesitis-related juvenile idiopathic arthritis (ERA), and
- undifferentiated arthritis.

Juvenile idiopathic arthritis accounts for approximately 75% of all pediatric anterior uveitis cases, and is the most common systemic disorder associated with uveitis in childhood. Uveitis is reported to occur in about 30% of patients with JIA who are ANA-positive, regardless of the type of arthritis present. These patients typically develop chronic, bilateral, nongranulomatous, and asymptomatic anterior uveitis (Thorne et al. 2007). Despite current screening and treatment options, up to 15% of children with JIA-U develop visual impairment in both eyes, and may be certified as legally blind (Ramanan et al. 2017).

The SYCAMORE study, a double-blind, randomized, placebo-controlled study that assessed the efficacy, safety, and cost-effectiveness of adalimumab plus MTX in JIA-U, was completed in 2017. SYCAMORE was stopped early for efficacy after 90 of the planned 114 patients had been randomized (Ramanan et al. 2017). Analysis of the primary endpoint (time to treatment failure) showed a positive treatment effect in favor of adalimumab (hazard ratio [HR] 0.25 [95% confidence interval {CI} 0.12 to 0.49]; $p<0.0001$).

Results of the SYCAMORE study now make a placebo-controlled study ethically and logistically challenging. Eli Lilly and Company (Lilly) has, therefore, planned this uveitis study with an alternative design to study baricitinib as a treatment for JIA-U.

Methotrexate is well established as the immunosuppressive therapy of choice for patients with JIA-U who have not responded adequately to topical corticosteroid therapy. Biologic DMARDs are not usually initiated until after classic immunosuppressives have been tried. If uveitis persists despite a regimen of adequate topical corticosteroid and immunosuppressive therapy (usually MTX), anti-inflammatory treatment is intensified by addition of a TNF inhibitor or cyclosporine A to the previous treatment (Heiligenhaus et al. 2012). The patient population to be enrolled into this study comprises patients eligible for intensification of anti-inflammatory treatment through the introduction of bDMARD therapy; namely, patients who have been treated with adequate doses of topical steroids for at least 4 weeks and MTX for at least 12 weeks, or patients with intolerance to MTX. Concomitant treatment with MTX is not required in the study, to allow for the inclusion of MTX-IR or intolerant patients.

Children with chronic ANA-positive uveitis without systemic features have a similar clinical course and treatment response to children with a diagnosis of JIA-U. In keeping with recommendations from an EU Regulatory Ophthalmology Workshop, children with chronic anterior ANA-positive uveitis without systemic features will be included in the trial because of the similarity of the condition to JIA-U (EMA/450332/2012).

The choice of primary and secondary endpoints arise from work started in 2005, when the Standardization of Uveitis Nomenclature (SUN) Working Group provided a standardized nomenclature for uveitis, inflammation grading, and outcome measures (Jabs et al. 2005). This nomenclature has been reviewed by a working group of ophthalmologists and pediatric rheumatologists to create recommendations for reporting clinical outcomes in JIA-U clinical

studies (Heiligenhaus et al. 2012). The primary endpoint is the proportion of patients with response at Week 24. Response is defined as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to 0, and this matches the SUN definition of improved activity for uveitis (Jabs et al. 2005). In the SYCAMORE study, significantly more patients treated with adalimumab showed response at 3 months compared with patients treated with placebo (57% versus 17%, respectively; p = 0.004; 95% CI = 0.4 to 0.74). The time to treatment response during the SYCAMORE study informed selection of 24 weeks as the time point for the primary endpoint in this baricitinib study.

The primary endpoint will be supported by key secondary outcomes to assess age-appropriate visual acuity, change in vitreous haze, grade of flare in the anterior chamber, length of time to inactive disease (as defined by SUN criteria), tapering of concomitant steroids, pediatric clinical outcomes assessments and patient-reported outcomes, and overall uveitis-related disability. Change in grade of cells in the anterior chamber from baseline to Week 12 will also be assessed. Visual acuity is also considered to be particularly important for demonstrating clinical benefit. However, assessment of visual acuity has been included as a secondary (rather than as a co-primary) endpoint, as intraocular inflammation and visual function may improve without a discernible change in acuity measurements, particularly in the presence of prior structural damage (such as cataracts and macular scars). Such damage can limit improvement in acuity even if inflammation is controlled.

3.3. Benefit/Risk Assessment

As summarized in Section 3.1, baricitinib showed clear efficacy in adults with RA, with improvements in signs and symptoms, physical function, radiographic progression of structural joint damage, and patient-reported outcomes, including pain, stiffness, tiredness, and health-related quality of life (HRQOL). Baricitinib is approved in multiple geographic regions for the treatment of adult patients with moderate-to-severe RA. Juvenile idiopathic arthritis, JIA-U, and ANA-positive uveitis share several immunological abnormalities identified in RA, such as overproduction of proinflammatory cytokines. Inhibition of the JAK1 and JAK2 signalling pathway reduces the activity of proinflammatory cytokines, including IL-6 and TNF-α, and provides evidence for potential efficacy for baricitinib in JIA-U and ANA-positive uveitis. Given the results observed in completed baricitinib clinical studies in adult RA populations and the nature of the pathophysiology of JIA, JIA-U, and ANA-positive uveitis, treating patients with these diseases with baricitinib is expected to provide beneficial and therapeutic outcomes for this population.

Section 9.2.2 describes adverse events (AEs) of special interest in this protocol. Risk mitigation measures added to the protocol to address the important potential risks include appropriate inclusion and exclusion criteria, safety monitoring, study drug interruption, and permanent discontinuation criteria.

Although infections were observed in about half of the study population exposed to baricitinib in the RA program, only 3.6% of patients reported a serious treatment-emergent infection, and rates were similar in both baricitinib- and placebo-treated patients. The nonserious infections noted in

the RA program (upper respiratory tract infections, herpes zoster, herpes simplex) are readily diagnosed, manageable, and typically resolve without long-term sequelae. Prior to receiving baricitinib, the vaccination status of patients must be up to date with all immunizations, and follow the local requirements for vaccination guidelines for immunosuppressed patients. Exclusion criteria have been added to the protocol to limit enrollment of patients who are at increased risk of infection.

Hepatotoxicity has not been identified with baricitinib use, but increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin have occurred in patients with RA treated with baricitinib. Most increases improved with continued use or temporary discontinuation of baricitinib with no long-term effects. In addition to criteria to exclude patients with liver failure or increased liver analytes, appropriate monitoring of hepatic analytes and discontinuation criteria have been included in the protocol.

Effects of baricitinib on human fetal development are not known. The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity, which can affect early embryonic development. Based on the mechanism of action and findings of maternal and embryo-fetal toxicities, including skeletal anomalies in animals dosed in excess of the maximum human exposure, baricitinib should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

The study protocol excludes pregnant patients and contraceptive use is required for patients who may become pregnant. In clinical pharmacology studies, coadministration of baricitinib with the cytochrome (CYP3A) substrates ethinyl estradiol or levonorgestrel resulted in no clinically meaningful changes in the pharmacokinetics (PK) of these medicinal products.

Venous thromboembolic events (VTE; deep vein thrombosis [DVT] or pulmonary embolism [PE]) have been determined to be an important potential risk for baricitinib. There was a numerical imbalance in reports of VTEs in the 24-week placebo-controlled period of the Phase 3 studies of adult patients with RA. Available evidence does not establish a causal association. The exposure-adjusted incidence rate of VTE for baricitinib-treated RA patients over long-term exposures was similar to the background rates published in the literature for the target population. There was no pattern of increased or decreased risk during long-term exposures, and cases observed with baricitinib were confounded by 1 or more recognized risk factors for VTE. Venous thromboembolic event risk can be managed through risk-mitigation strategies. Exclusion and discontinuation criteria have been added to the protocol to limit participation of patients who are at increased risk of VTE.

Baricitinib is being used to treat pediatric patients participating in an expanded access program (protocol I4V-MC-JAGA [JAGA]: *Compassionate Use Protocol for the Treatment of Autoinflammatory Syndromes*), which has been ongoing since 2011 (Kim et al. 2018; Sanchez et al. 2018). More than 30 patients ages 2 months to <18 years have been enrolled in the program as of June 2018. Safety information from the expanded access program has not identified any new safety signals for baricitinib beyond those identified in the Phase 3 studies in adult patients with RA for the range of doses tested (1- to 12-mg/day). As children generally have fewer

age-related comorbidities, such as diabetes and heart disease, they are expected to be at a lower risk for some of the AEs related to comorbidities observed in RA studies, and are not anticipated to be at any higher risk of AEs potentially associated with baricitinib.

Therefore, based on the efficacy of baricitinib demonstrated in the Phase 3 RA program and the observed safety profile, the probability of a positive benefit/risk warrants this study to be conducted, given the unmet need in patients with JIA-U and ANA-positive uveitis.

More information about the known and expected benefits, risks, serious AEs (SAEs) and reasonably anticipated AEs of baricitinib is found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

Table JAHW.5 shows the objectives and endpoints of the study.

Table JAHW.5. Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the efficacy of baricitinib in children with JIA-U or ANA-positive uveitis	• Proportion of responders at Week 24. Response is defined according to the SUN criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through Week 24, in the eye most severely affected at baseline.
Secondary for Part A • To evaluate the efficacy of baricitinib in children with JIA-U or ANA-positive uveitis in the most severely affected eye and less affected eye • To evaluate the efficacy of adalimumab in children with JIA-U or ANA-positive uveitis in the most severely affected eye and less affected eye	• Change in SUN grade of cells in the anterior chamber through Week 24 in the most severely affected eye. • Change in SUN grade of cells in the anterior chamber through Week 24 in the less severely affected eye (if applicable). • In patients with bilateral uveitis disease at baseline: Proportion of responders at Week 24, defined according to the SUN criteria as a 2-step decrease in the level of anterior chamber cells in the most severely affected eye at baseline (or both eyes if the inflammation grade is the same in both eyes) and a 1-step decrease in the level of anterior chamber cells in the less severely affected eye at baseline[a]. • Change in visual acuity measured by age-appropriate LogMAR test through Week 24. • Change in vitreous haze through Week 24 in each affected eye. • Change in grade of flare in the anterior chamber through Week 24 in each affected eye. • Change in overall uveitis-related disability: ○ Change in Patient Uveitis-related Disease Activity through Week 24. ○ Change in Patient Uveitis-related Improvement at Week 12 and Week 24. ○ Change in Patient Arthritis Disease Activity through Week 24. ○ Change in Patient Arthritis Improvement at Week 12 and Week 24. ○ Change in Ophthalmologist Uveitis-related Disease Activity through Week 24.

Objectives	Endpoints
	○ Change in Ophthalmologist Uveitis-related Improvement at Week 12 and Week 24. • Proportion of patients with inactive anterior uveitis (using SUN definition) in each affected eye through Week 24. • Time to inactive anterior uveitis disease (using SUN definition) in each affected eye. • Proportion of patients who are able to taper concomitant topical corticosteroids to <2 drops per day and to 0 drops per day. • PediACR30/50/70/90/100 response rates (for patients with JIA-U).
• To evaluate the safety of baricitinib in children with JIA-U or ANA-positive uveitis	• Adverse events including serious adverse events. • Permanent discontinuation of investigational product due to AE. • Temporary interruption of investigational product.
Secondary for Part B (OLE) • To describe the efficacy of baricitinib in children with JIA-U or ANA-positive uveitis in the most severely affected eye and less affected eye (among the responders at Week 24)	• Number of responders through Week 284. Response is defined according to the SUN criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through Week 284, in the eye most severely affected at baseline. • Change in SUN grade of cells in the anterior chamber through Week 284 in the most severely affected eye. • Change in SUN grade of cells in the anterior chamber through Week 284 in the less severely affected eye (if applicable). • In patients with bilateral uveitis disease at baseline: Number of responders through Week 284, defined according to the SUN criteria as a 2-step decrease in the level of anterior chamber cells in the most severely affected eye at baseline (or both eyes if the inflammation grade is the same in both eyes) and a 1-step decrease in the level of anterior chamber cells in the less severely affected eye at baseline. • Change in grade of flare in the anterior chamber through Week 284 in each affected eye. • Description of inactive anterior uveitis including time to inactive anterior uveitis disease (using SUN definition) in each affected eye through Week 284. • Number of patients who are able to taper concomitant topical corticosteroids to <2 drops per day and to 0 drops

Objectives	Endpoints
	per day. Number of patients who are able to taper concomitant oral corticosteroids to <5 mg per day and to 0 mg per day.
• To evaluate the safety of baricitinib in children with JIA-U or ANA-positive uveitis	• Adverse events including serious adverse events. • Permanent discontinuation of investigational product due to AE. • Temporary interruption of investigational product.

Abbreviations: AE = adverse event; ANA = antinuclear antibody; JIA = juvenile idiopathic arthritis; LogMAR = logarithm of the minimum angle of resolution; OLE = open-label extension; PediACR = Pediatric American College of Rheumatology; PK = pharmacokinetic(s); SUN = Standardization of Uveitis Nomenclature.

a Response is defined according to the SUN criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to 0 through Week 24 in the eye most severely affected at baseline.

5. Study Design

5.1. Overall Design

Study JAHW is a multicenter, open-label, active-controlled Phase 3 study in patients with active JIA-U or chronic ANA-positive uveitis without systemic features, despite prior treatment with topical steroid therapy and MTX. The study will be conducted in 2 parts. Part A will include the screening period and treatment period that includes open-label treatment with baricitinib and adalimumab up to Week 24. Part B will provide an open label extension period for up to 5 years after Part A.

In the original study design (Figure JAHW.1), patients receiving baricitinib during Part A continued to receive baricitinib during Part B. Patients receiving adalimumab during Part A continued to receive adalimumab for an additional 96 weeks and were then switched to baricitinib for the remaining 164 weeks of Part B.

Since then, the protocol and study design have been modified (Figure JAHW.2). Patients currently assigned to baricitinib who have completed the primary endpoint as a responder will continue receiving baricitinib until the end of study or discontinuation from the study. Investigator may consult the study team for guidance on study continuation in the event the patient is a nonresponder at the primary endpoint, but demonstrates clinically meaningful benefit from baricitinib. Patients on adalimumab will discontinue the study after Week 24.

Interim analyses are described in Section 10.3.7 . Interim analyses will occur during Part A and when Part A is complete (Week 24).

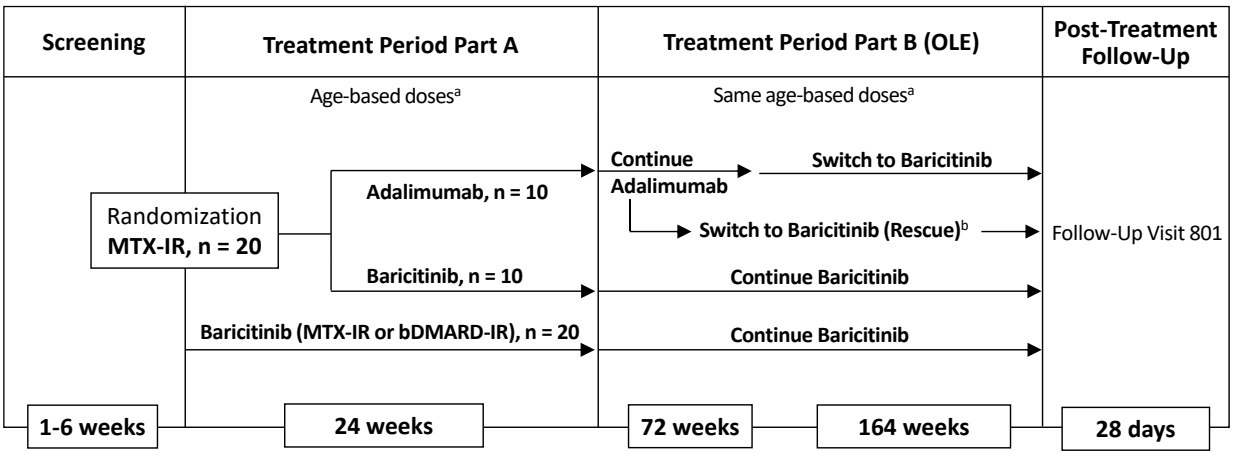
The study will enroll at least 20 and up to 40 patients who have had an inadequate response or intolerance to MTX (MTX-IR) and/or bDMARDs (bDMARD-IR) as follows:

Baricitinib arm: At least 20 patients (MTX-IR and/or bDMARD-IR) evaluable for primary endpoint.

Adalimumab arm: At least 4 patients evaluable for the primary endpoint.

This study will be conducted at centers offering combined pediatric rheumatology/ophthalmology service.

Figure JAHW.1 illustrates the study design from the previous Amendment (d).



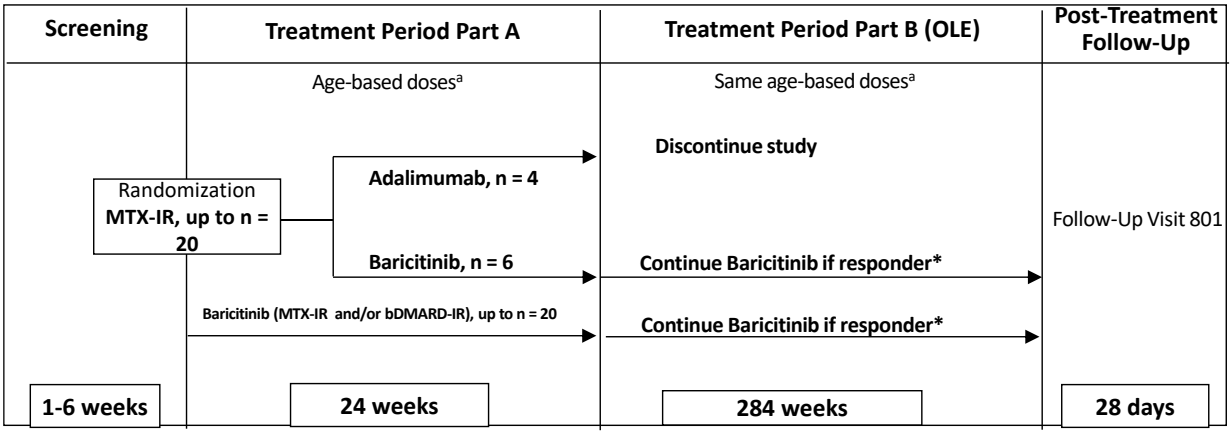
Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; IR = inadequate response or intolerance to; MTX = methotrexate; OLE = open-label extension.

[a] Patients ≥6 to <12 years old assigned to baricitinib have the option of receiving the oral suspension or tablets. Patients >12 years old assigned to baricitinib will receive tablets. Patients assigned to adalimumab weighing <30 kg will receive 20 mg, and those ≥30 kg will receive 40 mg.

[b] Patients receiving adalimumab who experience a treatment failure after at least 24 weeks of treatment may receive rescue therapy with baricitinib. Rescued patients will receive baricitinib for the remainder of the study.

Figure JAHW.1. Study design for Clinical Protocol I4V-MC-JAHW (d).

Figure JAHW.2 illustrates the modified study design for Amendment (e).



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; IR = inadequate response or intolerance to; MTX = methotrexate; OLE = open-label extension.

[a] Patients ≥6 to <12 years old assigned to baricitinib have the option of receiving the oral suspension or tablets. Patients >12 years old assigned to baricitinib will receive tablets. Patients assigned to adalimumab weighing <30 kg will receive 20 mg, and those ≥30 kg will receive 40 mg.

* Please refer to Section 5.1.3 for details.

Figure JAHW.2. Study design for Clinical Protocol I4V-MC-JAHW (e).

The study allows for treatment with background conventional synthetic DMARDs (csDMARDs), corticosteroids, and/or nonsteroidal anti-inflammatory drugs (NSAIDs) at a stable dose (refer to Section 7.7).

Study governance considerations are described in detail in Appendix 3.

5.1.1. Screening and Baseline Periods

The Screening Period is up to 42 days prior to baseline. At screening, the parent or legal guardian will sign the informed consent form (ICF) and the patient will sign the assent form (as appropriate) per local requirements prior to any study assessments, examinations, or procedures being performed (Appendix 3). All screening procedures will be performed according to the Schedule of Activities (Section 2).

Patients who receive a purified protein derivative (PPD) skin test at screening must return within 48 to 72 hours to read the skin test. Treatment with concomitant JIA therapies and topical corticosteroids during the study is permitted only as described in Section 7.7. Patients will remain on background MTX, other csDMARDs, and oral, topical or ophthalmic corticosteroids if patients are on stable doses of these treatments at screening (see Sections 6.2 and 7.7 for details). Patients who have previously been treated with bDMARDs are eligible for the study. However, treatment must have been discontinued 1 week prior to screening for anakinra, 4 weeks prior to screening for TNF inhibitors, other IL-1 inhibitors, IL-6 inhibitors, or abatacept and 6 months prior to screening for rituximab.

Investigators should review the vaccination status of their patients and ensure that patients are up to date with all immunizations, and follow the local requirements for vaccination guidelines and schedule for immunosuppressed patients. If a patient received a live vaccine within 28 days prior to baseline or intends to receive a live vaccine (except booster immunization with attenuated vaccine for measles, mumps, and rubella [MMR] or varicella zoster virus [VZV]) during the course of the study or up to 28 days after the last dose of investigational product, the patient is not eligible for the study. Considering the European League Against Rheumatism (EULAR) recommendations (Heijstek et al. 2011) and accumulated evidence (Groot et al. 2015; Sousa et al. 2017), booster vaccination for MMR or VZV may be considered if it is essential based on the local guideline and/or in the opinion of the investigator. If a patient becomes eligible for vaccination with tetanus, diphtheria, and pertussis (TDaP) and/or pneumococcal

conjugate vaccine during the study period according to local recommended schedule of vaccination, antibody titres to the vaccine will be evaluated pre-immunization and at 4 and 12 weeks post immunization. A primary immune response will be assessed in patients who have never received TdaP or pneumococcal conjugate vaccines previously, and secondary/booster responses will be assessed if the patients have previously received the vaccines.

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

At baseline, study eligibility for each patient will be reviewed, based on all inclusion and exclusion criteria (Section 6), and laboratory test results. Patients who meet all criteria will proceed to the subsequent period. Laboratory samples will be collected at baseline and all assessments should be completed before the patient takes the first dose of investigational product. Owing to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in a sponsor-provided weight-based prioritization chart.

5.1.2. Open-Label Treatment Period – Part A

Part A is an open-label treatment period. Up to 10 MTX-IR (but not bDMARD-IR) patients will be randomly assigned to receive either oral baricitinib once-daily or subcutaneous adalimumab every other week for approximately 24 weeks. Approximately 20 additional patients who are MTX-IR and/or bDMARD-IR will receive oral baricitinib once daily for approximately 24 weeks.

5.1.3. Open-Label Treatment Period – Part B

Part B is an open-label extension period. In the previous study design (amendment d or prior), all patients who were receiving baricitinib in Part A received oral baricitinib once daily for approximately 260 weeks. Patients who were randomized to adalimumab treatment in Part A continued to receive adalimumab for approximately 96 weeks in Part B and were then switched to baricitinib for the remaining weeks. The first dose of baricitinib was given approximately 2 weeks after the last injection of adalimumab.
Since then, the protocol and study design has been modified (Amendment e). Patients receiving adalimumab will be discontinued from the study after Week 24.

Patients currently assigned to baricitinib who have completed the primary endpoint as a responder will continue receiving baricitinib until the end of study or discontinuation from the study. Investigator may consult the study team for guidance on study continuation in the event the patient is a nonresponder at the primary endpoint, but demonstrates clinically meaningful benefit from baricitinib.

5.1.4. Post-Treatment Follow-Up Period

Patients who complete the study or discontinue early from the study will return for the post-treatment safety follow-up visit (Visit 801) approximately 28 days after the last dose of investigational product.

Patients who have received at least 1 dose of investigational product and terminate participation early must have an early termination visit (ETV).

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

Patients should not initiate new treatment during the post-treatment follow-up period. However, if patients or investigators must initiate a new treatment, patients should complete a Visit 801 prior to the first dose of the new therapy (if possible).

5.2. Number of Participants

- Baricitinib arm: At least 20 patients (MTX-IR and/or bDMARD-IR) evaluable for primary endpoint.
- Adalimumab arm: At least 4 patients evaluable for the primary endpoint.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient in the 28-day follow-up period.

5.4. Scientific Rationale for Study Design

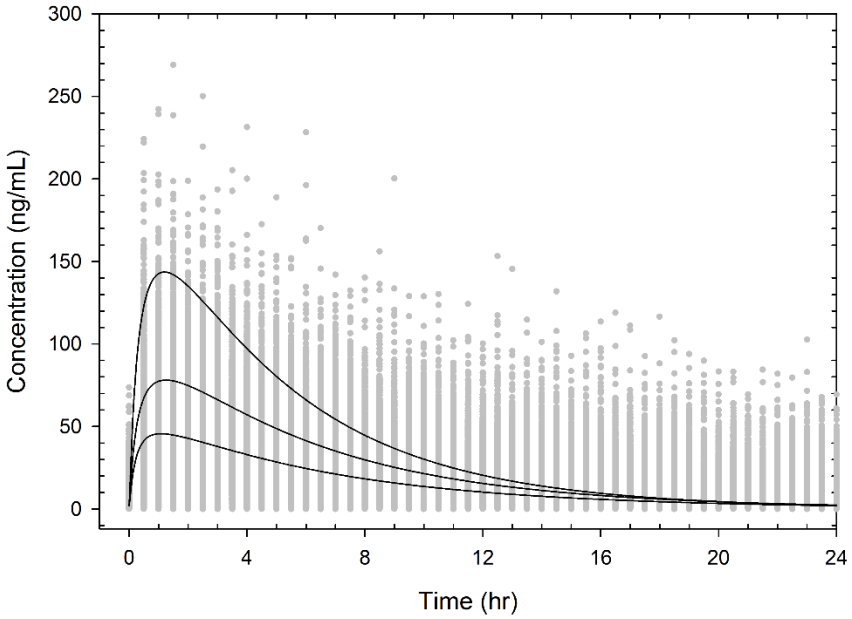
Randomized withdrawal designs have worked well in many studies of patients with polyarticular arthritis as well as in some studies of patients with systemic JIA. However, the randomized withdrawal design is likely to be particularly problematic for a JIA-U trial due to the variable nature of the disease and the limited understanding of the long-term disease course. Randomized placebo-controlled withdrawal designs for JIA-associated uveitis were debated at a European Medicines Agency (EMA) regulatory workshop on ophthalmology (EMA/450332/2012) and concern was raised that the natural history of uveitis was unknown, which could affect this design.

This open-label Study JAHW of baricitinib in children with JIA-U or ANA-positive uveitis is similar in design to the APTITUDE study of tocilizumab conducted in 22 patients with JIA-U refractory to anti-TNF therapy (EudraCT 2015-001323-23). Study JAHW will incorporate Bayesian analysis techniques, which are more suitable for clinical trials in rare conditions such as JIA-U. Bayesian analysis techniques are potentially more useful for assessing treatment options than conventional frequentist analysis methods when limited available data do not allow conclusive inferences to be made (Hampson et al. 2014; Bayarri and Berger 2004).

5.5. Justification for Dose

The dose selection for baricitinib in this patient population is informed by the Phases 2 and 3 data in adults with RA, which demonstrated a positive benefit/risk profile for the 4-mg QD dose. The PK of baricitinib in pediatric patients with JIA will be investigated in Study I4V-MC-JAHV (JAHV), and the doses selected in this study will also be used in Study JAHW (see Appendix 8 for updated dosing based on the current JAHV data).

Predicted concentration-versus-time data in patients with RA were simulated using physiologically based pharmacokinetic (PBPK) modeling. The modeling predicted that baricitinib concentrations in adolescents 12 to <18 years old and in children 9 to <12 years old would be expected to be similar to those in adults (Figure JAHW.3); therefore, these patients will initially receive the 4-mg QD dose in Study JAHV. Conversely, concentrations in children aged <9 years would be expected to be toward the higher end of the range observed in adults; therefore, these patients will initially receive a lower 2-mg QD dose.



These graphs are overlay plots comparing model-predicted mean concentration–time curves in pediatric age groups to model-predicted plasma concentrations in adults. Solid lines are model-predicted mean concentrations in age groups 2 to <6 years (top line), 6 to <12 years (middle line), and 12 to <18 years (bottom line). These lines were developed using a physiologically-based pharmacokinetic (PK) model implemented with Simcyp®, based on adult data with adjustment for age. The gray dots indicate individual concentrations derived from simulations of the final population PK model for baricitinib in adult patients with rheumatoid arthritis.

Figure JAHW.3. Comparison of predicted steady-state concentrations of baricitinib in pediatric (solid lines) versus adults (gray dots) receiving 4-mg QD.

The PK assessment period of Study JAHV will determine if baricitinib exposure in pediatric patients with JIA is consistent with baricitinib 4-mg exposure in adults with RA. The baricitinib dose will be adjusted as necessary if baricitinib exposure is not consistent between these patient populations. The final age-based dose selected in the PK assessment period of Study JAHV will be used in Study JAHW. Therefore, enrollment in Study JAHW may be restricted to the age cohorts for which PK data are available from Study JAHV.

Due to the overlap between the conditions, JIA and JIA-U are typically treated with the same therapies and doses. For example, the same dose of adalimumab is approved for JIA and JIA-U

(adalimumab SmPC), and similar doses of MTX are recommended for both indications (Ferrara et al. 2018). Therefore, the same dose of baricitinib should be appropriate for patients with JIA and JIA-U.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to enroll in the study only if they meet all of the following criteria at screening and at baseline:

Patient and Disease Characteristics

[1] Are at least 2 years and less than 18 years of age; full date of birth will be collected except in countries in which it is not allowed.

[2] Have a diagnosis of JIA-U or chronic ANA-positive uveitis without systemic features.

[3] Have active anterior uveitis, defined as cellular infiltrate in the anterior chamber of SUN criteria grade ≥1+ at Visit 1 (screening) and Visit 2 (potential randomization), despite prior treatment with adequate doses of topical steroid therapy and MTX.

[4] Have an inadequate response or intolerance to MTX (minimum dose of 10 mg/m^2/week, with a maximum dose of 25 mg/m^2/week). Patients considered to have inadequate response must have received MTX for at least 12 weeks before an inadequate response may be determined, and must have been on a stable dose for at least 4 weeks prior to screening if continuing MTX therapy during the study.

[5] Are receiving topical corticosteroid eye drops at a stable dose for at least 2 weeks prior to screening (maximum of 4 drops/day per eye at screening).

Informed Consent

[6] Both a parent or legal guardian and the patient (as appropriate) are able to understand and fully participate in the activities of the study and sign their consent and assent, respectively, in accordance to local guidelines.

Contraception

[7] Male or nonpregnant, nonbreastfeeding female patients

Patients of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) must agree to remain abstinent.

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

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

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

- Highly effective birth control methods:
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or implantable
  - Intrauterine device/intrauterine hormone-releasing system
  - Vasectomized partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Effective birth control methods:
  - Male or female condom with spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.
  - Diaphragm with spermicide
  - Cervical sponge
  - Cervical cap with spermicide

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

Adolescent females who have started menses (even 1 cycle and any amount of spotting) are considered to be of child-bearing potential.

Women of nonchild-bearing potential are not required to use birth control and they are defined as:

- Women who are infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) and congenital anomaly such as mullerian agenesis.

6.2. Exclusion Criteria

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

Medical Conditions

[8] Have uveitis without a diagnosis of JIA or CAU without positive ANA.

[9] Have a history or presence of any autoimmune inflammatory condition other than JIA, such as Crohn's disease or ulcerative colitis.

[10] Have any contraindications to adalimumab as addressed in local product labeling or local clinical practice that would preclude the patient from participating in this study.

Exception: Patients who are bDMARD-IR with a contraindication to adalimumab may be enrolled, as they will be assigned to baricitinib.

[11] Have increased intraocular pressure ≥25 mm Hg or that required treatment, including increases in medications, surgery, or hospitalization, within 4 weeks prior to baseline that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

[12] Have had intraocular surgery within the 3 months prior to screening (such as for cataract(s), glaucoma or vitrectomy).

[13] Are pregnant or breastfeeding. Prior to initiation of treatment, female patients of child-bearing potential must have a negative serum pregnancy test at the central laboratory during screening and a negative urine pregnancy test at Visit 2.

[14] Have a current or recent (<4 weeks prior to baseline) clinically serious viral, bacterial, fungal, or parasitic infection or any other active or recent infection that, in the opinion of the investigator, would pose an unacceptable risk to the patient if participating in the study.

Note: For example, a recent viral upper respiratory tract infection or uncomplicated urinary tract infection need not be considered clinically serious.

[15] Have had an infection of bone or joint within 6 months prior to screening.

[16] Have symptomatic herpes simplex at baseline.

[17] Have had symptomatic herpes zoster infection within 12 weeks prior to baseline.

[18] Have a history of multidermatomal herpes zoster, or complicated herpes zoster (e.g., ocular or motor nerve involvement or disseminated herpes zoster such as systemic infection).

[19] Have a positive test for hepatitis B virus (HBV) at screening defined as:

a. positive for hepatitis B surface antigen (HBsAg), or
b. positive for hepatitis B core antibody (HBcAb) and positive for HBV deoxyribonucleic acid (DNA)

Note: Patients who are HBcAb-positive and HBV DNA-negative may be enrolled in the study but will require additional HBV DNA monitoring during the study.

[20] Have hepatitis C virus (HCV) infection (hepatitis C antibody-positive and confirmed presence of HCV ribonucleic acid [RNA]).

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

[21] Have evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies.

[22] Have had household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB.

[23] Have evidence of active TB or untreated/inadequately/inappropriately treated latent TB

a. Have evidence of active TB, defined in this study as the following:
   - Positive PPD test (≥5 mm induration between approximately 48 and 72 hours after application, regardless of vaccination history), medical history, and clinical features.
   - 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, have no clinical features of active TB, and have had a screening chest x-ray within the prior 6 months 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 had a screening chest x-ray within the prior 6 months.

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

- QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be considered to have latent TB. If the test is not negative, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).

Exception: Patients who have evidence of latent TB may be enrolled if at least 4 weeks of appropriate treatment is completed prior to Visit 2 and the remainder of treatment will be completed while in the study.

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, have no clinical features of active TB, and have had a screening chest x-ray within the prior 6 months 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 had a screening chest x-ray within the prior 6 months.

[24] Had 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.

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

[26] Have a history of a VTE or are considered at high risk of VTE as deemed by the investigator.

[27] Are largely or wholly incapacitated, such as being bedridden.

[28] Have a history of lymphoproliferative disease; have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; have active primary or recurrent malignant disease; or have been in remission from clinically significant malignancy for <5 years prior to Visit 2.

The following may be exempted:

a. Patients with cervical carcinoma in situ that has been resected with no evidence of recurrence or metastatic disease for at least 3 years may participate in the study.
b. Patients with nonmelanoma skin cancers (basal cell or squamous epithelial skin cancers) that have been completely resected with no evidence of recurrence for at least 3 years may participate in the study.

[29] Have body temperature ≥38°C (100.5°F) at baseline (Visit 2).

Prior/Concomitant Therapy

[30] Have initiated or changed dosage of concomitant mycophenolate mofetil or csDMARDs (other than MTX) within 4 weeks prior to screening (such as, but not limited to, hydroxychloroquine, sulfasalazine, gold salts, cyclosporine, or azathioprine).

[31] Are currently receiving concomitant treatment with combination of >2 csDMARDs (including MTX).

[32] Have received prior bDMARDs for any indication less than 1 week prior to screening for anakinra, less than 4 weeks prior to screening for TNF inhibitors (e.g., etanercept, infliximab, certolizumab, adalimumab, golimumab), other IL-1 inhibitors, IL-6 inhibitors (e.g., tocilizumab), or abatacept, and less than 6 months prior to screening for rituximab.

[33] Have received an unstable dose of analgesics, including NSAIDs, within 1 week prior to Visit 2.

[34] Have received treatment with any parenteral corticosteroid administered by intra-articular, intramuscular, or intravenous injection within 4 weeks prior to Visit 2.

[35] Are using oral corticosteroids at average daily doses of greater than 10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less, or have done so within 2 weeks prior to screening. If continuing oral corticosteroids, must be on stable dose for 4 weeks prior to baseline (see Section 7.7).

[36] Have received a depot peri-ocular, peri-ocular or intraocular corticosteroid injection within 30 days prior to Visit 2.

[37] Have received an intraocular steroid implant within 6 months (e.g., Ozurdex) or 18 months (e.g., Iluvien) prior to Visit 2.

[38] Have received intraocular disease-modifying agents, including anti-vascular endothelial growth factor (VEGF) injections, for 30 days prior to Visit 2.

[39] Are being treated with a strong organic anion transporter 3 (OAT3) inhibitor, such as probenecid, that cannot be discontinued for the duration of the study.

[40] Have received a live vaccine within 28 days prior to baseline or intend to receive a live vaccine (except booster immunization with attenuated vaccine for measles, mumps, and rubella [MMR] or varicella-zoster virus [VZV]) during the course of the study or up to 28 days after the last dose of investigational product. Booster vaccination for MMR or VZV may be considered if it is essential based on the local guideline and/or in the opinion of the investigator.

[41] Have been treated with a JAK inhibitor.

[42] Have experienced hypersensitivity to the active substance or to any of the excipients.

[43] Have been treated with interferon therapy (such as Roferon-A, Intron-A, Rebetron, Alferon-N, Peg-Intron, Avonex, Betaseron, Infergen, Actimmune, Pegasys) within 4 weeks prior to study entry or are anticipated to require interferon therapy during the study.

[44] Have commenced thyroxine therapy or changed dosage within 12 weeks prior to baseline, or have thyroid-stimulating hormone (TSH) levels outside the laboratory's reference range.

Exception: Patients who are receiving stable thyroxine replacement therapy for ≥12 weeks prior to baseline 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.

Diagnostic Assessments

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

- AST or ALT ≥2 x upper limit of normal (ULN)
- Total bilirubin level (TBL) ≥1.5 x ULN
- Alkaline phosphatase (ALP) ≥2 x ULN
- Hemoglobin <10.0 g/dL (100.0 g/L)
- Total white blood cell count <3000 cells/μL (<3.00 x 10^3/μL or <3.00 billion/L)
- Neutropenia (absolute neutrophil count [ANC] <1500 cells/μL) (<1.50 x 10^3/μL or <1.50 billion/L)
- Lymphopenia (lymphocyte count <1000 cells/μL) (<1.00 x 10^3/μL or <1.00 billion/L)
- Thrombocytopenia (platelets <100,000/μL) (<100 x 10^3/μL or <100 billion/L)
- eGFR <40 mL/min/1.73 m^2 (Bedside Schwartz formula 2009)

In the case of any of the aforementioned laboratory abnormalities, the tests may be repeated once during screening and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

[46] 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.

Prior/Concurrent Clinical Study Experience

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

[48] Discontinued within 30 days of study entry from any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

[49] Previously completed or withdrew from this study or any other study investigating baricitinib.

Other Exclusions

[50] Donated blood within 4 weeks prior to screening or intend to donate blood during the course of the study.

[51] Are immediate family of investigator or site personnel directly affiliated with this study. Immediate family is defined as a child, or sibling, whether biological or legally adopted.

[52] Are Lilly or Incyte employees or immediate family.

[53] Are unwilling or unable to comply with the use of a data collection instrument to directly record data from the patient.

6.2.1. Rationale for Exclusion of Certain Study Candidates

The rationale for the exclusion criteria is as follows:

- Exclusion Criteria [8] to [13] exclude individuals with conditions that may confound safety or efficacy analyses.
- Exclusion Criteria [14] to [23] exclude individuals who are at an increased risk for infections or infectious complications.
- Exclusion Criteria [24] to [29] exclude individuals with previous or concomitant medical conditions that increase the risk for their participation in the study.
- Exclusion Criteria [30] to [44] exclude individuals who are taking or who may take JIA or JIA-U medications or treatments that interfere with the ability to assess the safety and efficacy of baricitinib.
- Exclusion Criteria [45] to [46] exclude individuals with laboratory parameters that may increase the risk for their participation in the study.
- Exclusion Criteria [47] to [53] exclude individuals whose participation in the study may introduce bias.

6.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times. The interval between rescreenings should be at least 4 weeks. Each time rescreening is performed the legal representative must sign a new ICF and the child must sign an assent, as applicable. The individual will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

The dose selection for baricitinib in this patient population is informed by the Phases 2 and 3 data in adults with RA, which demonstrated a positive benefit/risk profile for the 4-mg QD dose. The PK of baricitinib in pediatric patients with JIA will be investigated in Study I4V-MC-JAHV (JAHV), and the doses selected in this study will also be used in Study JAHW (see Appendix 8 for updated dosing based on the current JAHV data).

Adalimumab will be administered as a subcutaneous injection. The first dose of adalimumab will be administered by the research team. All participants or a family member/caregiver will be invited to (self-)administer adalimumab after the first dose, and taught to do this under the procedures in place within each participating center. The first dose they administer may also be under the supervision of the clinical team, who will ensure the appropriateness and accuracy of the technique. If the patient, family member or caregiver do not want to (self-)administer adalimumab, then arrangements will be put in place on an individual basis to ensure that trial medication is administered as prescribed.

Table JAHW.6 shows the treatment regimens.

Table JAHW.6. Treatment Regimens

Treatment Group	Treatments Administered (Intervention name, dosage level, and route of administration)	Authorized as defined by EU Clinical Trial Regulations
Baricitinib 4-mg	Baricitinib 4-mg oral tablet	Authorized in EU and not used according to authorization
	Baricitinib 2-mg/mL oral suspension	Not authorized in EU
Baricitinib 2-mg	Baricitinib 2-mg oral tablet	Authorized in EU and not used according to authorization
	Baricitinib 2-mg/mL oral suspension	Not authorized in EU
Baricitinib 1-mg	Baricitinib 1-mg oral tabletBaricitinib 2-mg/mL oral suspension	Not authorized in the EU Not authorized in the EU
Adalimumab	Adalimumab 20 mg in those weighing <30 kg or 40 mg in those ≥30 kg	Authorized and used according to authorization

Note: The oral suspension dose may be administered as 4-mg, 2-mg, 1-mg, and 0.5-mg as needed. The oral suspension contains sorbitol solution (70% sorbitol) at a concentration of 150 mg/mL, which is equivalent to 105 mg of sorbitol per mL. Patients with hereditary fructose intolerance should not exceed 5 mg/kg/day of sorbitol, according to the guideline on "Excipients in the labelling and package leaflet of medicinal products for human use (EMA/CHMP/302620/2017; EMA [WWW])."

Note: Patients with renal impairment or renal immaturity (defined as eGFR <60 mL/min/1.73 m^2) at baseline will have their baricitinib dose reduced by 50%. Patients with renal impairment or renal immaturity who would have received the 2-mg or 1-mg dose will be dose-reduced to 1-mg or 0.5-mg, respectively, using the oral suspension.

The investigator or appointed designee is responsible for the following:

- Explaining the correct use of the investigational agent(s) to the parent or legal guardian

- Verifying that instructions are followed properly
- Maintaining accurate records of investigational product dispensing and collection
- At the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

The sponsor (or its designee) will supply the following investigational products in accordance with current Good Manufacturing Practice:

- Tablets containing 4-mg of baricitinib
- Tablets containing 2-mg of baricitinib
- Tablets containing 1-mg of baricitinib
- Suspension containing 2-mg/mL of baricitinib
- Vials or syringes of adalimumab for injection

Each tablet has a distinctive shape and color: 4-mg versus 2-mg versus 1-mg. Baricitinib oral suspension (containing 2 mg/mL baricitinib) will be supplied as a ready-to-use oral suspension. Baricitinib oral suspension will be provided in a bottle and doses will be delivered to the patient using a standard oral syringe.

Study interventions will be labeled as appropriate for country requirements.

7.2. Method of Treatment Assignment

Patients will receive the final age-based dose of baricitinib selected in the PK assessment period of Study JAHV (Section 7.2.1). Pharmacokinetic data from Study JAHV will be provided by age cohort (12 to <18 years, 9 to <12 years, 6 to <9 years, and 2 to <6 years; see Appendix 8 for updated dosing based on the current data). Enrollment in Study JAHW may be restricted to patients represented in the age cohorts for which PK data are available from Study JAHV, until JAHV PK data become available for other age groups.

All patients <6 years of age will receive oral suspension. Patients ≥6 to <12 years of age have the option of receiving the oral suspension. Patients >12 years will be supplied tablets only.

- Baricitinib arm: At least 20 patients (MTX-IR and/or bDMARD-IR) evaluable for primary endpoint.
- Adalimumab arm: At least 4 patients evaluable for the primary endpoint.

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign investigational product to each patient.

Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the packages into the IWRS before dispensing to the patient.

7.2.1. Selection and Timing of Doses

Baricitinib:

Baricitinib should be administered at approximately the same time each day. Patients will receive the final age-based dose of baricitinib selected in the PK assessment period of Study JAHV. Based on PBPK modeling, this is expected to be 4-mg for patients ≥9 to <18 years of age and 2-mg for patients <9 years of age, in order to produce exposures similar to those in adults after 4-mg QD administration; see Appendix 8 for updated dosing based on the current data. Refer to Section 5.5 for additional information.

Adalimumab:

Adalimumab will be administered as a subcutaneous injection once every 2 weeks. The dose will be based on body weight: 20 mg every 2 weeks for participants weighing <30 kg, or 40 mg every 2 weeks for patients weighing ≥30 kg (adalimumab SmPC).

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Baricitinib:

The baricitinib dose and formulation for an individual patient will not change during Part A of this study. During Part B, as patients age over 9 years old, they will receive baricitinib 4 mg at their next scheduled visit, and as patients age over 6 years old, they will have the option of receiving tablets instead of suspension. For patients who progress to the ≥18 years age group, their current dose will be maintained.

The baricitinib dose will be reduced by 50% in patients with renal impairment (defined as eGFR <60 mL/min/1.73 m^2) at baseline.

Adalimumab:

The adalimumab dose will be based on body weight (20 mg for patients weighing <30 kg or 40 mg for patients weighing ≥30 kg; adalimumab SmPC). Dose modifications are NOT permitted in patients whose body weight changes from less than 30 kg to greater than 30 kg or from greater than 30 kg to less than 30 kg during Part A.

7.5. Preparation/Handling/Storage/Accountability

All investigational products (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 study materials.

Investigators and site personnel will follow storage and handling instructions on the investigational product packaging.

Only participants enrolled in the study, or their parent or legal guardian, may receive investigational product and only authorized site staff may supply investigational product. All investigational products should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator is responsible for investigational product accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

Patient compliance with study medication will be assessed during the treatment period of Part A and Part B per the Schedule of Activities.

Patients treated with baricitinib or adalimumab will be considered noncompliant if they miss ≥20% of the prescribed doses during the study (unless the patient's investigational product was withheld by the investigator for safety reasons). For adalimumab, a patient will be considered significantly noncompliant if his or her study medication compliance rate is <80% or if there are any consecutive missed injections, unless the patient's investigational product was withheld by the investigator for safety reasons.

Similarly, patients will be considered noncompliant if they are judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of study medication. Patients found to be noncompliant with the investigational product should be assessed to determine the reason for noncompliance and educated and/or managed as deemed appropriate by the investigator to improve compliance.

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

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

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication electronic case report form (eCRF).

Patients will be instructed to consult the investigator or other appropriate study personnel at the site before taking any new medications or supplements during the study.

Additional drugs are to be avoided unless required to treat AEs or for the treatment of an ongoing medical condition. If the need for other concomitant medications arises, discontinuation of the patient from the investigational product or the study will be at the discretion of the investigator in consultation with Lilly or its designee (Section 8.2).

Treatment with concomitant therapies during the study is permitted only as described below and in Table JAHW.7. During Part A, the dosages of concomitant treatment may only be adjusted for safety reasons, with the exception of topical corticosteroid eye drops.

Methotrexate, mycophenolate mofetil, and csDMARDs:

- Chronic stable use of MTX is permitted up to a maximum dose of 25 mg/m^2/week throughout the study.
- Patients must be on a stable dose of MTX for at least 4 weeks prior to screening, and remain on the same dose throughout Part A.
- During Part B, MTX may be initiated or the dose increased, decreased, or discontinued, at the discretion of the investigator, and according to local clinical practice.
- Local standard of care should be followed for concomitant administration of folic acid.
- Chronic stable use of csDMARDs (other than MTX) and mycophenolate mofetil is permitted. Patients must be on a stable dose for at least 4 weeks prior to screening.
- During Part A, initiation of new csDMARDs and/or increases in dose are not permitted.
- During Part B, other csDMARDs or mycophenolate mofetil may be initiated, or the dose increased, decreased, or discontinued, at the discretion of the investigator, and according to local clinical practice.
- Concomitant use of >2 csDMARDs (including MTX) is not allowed.

Topical steroid eye drops:

- Topical steroid eye drops, with a maximum of 4 drops/day per eye at screening, are permitted as background therapy during the study. The dose must have been stable for at least 2 weeks prior to screening.
- Steroid drop tapering is recommended as shown in the following table:

Study Interval	Dose Reduction
Week 0–Week 4	No dose changes permitted
Week 4–Week 8	Reduce drops to a maximum of 3 drops/day per eye
Week 8–Week 20	Reduce drops to a maximum of 2 drops/day per eye
Week 20–Week 24	No dose changes permitted
Week 24 onward (Part B)	Reduce drops at the discretion of the treating clinician to any dose, including zero

- If tapering is not tolerated during Part A or Part B, the number of drops can be increased up to the number received at screening.
- The topical steroid eye drop formulation (Maxidex, Predforte, or equivalent) should remain the same as that used at screening and will not change for individual patients throughout Part A, unless required for safety or supply issues; the formulation may be changed during Part B.

Oral corticosteroids:

- Chronic stable use of oral corticosteroids is permitted and defined as daily doses of ≤10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less.
- Patients must be on a stable dose for at least 2 weeks prior to screening and 4 weeks prior to baseline, and remain on the same dose throughout Part A, except for treatment of an AE.

- During Part B, oral corticosteroids may be initiated, or the dose increased, decreased, or discontinued, at the discretion of the investigator.

Intra-articular corticosteroid joint injections:
- A maximum of 8 injections are permitted per year.
- No more than 2 injections are permitted in a single session.
- No injections are permitted within 4 weeks prior to Visit 2.

Intraocular corticosteroid injections:
- Depot peri-ocular, peri-ocular or intraocular corticosteroid injections are not permitted within 30 days prior to Visit 2 or during Part A.
- Intraocular or peri-ocular corticosteroid injections are permitted during Part B at the discretion of the investigator.

Other corticosteroids
- With the exception of oral and intra-articular corticosteroids, patients should not receive other systemic corticosteroids during Part A, including intramuscular corticosteroids.
- During Part B, other systemic steroids may be administered; however, the daily dose should be ≤10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less.
- Topical, intranasal, and inhaled corticosteroids are permitted.

Analgesics and NSAIDs
- Chronic stable use of NSAIDs and analgesics is permitted. Patients must be on a stable dose for at least 1 week prior to Visit 2.
- Increases in dose and/or introduction of new NSAIDs and analgesics are not permitted during Part A, except for treatment of an AE.
- During Part B, other analgesics or NSAIDs may be initiated or dose may be increased at the discretion of the investigator.
- Dose reductions and/or termination of NSAIDs and analgesics are permitted.

Permitted analgesics include
  - acetaminophen
  - NSAIDs, e.g. ibuprofen
  - cyclooxygenase-2 inhibitors, e.g. celecoxib
  - opioids, e.g. tramadol, codeine, or morphine
  - local anaesthetics, e.g. lidocaine, and
  - topical anaesthetics, e.g. EMLA cream.

The following therapies will not be permitted during the course of the study as specified in the exclusion criteria (Section 6.2):

- bDMARDs
- Intraocular steroid implants
- Intraocular disease modifying agents, including anti-VEGF injections
- Strong OAT3 inhibitors, e.g. probenecid
- Interferon therapy
- Live vaccine within 28 days prior to baseline or expect to need/receive live vaccine during the course of the study (except booster immunization with attenuated vaccine for MMR or VZV). Booster vaccination with attenuated vaccine for MMR or VZV may be considered if it is essential based on the local guideline and/or in the opinion of the investigator.

Table JAHW.7. Concomitant JIA Therapies

Drug Class	As Needed	Chronic Use	Conditions for Use During Part A
MTX[a]	No	Yes	• Maximum of 25 mg/m^2/week. • Stable dose is required for at least 4 weeks prior to screening. • Must continue on same dose throughout Part A. • May initiate, increase or decrease the dose, or discontinue during Part B.
csDMARDs other than MTX[a]	No	Yes	• Stable dose is required for at least 4 weeks prior to screening. • Must continue on same dose throughout Part A. • May initiate, increase or decrease dose, or discontinue during Part B. • Maximum of 2 concomitant csDMARDs (including MTX).
Mycophenolate mofetil	No	Yes	• Stable dose is required for at least 4 weeks prior to screening. • Must continue on same dose throughout Part A. • May initiate, increase or decrease the dose, or discontinue during Part B.
Topical steroid eye drops	No	Yes	• Maximum of 4 drops/day per eye at screening. • Stable dose is required for at least 2 weeks prior to screening. • In Part A, drops may be tapered between Week 4 through Week 20. • In Part B, drops may be tapered after Week 24 to any dose, including zero. • Formulation may not change during Part A, but may change during Part B.
Oral corticosteroids	No	Yes	• Maximum dose of 10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less. • Stable dose is required for at least 2 weeks prior to screening and 4 weeks prior to baseline. • Must continue on same dose throughout Part A, except for treatment of an AE. • May initiate, increase or decrease dose, or discontinue during Part B.
Intra-articular corticosteroid joint injections	No	No	• Maximum of 8 injections per year. • Maximum of 2 injections in a single session. • Not permitted within 4 weeks prior to Visit 2.
Intraocular corticosteroid injections	No	No	• Not permitted within 30 days prior to Visit 2. • Not permitted during Part A. • Permitted during Part B.
Systemic corticosteroids (other than oral and intra-articular)	No	Yes	• Not permitted during Part A. • Permitted during Part B at a maximum dose of 10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less.
Analgesics & NSAIDs	No	Yes	• Stable dose is required for at least 1 week prior to Visit 2. • Must continue on same dose throughout Part A, except for treatment of an AE. • May initiate, increase or decrease dose, or discontinue during Part B.

Abbreviations: csDMARD = conventional synthetic disease-modifying antirheumatic drug; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug.

[a] Concomitant use of >2 of any csDMARDs (including MTX) is not allowed.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

After the conclusion of the study, continued access to baricitinib will not be provided.

7.8.2. Special Treatment Considerations

Patients receiving baricitinib who experience a treatment failure after at least 24 weeks of treatment can have concomitant medication altered (as described in Section 7.7), but should also be considered for discontinuation from the study (see Section 8.2).

Treatment failure is defined by the presence of 1 or more of the following:

- A 2-step increase in SUN cell-activity score (anterior chamber cells) over 2 consecutive readings for patients with a baseline grade of 1+ or 2+.
- Sustained non-improvement in SUN cell-activity score for 2 consecutive readings for patients with a baseline grade of 3+ or greater.
- Only partial improvement of other ocular co-morbidity for 2 consecutive assessments.
    - Ocular co-morbidities are defined as:
        - Disc swelling and/or cystoid macular edema, as gauged clinically and confirmed by optical coherence tomography (OCT) evidence
        - Sustained raised intraocular pressure (>25 mm Hg) for more than 1 month, not responding to topical anti-hypertensives
        - Sustained hypotony (<6 mm Hg) for more than 1 month
        - Reduction in vision (LogMAR test) of 15 letters, secondary to active uveitis (excluding cataract)
    - **Note:** Patients can remain in the study in the event of cataract.
- No improvement in SUN cell-activity score over 2 consecutive readings after 6 months of therapy.
- Worsening of existing (on enrollment) ocular co-morbidity (as defined above) after 12 weeks of therapy.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Temporary Interruption of Investigational Product

In some circumstances, patients may need to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational product. 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 JAHW.8.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table JAHW.8, 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 is at the discretion of the investigator. Investigational product that was temporarily interrupted because of an AE or abnormal laboratory value not specifically covered in Table JAHW.8 may be restarted at the discretion of the investigator.

Table JAHW.8. 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 x 10^3/µL or <2.00 billion/L)	WBC count ≥3000 cells/µL (≥3.00 x 10^3/µL or ≥3.00 billion/L)
ANC <1000 cells/µL (<1.00 x 10^3/µL or <1.00 billion/L)	ANC ≥1500 cells/µL (≥1.50 x 10^3/µL or ≥1.50 billion/L)
Lymphocyte count <500 cells/µL (<0.50 x 10^3/µL or <0.50 billion/L)	Lymphocyte count ≥1000 cells/µL (≥1.00 x 10^3/µL or ≥1.00 billion/L)
Platelet count <75,000/µL (<75 x 10^3/µL or <75 billion/L)	Platelet count ≥100,000/µL (≥100 x 10^3/µL or ≥100 billion/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 x ULN	ALT and AST return to <2 x ULN, and IP is not considered to be the cause of enzyme elevation
Hemoglobin <8 g/dL (<80.0 g/L)	Hemoglobin ≥10 g/dL (≥100.0 g/L)
Symptomatic herpes zoster	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection that, in the opinion of the investigator, merits the IP being restarted

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

8.1.2. Permanent Discontinuation from Investigational Product

Investigational product must be permanently discontinued if the patient or the patient's designee requests to discontinue investigational product.

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

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks after temporary interruption of investigational product
- ALT or AST >3 x ULN and TBL >2 x ULN or international normalized ratio (INR) >1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 x ULN that is deemed to be of liver origin and drug-related
- ALP >2.5 x ULN and TBL >2 x ULN
- ALP >2.5 x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

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

- White blood cell count <1000 cells/µL (1.00 x 10^3/µL or 1.00 billion/L)
- ANC <500 cells/µL (0.50 x 10^3/µL or 0.50 billion/L)
- Lymphocyte count <200 cells/µL (0.20 x 10^3/µL or 0.20 billion/L)
- Hemoglobin <6.5 g/dL (<65.0 g/L)

Note: Temporary interruption rules (see Section 8.1.1) must be followed where applicable. For laboratory values that meet permanent discontinuation thresholds, investigational product should be discontinued. However, if in the opinion of the investigator the laboratory abnormality is due to intercurrent illness such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when the laboratory value meets resumption thresholds (Table JAHW.8) following the resolution of the intercurrent illness or other identified factor may the investigator restart investigational product after consultation with the Lilly-designated medical monitor.

Use of analgesics "as needed" must lead to a thorough diagnostic assessment of all potential underlying causes and, if lack of efficacy cannot be ruled out, to considering permanent discontinuation of the investigational product.

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

- Pregnancy
- Malignancy
- HBV DNA detected with a value above the limit of quantitation (see Section 9.4.4)
- Development of a VTE (DVT/PE) during the study

Patients discontinuing from the investigational product prematurely for any reason should complete follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety).

8.1.3. Discontinuation of Inadvertently Enrolled Patients

The following paragraph is retained and applicable to sites in France.

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow-up should be performed as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety).

The following paragraph is not applicable to sites in France.

If the investigator and the sponsor-designated medical monitor agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor-designated medical monitor to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product where locally permitted.

8.2. Discontinuation from the Study

Patients may choose to withdraw from the study for any reason at any time; the reason for early withdrawal will be documented.

Possible reasons that may lead to permanent discontinuation include the following:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Determination that clinically meaningful adverse trends in patient growth (either at an individual or at an age-group level) are observed.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- Investigator decision
    - The investigator decides that the patient should be discontinued from the study. If this decision is made because of an intolerable AE or a clinically significant laboratory value, appropriate measures are to be taken.
    - If the patient, for any reason, requires treatment with a therapeutic agent excluded per the criteria described in Section 7.7, discontinuation from the study occurs prior to introduction of the new agent.

- Patient decision
    - The patient or the patient's designee (e.g., parent or legal guardian) requests 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 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety).

8.3. Lost to Follow-Up

Patients will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients/legal representatives who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

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

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

Unless otherwise stated in the following subsections, 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.

Investigators or relevant clinical staff will provide age-appropriate explanations to all children, prior to any assessment or procedure. Investigators should assess and monitor physical pain and distress at each visit.

Staff trained or experienced in pediatric phlebotomy should perform blood draws at the clinic. Blood draws should be consolidated and the number of attempts should be kept to the minimum number required. The number of sampling attempts should be minimized, in accordance with local guidelines and procedures. For example, it is recommended that after one unsuccessful attempt, another experienced person should take over the procedure.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessment

The primary efficacy assessment is to determine the proportion of patients with a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero through Week 24 in the eye most severely affected at baseline.

In order to reduce the confounding effects of variations in disease activity and time, it is optimal to perform the ophthalmologic and rheumatologic examinations on the same day, although a separation of up to 3 days is acceptable.

9.1.2. Secondary Efficacy Assessments

Secondary endpoints (assessed at each visit) are as follows:

- Change in SUN grade of cells in the anterior chamber through Week 24 (Part A) and through Week 284 (Part B) in the most severely affected eye.
- Change in SUN grade of cells in the anterior chamber through Week 24 and Week 284 in the less severely affected eye (if applicable).
- In patients with bilateral uveitis disease at baseline: proportion of responders at Weeks 24 and 284, defined according to the SUN criteria as a 2-step decrease in the level of anterior chamber cells in the most severely affected eye at baseline (or both eyes if the inflammation grade is the same in both eyes) and a 1-step decrease in the level of anterior chamber cells in the less severely affected eye at baseline.
- Change in visual acuity measured by age-appropriate LogMAR test through Week 24.

- Change in vitreous haze through Week 24 in each affected eye.
- Change in grade of flare in the anterior chamber through Week 24 and Week 284 in each affected eye.
- Change in overall uveitis-related disability:
    - Change in Patient Uveitis-related Disease Activity through Week 24.
    - Change in Patient Uveitis-related Improvement at Week 12 and Week 24.
    - Change in Patient Arthritis Disease Activity through Week 24.
    - Change in Patient Arthritis Improvement at Week 12 and Week 24.
    - Change in Ophthalmologist Uveitis-related Disease Activity through Week 24.
    - Change in Ophthalmologist Uveitis-related Improvement at Week 12 and Week 24.
- Proportion of patients with inactive anterior uveitis (using SUN definition) in each affected eye through Week 24 and Week 284.
- Time to inactive anterior uveitis disease (using SUN definition) in each affected eye.
- Proportion of patients who are able to taper concomitant corticosteroids.
- Time to treatment response: response is defined by a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero in the eye most severely affected at baseline.
- Proportion of responders at Week 284.
- Pediatric American College of Rheumatology (PediACR)30/50/70/90/100 response rates (for patients with JIA-U).
- Safety variables:
    - AEs, including SAEs
    - Permanent discontinuation of investigational product due to AE, and
    - Temporary interruption of investigational product.

9.1.2.1. Ophthalmic Assessments

9.1.2.1.1. SUN Cell-Activity Score

Anterior chamber cells will be examined using a slit-lamp, and graded using the SUN grading scheme (Table JAHW.9). This is a quantitative assessment of cell number in the anterior chamber, which is graded 0-4 (Jabs et al. 2005).

Table JAHW.9. SUN Grading Scheme for Anterior Chamber Cells

Grade	Cells in Field[a]
0	<1
0.5+	1-5
1.0+	6-15
2.0+	16-25
3.0+	26-50
4.0+	>50

Abbreviation: SUN = Standardization of Uveitis Nomenclature.

[a] Field size is a 1 mm by 1 mm slit beam.

9.1.2.1.2. Anterior Chamber Flare

Flare will be assessed using a slit-lamp, and graded using the SUN grading scheme (Table JAHW.10; Jabs et al. 2005).

Table JAHW.10. SUN Grading Scheme for Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Abbreviation: SUN = Standardization of Uveitis Nomenclature.

9.1.2.1.3. Visual Acuity

Visual acuity will be assessed in both eyes using an age-appropriate LogMAR test (Kay picture and crowded LogMAR test).

9.1.2.1.4. Vitritis

Binocular indirect ophthalmoscopy score will be used to grade vitritis and vitreous haze in each affected eye (Nussenblatt et al. 1985).

9.1.2.2. Uveitis Disease Activity

The definition of uveitis disease activity used in this study is based on the SUN Working Group criteria (Table JAHW.11; Jabs et al. 2005). Inactive disease is defined as the presence of 0 anterior chamber cells upon slit-lamp examination.

Table JAHW.11. Uveitis Disease Activity Terminology

Term	Definition
Inactive	Grade 0 cells[a]
Worsening activity	2-step increase in level of inflammation (e.g., anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+
Improved activity	2-step decrease in level of inflammation (e.g., anterior chamber cells, vitreous haze) or decrease to grade 0
Remission	Inactive disease for ≥3 months

[a] Applies to anterior chamber inflammation.

9.1.2.3. PediACR30/50/70/90/100 Assessments

The PediACR30 consists of the 6 core criteria listed below. The definition of improvement is at least 30% improvement from baseline in 3 of any 6 variables in the core set, with no more than 1 of the remaining variables worsening by >30%.

- Number of active joints (defined as a joint that is swollen or in the absence of swelling has loss of passive motion accompanied by either pain on motion or joint tenderness) in 73 joints
- Number of joints with limited range of motion in 69 joints

- Physician's Global Assessment of Disease Activity (21-circle visual analogue scale [VAS]) (Section 9.1.2.4)
- Parent's Global Assessment of Well-Being (Section 9.1.3)
- Physical function as assessed by the Childhood Health Assessment Questionnaire (CHAQ) (Section 9.1.3)
- Acute-phase reactant (high-sensitivity C-reactive protein [hsCRP] and erythrocyte sedimentation rate [ESR])

PediACR50/70/90/100 responses are efficacy measures that are calculated as improvements of at least 50%, 70%, 90% and 100%, respectively, in the PediACR Core Set values listed above.

9.1.2.4. Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity is used by the physician to assess the patient's current disease activity, as it relates to their signs and symptoms. The instrument uses a 21-circle VAS ranging from 0 to 10 (using 0.5 increments), where 0 = "no activity" and 10 = "maximum activity" (Filocamo et al. 2010).

9.1.3. Health Outcomes

Childhood Health Assessment Questionnaire

The CHAQ assesses health status and physical function in children with juvenile arthritis over the past week, which the parent or legal guardian completes, regardless of the age of the patient.

The CHAQ has 2 indices – the Disability Index and the Discomfort Index. The Disability Index contains 30 items grouped into the following 8 domains (not including assistive devices/aids questions): dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. The domains are averaged to calculate the Disability Index (physical function). Each item is scored from 0 to 3 (0 = no difficulty; 1 = some difficulty; 2 = much difficulty; and 3 = unable to do or not applicable). A higher score indicates worse physical function (Singh et al. 1994). Data will be captured on an electronic tablet.

The Discomfort Index of the CHAQ includes the following (Ruperto et al. 2001):

- Parent's Global Assessment of Well-Being
  - This is a component of the PediACR core response set, as well as the Juvenile Arthritis Disease Activity Score-27 (JADAS-27).
  - The instrument is a 0-100 mm VAS assessing the current level of well-being, where 0 = "Very well" and 100 = "Very poor".
- Pain assessment due to illness
  - This instrument is a 0-100 mm VAS that assesses the current level of pain severity over the past week, where 0 = "No pain" and 100 = "Very severe pain".

Childhood Health Questionnaire-Parent Form 50

The Childhood Health Questionnaire-Parent Form 50 (CHQ-PF50) is a generic observer-reported instrument designed to capture the health-related quality of life of children and adolescents (from

5- to 18-years of age), as well as the impact of the child's disease on the caregivers (HealthActCHQ 2013). The CHQ-PF50 is completed by the caregivers and has been validated for use in patients with JIA (Ruperto et al. 2001).

The CHQ-PF50 consists of 50 questions covering 14 health concepts: Global Health; Physical Functioning; Role/Social Limitations-Physical; Role/Social Limitations-Emotional/Behavioral; Bodily Pain/Discomfort; General Behavior; Mental Health; Self-Esteem; General Health Perceptions; Change in Health; Parental Impact-Emotion; Parental Impact-Time; Family-Activities; and Family-Cohesion.

Overall means for the individual CHQ scales and items will be scored according to the scoring manual. Scores will be transformed to ensure that all items are positively scored so that a higher score indicates better health (HealthActCHQ 2013). In addition, 2 summary scores, the Physical Summary Score (PhS) and Psychosocial Summary Score (PsS), will be evaluated based upon 10 scales of the CHQ-PF50. United States norms are available for the CHQ-PF50. The response options for the CHQ-PF50 vary from 4 to 6 levels for the scales. The majority of the items have a recall period of 4 weeks. Data will be captured on an electronic tablet.

Morning Joint Stiffness Duration

As one of the assessments to determine inactive disease, the physician will ask the parent/legal guardian if the duration of their child's morning joint stiffness was >15 minutes since the previous visit; inactive disease is ≤15 minutes in duration. Responses are yes/no.

Patient Uveitis-related Disease Activity

The Patient Uveitis-related Disease Activity instrument is a single-item question. It is completed by caregivers/legal guardians (proxy) for children less than 8 years; for children aged 8 years or older, this will be self-completed. The single item asks the respondent to rate their eye problems "at this time". It uses a 4-item Likert scale (1 = "None", 2 = "Mild", 3 = "Moderate", and 4 = "Severe").

Patient Uveitis-related Improvement

The Patient Uveitis-related Improvement instrument is a single-item question. It is completed by caregivers/legal guardians (proxy) for children less than 8 years; for children aged 8 years or older, this will be self-completed. The item asks the respondent to rate the overall change in their eye problems since they started taking study medication. It uses a 5-item Likert scale (1 = "Much Better", 2 = "A little Better", 3 = "No Change", 4 = "A Little Worse", and 5 = "Much Worse").

Patient Arthritis Disease Activity

The Patient Arthritis Disease Activity instrument is a single-item question. It is completed by caregivers/legal guardians (proxy) for children less than 8 years; for children aged 8 years or older, this will be self-completed. The item asks the respondent to rate their arthritis "at this time". It uses a 4-item Likert scale (1 = "None", 2 = "Mild", 3 = "Moderate", and 4 = "Severe").

Patient Arthritis Improvement

The Patient Arthritis Improvement instrument is a single-item question. It is completed by caregivers/legal guardians (proxy) for children less than 8 years; for children aged 8 years or older, this will be self-completed. The question asks the respondent to rate the overall change in their arthritis since they started taking study medication. It uses a 5-item Likert scale (1 = "Much Better", 2 = "A little Better", 3 = "No Change", 4 = "A Little Worse", and 5 = "Much Worse").

Ophthalmologist Uveitis-related Disease Activity

The Ophthalmologist Uveitis-related Disease Activity instrument is a single-item question asking the ophthalmologist to rate their patients' disease activity in each eye "at this time". It uses a 4-item Likert scale (1 = "None", 2 = "Mild", 3 = "Moderate", and 4 = "Severe").

Ophthalmologist Uveitis-related Improvement

The Ophthalmologist Uveitis-related Improvement instrument is a single-item question asking the ophthalmologist to rate the overall change in their patients' uveitis in each eye since they started taking study medication. It uses a 5-item Likert scale (1 = "Much Better", 2 = "A little Better", 3 = "No Change", 4 = "A Little Worse", and 5 = "Much Worse").

9.1.4. Exploratory Efficacy Assessments

Efficacy Exploratory Assessments have been removed.

9.1.5. Immunological Measurements

Potential effects of baricitinib on the cellular and humoral immune system will be evaluated through the analysis of immunoglobulin levels, immunophenotyping (including T and B cells, T-cell subsets, and natural killer [NK] cells), white blood cells (WBC), and WBC differential.

Changes from baseline in immunoglobulin levels and peripheral blood immunophenotyping (including T and B cells, T cell subsets, and NK cells) will be assessed at the following weeks:

- Part A: Week 12 and Week 24.
- Part B: Week 48, Week 96, Week 144, Week 192, Week 240, and Week 284.

In addition, patients will be immunized with appropriate vaccinations as part of or in the course of their usual care according to the local requirement throughout the study period. When the patients become eligible for a TDaP and/or a pneumococcal conjugate vaccine during the study period, they will be immunized with the vaccines, and their antibody titres to the antigens will be evaluated pre-immunization and at 4 and 12 weeks post-immunization. A primary immune response will be assessed in patients who have never received TDaP or pneumococcal conjugate vaccines previously and secondary/booster responses will be assessed if the patients have previously received the vaccines.

9.1.6. Appropriateness of Assessments

All assessments utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant, except for the Uveitis-related Disease Activity and Improvement,

and Arthritis Disease Activity and Improvement scales, which are novel instruments developed by Lilly.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves or until the event stabilizes with appropriate diagnostic evaluation. 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 and Assent Form (as applicable) are signed, study site personnel will record via electronic data entry 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 the following via eCRF for each AE: time of onset, time of termination, severity, and their assessment of the potential relatedness of each AE to protocol procedure and/or investigational product. The investigator will record all relevant AE/SAE information in the CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to investigational product, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a cause-and-effect relationship between the investigational product, study device, and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

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

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

9.2.1. 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
- Life-threatening experience (i.e., immediate risk of death)
- 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.

All AEs occurring after signing the ICF and Assent Form (as applicable) are recorded in the electronic data entry system and assessed for serious criteria. The SAE reporting to the sponsor begins after the parent/legal guardian has signed the ICF, and the patient has signed the Assent Form (as applicable) and received investigational product. However, if an SAE occurs after signing the ICF and Assent Form (as applicable), but prior to receiving investigational product, the SAE should be reported to the sponsor according to SAE-reporting requirements and timelines if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via initiation of a SAE eCRF. Once the SAE eCRF form is initiated, an email is automatically triggered to the Sponsor's global patient safety department. Investigators can contact the Sponsor via telephone at any time using the qualified medical personnel or Lilly affiliate medical contact details, which are provided in the site study file. If alerts are issued via telephone, they are to be immediately followed with official notification via completion of the SAE eCRF. If the eCRF is unavailable (for example, for system maintenance) for a period of time that would compromise the sites' ability to report an event within 24 hours of awareness, a paper version of the form should be downloaded from the Investigator Space portal, completed by the investigator, and submitted via fax to the Sponsor's global patient safety department. This form includes a fax cover page that is pre-populated with the appropriate fax number. Serious AEs submitted via the paper method are entered into the eCRF once the database is available. The 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 investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Study Directive 2001/20/EC, and European regulation 536/2014 and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

9.2.2. Adverse Events of Special Interest

Adverse events of special interest will include the following:

- Infections (including TB, herpes zoster, or opportunistic infections)
- Malignancies
- Hepatic events (see Section 9.4.5)
- Major adverse cardiovascular events (MACE) (see Section 9.4.7)
- Venous thromboembolism (DVT and PE)
- Arterial thromboembolic events (ATE)

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

9.2.3. Complaint Handling

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

Patients (or parents/legal guardians) will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Baricitinib single doses up to 40-mg and multiple doses of up to 20-mg daily for 10 days have been administered in clinical studies without dose-limiting toxicity. Pharmacokinetic data of a single dose of 40-mg in healthy volunteers indicate that >90% of the administered dose is

expected to be eliminated within 24 hours. In case of an overdose, the patient should be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

9.4. Safety

Any clinically significant findings from electrocardiogram (ECG) testing, physical examination, vital signs measurements, or laboratory measurements that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.1. Electrocardiograms

A single 12-lead standard ECG will be obtained locally at screening and read by a physician qualified to read pediatric ECGs (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria. Electrocardiograms may be obtained at additional times when deemed clinically necessary.

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via electronic data entry.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2). Use of local anesthetics (e.g., EMLA cream) consistent with local prescribing information are permitted during the study visit to ease discomfort associated with venipuncture. Owing to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in a sponsor-provided weight-based prioritization chart (Appendix 7).

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical study.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via electronic data entry.

9.4.4. Hepatitis B Virus DNA Monitoring

Hepatitis B virus DNA testing will be performed in enrolled patients who tested positive for HBcAb at screening (refer to the Schedule of Activities [Section 2]).

Patients who are HBcAb positive and HBV DNA negative (undetectable) at screening will require measurement of HBV DNA as shown in the Schedule of Activities (Section 2) and the follow-up visit, regardless of their hepatitis B surface antibody (HBsAb) status.

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

- If a single result is obtained with a value "below limit of quantitation," the test should be repeated within approximately 2 weeks.
- If the repeat test result is "target not detected," monitoring will resume according to the study schedule.
- If the patient has 2 or more test results with a value "below limit of quantitation," HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended.
- If a result is obtained with a value above the limit of quantitation, at any time during the study, the patient will be permanently discontinued from investigational product (see Section 8.1.2) and should be referred to a hepatology specialist.
    - In selected cases, investigators may temporarily continue investigational product in accordance with current immunomodulator management in the setting of HBV DNA positivity. This option may be considered in consultation with Lilly (or its designee) and evaluation of individual patient risks and benefits.

9.4.5. Hepatic Safety Monitoring and Data Collection

If a study patient experiences elevated ALT ≥3 x ULN, ALP ≥2 x ULN, or elevated TBL ≥2 x ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine phosphokinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels. Discontinuation criteria of investigational products, either temporary interruption or permanent discontinuation, due to abnormal ALT, AST, TBL, or ALP, are detailed in Section 8.1.

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

- ALT ≥5 x ULN confirmed by repeat testing
- ALP ≥2 x ULN confirmed by repeat testing
- TBL ≥2 x ULN confirmed by repeat testing (except for cases of known Gilbert's syndrome)
- Permanent discontinuation of investigational product due to hepatic event or hepatic laboratory abnormality
- Hepatic SAE

Refer to Appendix 4 for a description of hepatic laboratory values that warrant exclusion from the study, temporary or permanent discontinuation of investigational product (Section 8.1), or additional safety collection via the hepatic eCRF.

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

If safety issues are identified, the Data Monitoring Committee (DMC) (refer to Interim Analyses section, Section 10.3.7) can request additional analyses of the safety data or request changes to the conduct of the study.

The Lilly clinical research physician/scientist will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical research physician will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist and periodically review trends in safety data and laboratory analytes. Any concerning trends in frequency or severity noted by an investigator and/or Lilly (or designee) may require further evaluation.

All deaths and SAE reports will be reviewed by Lilly during the clinical study. These reports will be reviewed to ensure completeness and accuracy. If a death or a clinical AE is deemed serious, unexpected, and possibly related to investigational product, Lilly Global Patient Safety will report the event for regulatory reporting and safety monitoring purposes.

Investigators will monitor vital signs and review findings that may be associated with cardiovascular and venous thrombotic events. Adverse event reports and vital signs will be collected at each study visit. The cardiovascular monitoring plan includes the following:

- Regular monitoring of lipid levels
- Potential MACE (cardiovascular death, myocardial infarction [MI], stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary interventions), ATE, venous thrombotic events, and noncardiovascular deaths will be identified by the investigative site or through medical review and will be sent to a blinded Clinical Event Committee for adjudication at regular intervals.

9.4.6.1. Venous Thromboembolic Event Assessment

If a patient develops the clinical features of a DVT or PE, appropriate local laboratory tests and imaging is recommended, as necessary, for diagnosis of the event. For confirmed cases, additional laboratory testing should be performed as outlined in Appendix 5. All suspected VTE events will be independently adjudicated by a blinded Clinical Event Committee.

9.4.6.2. Growth Monitoring

Height and weight will be measured at screening and baseline and postbaseline for the assessment of physical growth according to the Schedule of Activities (Section 2). Height, weight, occipital frontal circumference, and growth velocity changes in pediatric patients (both at

an individual and group level) will be reviewed by the DMC. Height measurements will be made using a stadiometer.

Insulin-like growth factor (IGF)-1, the principal mediator of growth hormone, and IGF-binding protein-3, the principal carrier protein for IGF-1, will be collected for the assessment of growth-related disorders. Gonadal hormone (estradiol for females or testosterone for males) will be collected for the assessment of pubertal development with patients 8 to <18 years of age. For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

A semiannual wrist, hand, finger, and anteroposterior (AP) knee radiographs to monitor bone age and long-bone growth is required, with an option to consent to this procedure for patients already enrolled in the study.

If a local addendum is in place that specifies another mode of imaging (e.g., magnetic resonance imaging [MRI] instead of x-ray), the local addendum should be followed. Otherwise, the current protocol amendment should be followed.

Any symptomatic areas of bones/joints will be assessed and investigated as appropriate by study investigators. Any diagnoses made based on symptomatic areas of bones/joints or imaging data will be reported as appropriate (e.g. recorded on eCRF).

For study sites in Germany:

- MRI of the knee will be collected to monitor bone and cartilage growth and/or maturation.
    - MRI of the knee will be collected approximately every 6 months as shown in Section 2 . A central vendor will be used for reading of the MRI images.
    - An x-ray of the knee (anteroposterior) may be collected in place of the MRI in cases where MRI is not possible (e.g., site does not have MRI access, sedation is required, MRI is not medically advisable in the opinion of the investigator, parents/patients do not consent). The clinical site will document the rationale for collecting x-rays vs. MRIs. An appropriate physician at the clinical site will read the x-ray image, and if it is determined that the patient does not have growth potential (that is, the patient has completed skeletal maturity), then no further knee x-rays will be required. The clinical sites will document the decision that a patient has reached skeletal maturity.
- External tibial length measurement will be collected as an additional assessment of growth.
    - External tibial length will be measured approximately every 3 months as shown in Section 2. Guidance on measuring external tibial length will be provided by the Sponsor.

9.4.6.3. Tanner Stage Scale

The Tanner Stage Scales are a series of line drawings that are designed to assess sexual maturity of the patient, and will be included as a baseline assessment. The line drawings are intended for patient self-assessment; however, this assessment may be also conducted by an appropriate health care professional if the patient and legal guardian agree (Marshall and Tanner 1969, 1970; Tanner and Davis 1985; Chavarro et al. 2017). Assessment by the health care professional will not be completed if the patient and parent do not provide appropriate consent and assent. The self-assessment will only be collected if the appropriate translation of the scale is available for use at the time of the baseline assessment.

9.4.7. Vision-Related Safety Monitoring

9.4.7.1. Fundoscopy

Fundoscopy will be used to assess disc swelling, macular edema, and other structural changes in macular (epiretinal membrane) and optic nerve (optic disc swelling and glaucomatous neuropathy) and retina (neovascularization and retinal detachment). Fundoscopy will be assessed at all visits in each affected eye.

9.4.7.2. Optical Coherence Tomography

Optical coherence tomography (at least stratus II) will be used to assess macular edema and central macular thickness in each affected eye.

9.4.7.3. Cataract Scoring

The Lens Opacities Classification Score (LOCS) II grading will be used for cataract scoring (Chylack et al. 1989). The LOCS II standards for grading cataracts are shown in Appendix 6.

9.4.7.4. Intraocular Pressure

Intraocular pressure will be measured in each affected eye by I-Care, Goldmann tonometry or Tono-Pen, as deemed appropriate.

9.4.7.5. Other Structural or Vision-Related Complications

The following structural changes and vision related complications will be assessed and monitored:

- Band keratopathy
- Synechiae
- Iris bombe
- Glaucoma
- Neovascularization
- Cataract
- Cystoid macular edema
- Optic neuropathy
- Ocular hypertension: >21 mm Hg
- Ocular hypotony: <6 mm Hg
- Glaucomatous field loss and/or glaucomatous optic atrophy
- Epiretinal membrane formation, and
- Visual deterioration: worsening by 0.3 LogMAR in any eye

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Refer to Section 10.3.5.

9.6.1. Pharmacogenetics

9.6.1.1. Whole Blood Sample for Pharmacogenetic Research

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

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated. In the event of an unexpected AE, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to baricitinib. These investigations may be limited to targeted exome sequencing approach of known targets involved in drug metabolism or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples will be used only for investigations related to disease and drug or class of drugs under study in the context of this clinical program.

9.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics (PD), 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 for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

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

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 or site personnel.

Samples will be retained at a facility selected by the sponsor for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations require and ethical review boards impose shorter time limits. The duration allows the sponsor to respond to future regulatory requests related to the investigational product. Any samples remaining after 15 years will be destroyed.

9.8. Medical Resource Utilization and Health Economics

There will be no collection of healthcare resource utilization or calculation of utilities for economic modeling in this study.

10. Statistical Considerations

10.1. Sample Size Determination

The original sample size was determined by the following:

At least 20 and up to 40 patients will be enrolled.

- Baricitinib arm: At least 10 and up to 30 patients (MTX-IR and bDMARD-IR) ; at least 10 MTX-IR patients
- Adalimumab arm: At least 10 MTX-IR patients.

At least 20 MTX-IR (but not bDMARD-IR) patients will be randomized to baricitinib and adalimumab in a 1:1 ratio.

With a total sample size of 30 in the baricitinib arm, and assuming an observed response rate of 66.7%, the study will be able to detect a true baricitinib treatment response rate of greater than 57% with greater than 80% probability. The observed response rate of 66.7% is based on the assumption that 20 out of 30 patients in the baricitinib arm will achieve the primary endpoint. The response rate threshold of 57% was chosen to match the response rate observed for patients with JIA-associated uveitis treated with adalimumab in the SYCAMORE study (Ramanan et al. 2017).

Since the original sample size was determined, the study enrollment has been updated to the following:

- Baricitinib arm: At least 20 patients (MTX-IR and/or bDMARD-IR) evaluable for the primary endpoint.
- Adalimumab arm: At least 4 patients evaluable for the primary endpoint.

10.2. Populations for Analyses

Unless otherwise specified, the efficacy and health outcome analyses will be conducted on the modified intent-to-treat (mITT) analysis set in Part A. The mITT set is defined as the patients who take at least 1 age-based dose of investigational product in Part A. Patients will be analyzed according to the treatment to which they were assigned. For the efficacy and health outcomes analysis in Part B, the analysis will be conducted on as-observed data, which is defined in Section 10.3.1. Significant protocol violations will be described in the SAP.

Safety analyses will be carried out on all randomized patients who receive at least 1 dose of investigational product and who did not discontinue from the study for the reason “Lost to Follow-up” at the first postbaseline visit.

Further details of other populations will be described in the SAP.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. A detailed SAP describing the statistical methodologies will be developed by Lilly or its designee.

Bayesian analysis will be used as the primary analysis method for the primary endpoint and interim analysis. The posterior probability will be reported and the conclusion will be made based on the prespecified success criteria. The primary endpoint is the proportion of patients with response at Week 24. Response is defined as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero in the eye most severely affected at baseline, measured by SUN criteria (Jabs et al. 2005). If the study is not stopped for futility, the posterior probability of the treatment response rate exceeding 57% will be calculated, and the study objective will be successfully met (i.e., a positive study) if this probability is at least 80%. The detail of the analyses will be described in the SAP.

Unless otherwise specified, for the endpoints that may relate to both eyes, such as patients with uveitis affecting both eyes, the summary of the data for a given endpoint measure will be based on both affected eyes. The summary statistics may be grouped into “less severely affected eye” and “more severely affected eye,” or “right eye” and “left eye” subgroups. The details will be documented in the SAP.

Efficacy and health outcome endpoints will also be summarized using descriptive statistics for the baricitinib arm and adalimumab arm. No treatment comparison will be conducted.

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, and median. Categorical data will be summarized as frequency counts and percentages.

All safety data will be descriptively summarized.

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

The SAP will be approved before the first patient visit in Study JAHW.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

Missing Data Imputation

The following methods will be used to impute missing data in Part A:

Modified nonresponder imputation (mNRI):
For primary efficacy data, missing data due to lack of efficacy will be imputed as a nonresponder under mNRI. If primary efficacy data are missing for reasons other than this, available preceding data from patients with missing data will be reviewed by an independent and external Clinical Endpoints Committee (CEC), as outlined in the CEC charter. The CEC will ensure that patients with missing data are evaluated in a consistent manner. The CEC will consider the complete patient history and the reasons for the missing data, in order to determine whether responder or nonresponder status is appropriate on a case-by-case basis. Study sites should send any requested source documentation to the CEC in a timely fashion.

Nonresponder Imputation (NRI):
A patient is defined as a responder only if (i) they meet the clinical requirements for response at the predefined time and (ii) they remain on the assigned study treatment; failing either criteria by definition (i) or (ii) makes them a nonresponder.
Binary efficacy and health-outcome data, excluding the primary outcome data, will be imputed using NRI. Patients will be considered a nonresponder for the NRI analysis if they do not meet the clinical response criteria or are entirely missing the visit at the analysis time point. Patients without at least 1 postbaseline observation will also be defined as nonresponders for the NRI analysis.
Last observation carried forward (LOCF):
The LOCF method will be used for the analysis of continuous endpoints (unless otherwise stated). For patients who discontinue the study, the last nonmissing observation will be carried forward to the subsequent time points for evaluation.

The following method will be used to handle missing data in Part B:

As-observed analysis:
A summary based on observed data at each postbaseline visit will be provided. For "as-observed" analysis, only data from completers at the visit are relevant, and therefore, the analysis does not need to deal with missing data.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Patient disposition will be summarized for all enrolled patients. Frequency counts and percentages of patients who complete the study treatment visits or discontinue early from the study will be summarized by prior treatment group and overall.

A listing of patient disposition will be provided for all patients, with the extent of their participation in the study and the reason for discontinuation.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Baseline characteristics may include gender, age, height, weight, body mass index (BMI), race, geographic region, baseline disease severity, and subtypes of JIA. Baseline clinical measurements may include PediACR core set variables, vision assessment, slit lamp examination, number of topical steroid drops taken per day, intraocular pressure, and number of study eyes.

10.3.2.3. Concomitant Therapy

Concomitant medications will be descriptively summarized for patients who enter each treatment period. The medications will be coded accordingly.

10.3.2.4. Treatment Compliance

Treatment compliance with investigational product will be summarized for each treatment period. Patient compliance with investigational product will be assessed at each visit. Patients will be considered compliant for each study period if they miss <20% of the expected doses. Proportions of patients compliant will be summarized. Patient compliance will be further defined in the SAP.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary efficacy endpoint is the proportion of responders at Week 24. Response is defined according to the SUN criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero in the eye most severely affected at baseline.

A Bayesian posterior probability will be calculated based on the number of observed responders who complete or have the opportunity to complete 24 weeks of the study at each stage:

- Stage 1: 10 baricitinib-treated patients.
- Stage 2: 20 baricitinib-treated patients.
- Stage 3: up to 30 baricitinib-treated patients.

The details of the calculation of the posterior probability are as follows:

$$X_i: i\ th\ patient$$

$$X_i|\theta \sim Bern(\theta)$$

$$\theta \sim Beta(1,1)$$

Then,

$$Y^{stage1} = \sum_{I=1}^{10} X_i$$

$$Y^{stage2} = \sum_{I=1}^{20} X_i$$

$$Y^{stage3} = \sum_{I=1}^{30} X_i$$

The Bayesian posterior probability for futility at interim 1 (Stage 1) is calculated as

$$pr(\theta < 0.4|Y^{stage1}) = \frac{\Pr(Y^{stage1}|\theta < 0.4) \cdot \Pr(\theta < 0.4)}{\Pr(Y^{stage1})}$$

The Bayesian posterior probability for futility at interim 2 (Stage 2) is calculated as

$$pr(\theta < 0.4|Y^{stage2}) = \frac{\Pr(Y^{stage2}|\theta < 0.4) \cdot \Pr(\theta < 0.4)}{\Pr(Y^{stage2})}$$

The Bayesian posterior probability for study success at the end of study (Stage 3) is calculated as

$$pr(\theta > 0.57|Y^{stage3}) = \frac{\Pr(Y^{stage3}|\theta > 0.57) \cdot \Pr(\theta > 0.57)}{\Pr(Y^{stage3})}$$

10.3.3.2. Secondary Analyses

Secondary efficacy and health outcomes analyses (Table JAHW.12) will be based on all participants who take at least 1 age-based dose of investigational product for Part A. Baseline is defined as Week 0.

The secondary efficacy and health outcomes analysis for Part B will be addressed in the SAP.

Table JAHW.12. Secondary Efficacy Endpoint Analyses for Part A

Measure	Endpoint	Analysis Method
SUN grade of cells in the anterior chamber in the most severely affected eye	Change from baseline	Summary statistics
SUN grade of cells in the anterior chamber in the less severely affected eye (if applicable)	Change from baseline	Summary statistics
In patients with bilateral uveitis disease at baseline: Responders, defined according to the SUN criteria as a 2-step decrease in the level of anterior chamber cells in the most severely affected eye at baseline (or both eyes if the inflammation grade is the same in both eyes) and a 1-step decrease in the level of anterior chamber cells in the less severely affected eye at baseline.	Proportion of patients	Summary statistics
Visual acuity by age-appropriate LogMAR test in each eye	Change from baseline	Summary statistics
Vitreous haze in each affected eye	Change from baseline	Summary statistics
Grade of flare in the anterior chamber in each affected eye	Change from baseline	Summary statistics
Overall uveitis-related disability: ○ Change in Patient Uveitis-related Disease Activity through Week 24. ○ Change in Patient Uveitis-related Improvement at Week 12 and Week 24. ○ Change in Patient Arthritis Disease Activity through Week 24. ○ Change in Patient Arthritis Improvement at Week 12 and Week 24. ○ Change in Ophthalmologist Uveitis-related Disease Activity through Week 24. ○ Change in Ophthalmologist Uveitis-related Improvement at Week 12 and Week 24.	Change from baseline	Shift table
Proportion of patients with inactive anterior uveitis disease status in each affected eye	Proportion of affected eyes	Summary statistics
	Time to inactive disease status	Summary statistics

Measure	Endpoint	Analysis Method
Concomitant topical corticosteroid tapering status, for patients eligible for corticosteroid tapering	Proportion of patients	Summary statistics
PediACR 30/50/70/90/100	Proportion of responders	Summary statistics

Abbreviations: PediACR = Pediatric American College of Rheumatology; SUN = Standardization of Uveitis Nomenclature.

10.3.3.3. Exploratory Analyses

Not Applicable.

10.3.4. Safety Analyses

Safety variables will be summarized, which include the following, but are not limited to:

- Exposure to investigational product
- AEs
- SAEs
- Permanent discontinuation of investigational product
- Temporary interruption of investigational product
- AEs leading to discontinuation
- AEs of special interest
- Laboratory analytes
- Vital signs

Summaries of safety data will be presented for baricitinib and adalimumab. Further details will be described in the SAP.

10.3.4.1. Adverse Events

Adverse events are classified based on the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity on or after the date of the first dose of investigational product. The number of TEAEs as well as the number and percentage of patients who experienced at least 1 TEAE will be summarized using MedDRA for each system organ class (or a body system) and each preferred term by treatment group. For events that are gender-specific, the denominator and computation of the percentage will only include patients from the given gender.

Serious adverse events (including deaths), treatment-emergent AEs of special interest, and AEs that lead to investigational product discontinuation will also be summarized using MedDRA for each system organ class and each preferred term by treatment group. Potential AEs of special interest will be identified by a standardized MedDRA query or a Lilly-defined MedDRA listing. Details of the AEs of special interest (including but not limited to those listed in Section 9.2.2) and analysis will be documented in the SAP or program SAP. Adverse events of special interest will also be presented by severity. Adverse events of special interest will include the following:

- Infections (including TB, herpes zoster, or opportunistic infections)

- Malignancies
- Hepatic events (Section 9.4.5)
- MACE as adjudicated by the external Clinical Event Committee (Section 10.3.7.1)
- Thrombotic events (such as ATE, deep vein thrombosis and pulmonary embolism)

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

10.3.4.2. Clinical Laboratory Tests

All clinical laboratory results will be descriptively summarized. Individual results that are outside the 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.

10.3.4.3. Vital Signs, Physical Findings, and Other Safety Evaluations

Vital signs will be presented as mean changes from baseline and as incidence of abnormal values. Other data, including body weight and height data will be summarized. Weight, height, and BMI data will be merged to the Centers for Disease Control standard growth data by age and gender to compare subjects' growth with the standard. Other measures related to growth velocity (e.g., occipital circumference measurement) will be evaluated. Further analyses may be performed.

10.3.5. Evaluation of Immunological Measures

Change from baseline in immunoglobulin levels and peripheral blood immunophenotyping (including T and B cells, T cell subsets, and NK cells) will be evaluated and summarized using descriptive statistics. Patients who are immunized with TDaP or pneumococcal conjugate vaccines will have their IgG antibody titers to the antigens evaluated preimmunization and at 4 and 12 weeks postimmunization. A primary immune response will be assessed in patients who have never received TDaP or pneumococcal conjugate vaccines previously and secondary/booster responses will be assessed if the patients have previously received the vaccines. More detailed analytical methods will be described in the SAP.

10.3.6. Other Analyses

10.3.6.1. Subgroup Analyses

In Part A, efficacy and safety assessments will be summarized and analyzed at Week 24, by 3 age groups:

- 12 to 17 years old
- 6 to 11 years old, and
- 2 to 5 years old.

The details will be described in the SAP.

Age group efficacy summaries may include:

- Number and proportion of responders at Week 24 by each age group.
  Response is defined according to the SUN criteria as a 2-step decrease in the level of inflammation (anterior chamber cells) or decrease to zero in the eye most severely affected at baseline.
- Change in
  - SUN grade of cells in the anterior chamber
  - visual acuity measured by LogMAR test
  - vitreous haze, and
  - grade of flare

  at Week 24 by each age group, in each affected eye.
- Number and proportion of patients with inactive anterior uveitis at Week 24 by each age group, in each affected eye.

Age group safety summaries may include

- AEs, including SAEs
- permanent discontinuation of investigational product due to AEs, and
- temporary interruption of investigational product.

10.3.7. Interim Analyses

Two interim analyses will be performed to potentially stop the study early due to futility when 10 and 20 baricitinib-treated patients have completed, or had the opportunity to complete, 24 weeks of treatment. At each interim analysis, the posterior probability of the treatment response rate being lower than 40% will be calculated, and the study will be stopped if this probability is greater than 75%.

The above Bayesian decision rules can be translated to correspond to the following:

- At the first interim analysis, the study will be stopped if 2 or fewer of the 10 baricitinib-treated patients are responders.
- If the study continues, at the second interim analysis, the study will be stopped if 6 or fewer of the 20 baricitinib-treated patients are responders.

A DMC will oversee the conduct of all the Phase 3 clinical studies evaluating baricitinib in patients with JIA, JIA-U, or ANA-positive uveitis. The DMC will consist of members external to Lilly. This DMC will follow the rules defined in the DMC charter, focusing on potential and identified risks for this molecule and for this class of compounds. Membership to the DMC will include, at a minimum, specialists with expertise in pediatrics, rheumatology, statistics, and other appropriate specialties. The DMC will review and evaluate planned interim analyses on an approximate semiannual basis. This DMC will be coordinated with the DMC(s) for other ongoing studies of baricitinib in other indications, and this coordination may alter the number and timing of the interim analyses.

Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Data that the DMC will review include, but are not limited to, study discontinuation data, AEs including SAEs, clinical laboratory data, vital signs data, and growth. The DMC may recommend continuation of the study as designed, temporary suspension of enrollment, or discontinuation of a particular dose regimen or discontinuation of the entire study. The DMC may request to review efficacy data to investigate the benefit/risk relationship in the context of safety observations for ongoing patients in the study. Details of the DMC and interim safety analyses will be documented in a DMC charter and DMC analysis plan.

Additional analyses and snapshots of study data may be performed to fulfill the need for regulatory interactions or publication purposes.

10.3.7.1. Adjudication Committee

A blinded Clinical Event Committee will adjudicate potential MACE (cardiovascular death, MI, stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization such as coronary artery bypass graft or percutaneous coronary intervention), ATE, VTEs, and noncardiovascular deaths. Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the charter.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ACPA	anti-citrullinated protein antibodies
ACR30	30% improvement in American College of Rheumatology criteria
active joint	Joint with swelling or, in the absence of swelling, limitation of motion accompanied by pain on motion and/or tenderness
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
ANA	anterior antinuclear antibody
ANC	absolute neutrophil count
APC	activated protein C
APTT	activated partial thromboplastin time
assent	Affirmative agreement of a child to participate in research or to undergo a medical intervention. Lack or absence of expression of dissent or objection must not be interpreted as assent. When obtaining child assent, relevant elements of informed consent should be provided appropriate to the child's capability to understand (ICH 2016).
AST	aspartate aminotransferase
ATE	arterial thromboembolic events
bDMARD	biologic disease-modifying antirheumatic drug
blinding/masking	A single-blind study is one in which investigators and/or staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but investigators and/or staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigators or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index

Term	Definition
CAP	College of American Pathologists
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CEC	clinical endpoints committee
CHAQ	Childhood Health Assessment Questionnaire
CHQ-PF50	Child Health Questionnaire-Parent Form 50
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DVT	deep vein thrombosis
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERA	enthesitis-related juvenile idiopathic arthritis
ERB	ethical review board

Term	Definition
ESR	erythrocyte sedimentation rate
ETV	early termination visit
EULAR	European League Against Rheumatism
GCP	good clinical practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen-B27
HRQOL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
Ig	immunoglobulin
IGF-1	insulin-like growth factor-1
IL	interleukin
ILAR	International League of Associations for Rheumatology
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Term	Definition
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
IOP	intraocular pressure
IR	inadequate response or intolerance
ITT	intent-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
JADAS	Juvenile Arthritis Disease Activity Score
JAK	Janus kinase
JIA	juvenile idiopathic arthritis
JIA-U	juvenile idiopathic arthritis-associated uveitis
JPsA	juvenile psoriatic arthritis
JSpADA	Juvenile Spondyloarthritis Disease Activity Index
LOCF	last observation carried forward
LOCS	Lens Opacities Classification Score
LogMAR	logarithm of the minimum angle of resolution
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent-to-treat: patients who take at least 1 age-based dose of investigational product in Part A of Study JAHU
MMR	measles, mumps, and rubella
mNRI	modified nonresponder imputation
MTX	methotrexate

Term	Definition
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
OAT3	organic anion transporter 3
OCT	optical coherence tomography
OLE	open-label extension
PASI	Psoriasis Area and Severity Index
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic(s)
PE	pulmonary embolism
PediACR	Pediatric American College of Rheumatology
PhS	Physical Summary Score
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PPD	purified protein derivative
PsS	Psychosocial Summary Score
Q2W	once every 2 weeks
QD	once daily
QW	once every week
RA	rheumatoid arthritis
RF	rheumatoid factor
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SmPC	summary of product characteristics
SPARCC	Spondyloarthritis Research Consortium of Canada

Term	Definition
STAT	signal transducer and activator of transcription
SUN	standardization of uveitis nomenclature
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin level
TDaP	tetanus, diphtheria, and pertussis
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, and does not necessarily have to have a causal relationship with this treatment.
TIBC	total iron-binding capacity
TNFα	tumor necrosis factor-alpha
TSH	thyroid-stimulating hormone
TYK2	tyrosine kinase 2
ULN	upper limit of normal
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic events
VZV	varicella zoster virus
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Hematology[a]	**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 (ALP)
Mean cell hemoglobin concentration	Alanine aminotransferase (ALT)
Leukocytes (WBC)	Aspartate aminotransferase (AST)
Platelets	Blood urea nitrogen (BUN)
Mean platelet volume	Creatinine
Absolute counts of:	Uric acid
Neutrophils, segmented	Calcium
Neutrophils, juvenile (bands)	Glucose
Lymphocytes	Albumin
Monocytes	Total protein
Eosinophils	Estimated glomerular filtration rate (eGFR)[c]
Basophils	Creatine phosphokinase (CPK)
Urinalysis[a,d]	**Other Tests**[a]
Color	Hepatitis B Surface antigen (HBsAg)[e]
Specific gravity	Hepatitis B Core antibody (HBcAb)[e]
pH	Hepatitis B Surface antibody (HBsAb)[e]
Protein	Hepatitis C antibody[e,f]
Glucose	HBV DNA[g]
Ketones	Human immunodeficiency virus (HIV)[e]
Bilirubin	HLA-B27
Urobilinogen	Thyroid-stimulating hormone (TSH)
Blood	Exploratory storage samples (RNA, serum, and plasma)
Leukocyte esterase	Pharmacogenetic Sample (DNA)
Nitrite	Pregnancy Test (serum)[h]
	Pregnancy Test (urine)[h]
Lipids[a,b]	High sensitivity C-reactive protein (hsCRP)
Total cholesterol	Rheumatoid factor
Low-density lipoprotein	QuantiFERON®-TB Gold or T-SPOT®.TB[i]
High-density lipoprotein	Purified protein derivative (PPD)[j]
Triglycerides	ACPA (Anti-CCP)
	ESR (sponsor-provided; assayed by clinical study site)
	Iron studies (iron, TIBC and ferritin)
	Immunoglobulins (IgG, IgA, and IgM)
	Lymphocyte subsets (T, B, NK, and T-cell subsets)[j]
	Antinuclear antibodies
	IGF-1
	IGFBP-3
	Gonadal hormone (estradiol for females aged 8 to <18 years,

testosterone for males aged 8 to <18 years)

Abbreviations: DNA = deoxyribonucleic acid; ESR = erythrocyte sedimentation rate; HCV = hepatitis C virus; HBV = hepatitis B virus; HLA-B27 = human leukocyte antigen-B27; Ig = immunoglobulin; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor-binding protein-3; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; TIBC = total iron-binding capacity; WBC = white blood cell.

[a] Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.

[b] Fasting laboratory values for lipids will be required as per Schedule of Activities (Section 2). Patients should not eat or drink anything except water for 4-12 hours depending on weight and age as specified below. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Recommended fasting times by age and weight are as follows:

- Patients ≥12 years: fast for 12 hours prior to laboratory test
- Patients 8 to <12 years and weighing >50 kg: fast for 12 hours prior to laboratory test
- Patients 8 to <12 years and weighing ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 25 to ≤50 kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 10 to <25 kg: fast for 6 hours prior to laboratory test
- Children <8 years and weighing <10 kg: fast for 4 hours prior to laboratory test

[c] eGFR calculated by Bedside Schwartz 2009 formula.

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

[e] Test required at Visit 1 only to determine eligibility of patient for the study.

[f] A positive hepatitis C antibody result will be confirmed with presence of HCV RNA.

[g] HBV DNA testing will be done in those patients who are HBcAb+ at screening. For patients who are positive for HBcAb, a follow-up test for HBV DNA is required. Patients with a positive HBcAb will return to the site and have HBV DNA samples drawn, which will be processed centrally. Any enrolled patient who is HBcAb positive, regardless of HBsAb status or level, must undergo HBV DNA testing per the schedule.

[h] Serum pregnancy test for all females of appropriate age who are of child-bearing potential at screening only and will be performed centrally; after screening, urine pregnancy test will be performed locally for females of child-bearing potential.

[i] In countries where the QuantiFERON®-TB Gold test or T-SPOT® is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT® must be performed locally.

[j] Test results of lymphocyte subsets will be blinded after Week 12, and the test results will not be sent to the study sites.

Note: Due to blood volume restrictions, some laboratory tests may not be collected. Laboratory samples are recommended to be collected as described in a sponsor-provided weight-based prioritization chart.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for the following:

- Ensuring that the patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- Ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) and Assent Form per local requirements prior to the performance of any protocol procedures and prior to the administration of investigational product.
- Answering any questions the patient/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the willingness of the patient/patient's legal representative to continue his or her participation in the study.
- Ensuring that a copy of the ICF and Assent Form 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 and Assent Form (as applicable).
- Adequate informed consent for continued participation from pediatric participants once a child reaches the age of legal consent.
- Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Appendix 3.1.2. Recruitment

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

Appendix 3.1.3. Ethical Review

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

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

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

- protocol and related amendments and addenda, current Investigator's Brochure (IB) and updates during the course of the study
- Informed Consent Form and Assent Form
- other relevant documents (e.g., curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

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

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

Appendix 3.1.5. Investigator Information

Physicians with a specialty in pediatric rheumatology and ophthalmology (pediatric rheumatologist or other medically qualified physician) will participate as investigators in this clinical study.

Appendix 3.1.6. Protocol Signatures

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

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

Appendix 3.1.7. Final Report Signature

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

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

Appendix 3.2. Data Quality Assurance

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

- Provide instructional material to the study sites, as appropriate
- Provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax, and
- Review and verify data reported to detect potential errors.

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

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

Appendix 3.2.1. Data Protection and Data Capture System

Data protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor, will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration, or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

Data capture system

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (questionnaires, scales) will be collected by the patient/caregiver/investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Additionally, electronic Clinical Outcome Assessment (eCOA) data (questionnaires, scales) will be directly recorded by the patient/caregiver/investigator site personnel into an instrument. The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) will be stored at a third-party (at third parties). The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor (e.g., laboratory test data) will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy and Dissemination of Clinical Study Data

Publication policy

The publication policy for Study I4V-MC-JAHW is described in the Clinical Study Agreement.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

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 Lilly, its designee, or the clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
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	**Anti-smooth muscle antibody**
CPK	
	Alkaline phosphatase isoenzymes[a]
	Anti-Actin[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

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

Liver Function Testing and Hepatic Safety Monitoring

Analyte	Exclusion Criteria	Additional Hepatic Testing	Hepatic eCRF Reporting	Temporary Interruption of Investigational Product	Permanent Discontinuation of Investigational Product after Consultation with the Lilly Designated Medical Monitor
Protocol Section	Section 6.2	Section 9.4.5	Section 9.4.5	Section 8.1.1	Section 8.1.2
ALT/AST	≥2 x ULN	ALT ≥3 x ULN	ALT ≥5 x ULN on ≥2 consecutive tests	>5 x ULN	• >8 x ULN • >5 x ULN for >2 weeks after temporary interruption of investigational product • >3 x ULN and TBL >2 x ULN or INR >1.5 • >3 x ULN with symptoms[a]
ALP	≥2 x ULN	≥2 x ULN	≥2 x ULN on ≥2 consecutive tests	N/A	• >3 x ULN • >2.5 x ULN and TBL >2 x ULN • >2.5 x ULN with symptoms[a]
TBL	≥1.5 x ULN	≥2 x ULN	≥2 x ULN on ≥2 consecutive tests (excluding Gilbert's syndrome)	N/A	• ALT or AST >3 x ULN and TBL >2 x ULN • ALP >2.5 x ULN and TBL >2 x ULN

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

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

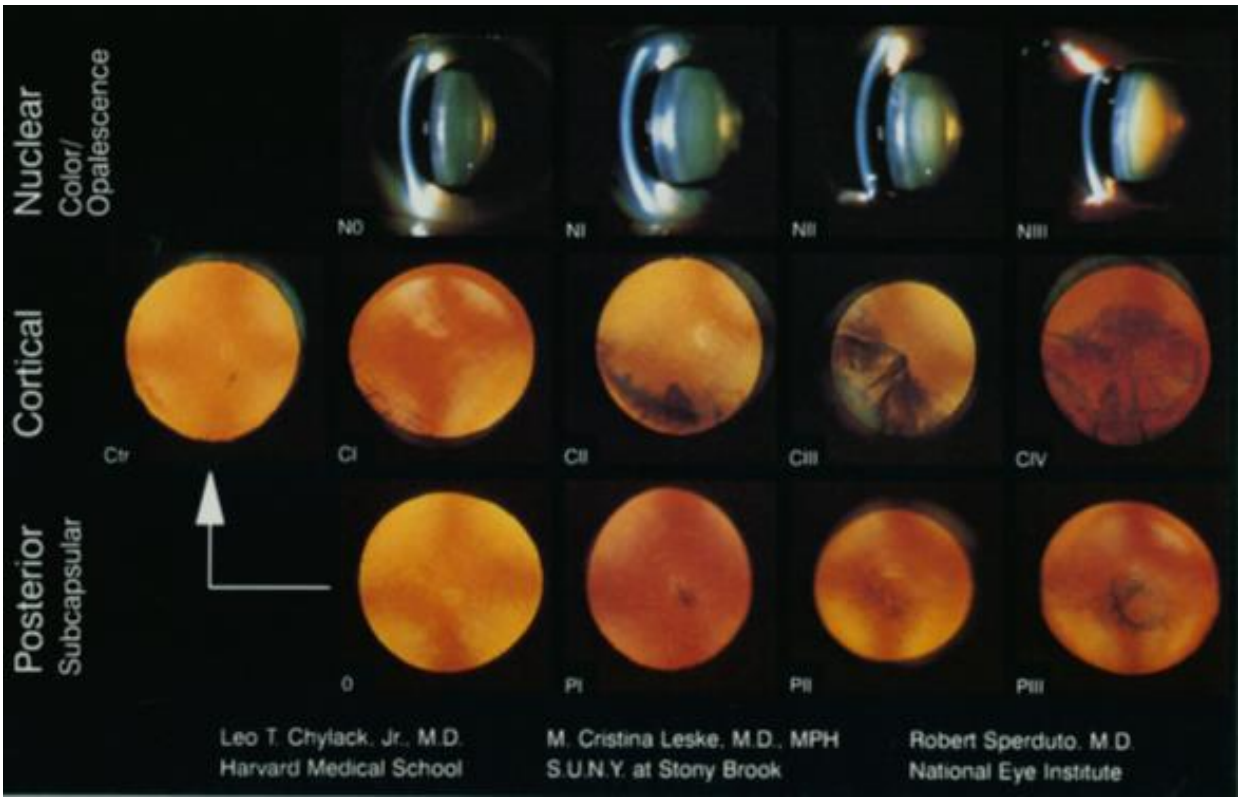
Appendix 5. Monitoring Tests for Confirmed VTE

Selected tests may be obtained in the event of a confirmed venous thromboembolic event (VTE) and may be required in follow-up with patients in consultation with Eli Lilly and Company, its designee, or the clinical research physician. The choice and optimal timing of these tests will be directed by the patient's management and may require ongoing follow-up after study discontinuation.

Protein C Functional
Protein S Clottable
Antithrombin III
APC Resistance
PT
APTT
Fibrinogen
Cardiolipin Antibodies
PT Gene
Factor VIII C Assay
Hexagonal Phase Phospholipid Neutralization
C-Reactive Protein
PTT Incubated Mixing
Dilute Russell Viper Venom
Platelet Neutralization
Factor V Leiden
MTHFR
Thrombin Time
Reptilase
Fibrinogen Antigen
Protein C Immunologic
Protein S Immunologic
Heparin fXa Inhibition

Abbreviations: APC = activated protein C; APTT = activated partial thromboplastin time; MTHFR = methylene tetrahydrofolate reductase; PT = prothrombin time; PTT = partial thromboplastin time.

Appendix 6. LOCS II Standards for Grading Cataracts



From Chylack et al. 1989.

Appendix 7. Weight-Based Prioritization Chart for Blood Sampling

Patients with a body weight lower than 25 kg will have a lower volume of blood taken, as certain tests will be excluded. The weight based prioritization chart shown below is recommended to be followed for Study JAHW. Lilly also recommends that purified protein derivative is used for tuberculosis testing instead of Quantiferon Gold or T-Spot in patients whose body weight is <18 kg.

Weight-Based Prioritization Chart for Blood Sampling

Weight	Excluded Testing – will not be collected
≥25 kg	N/A
≥18 to <25 kg	• Long-term storage samples at V2, V5, V8, and V30: RNA, serum, and plasma
<18 kg	• Long-term storage samples: RNA, serum, and plasma • Testosterone or estradiol • Flow cytometry

Abbreviations: N/A = not applicable; RNA = ribonucleic acid; V = visit.

Appendix 8. Data-based Dosing Cohorts

The dose selection for baricitinib in this patient population is informed by the Phases 2 and 3 data in adults with RA, which demonstrated a positive benefit/risk profile for the 4-mg QD dose. The PK of baricitinib in pediatric patients with JIA will be investigated in Study I4V-MC-JAHV (JAHV), and the doses selected in this study will also be used in Study JAHW.

Current JAHV data on age-based cohorts

Ages 12 to<18

The PK data from the 8 pediatric patients aged 12 to <18 years support continued dosing with the 4-mg QD dose of baricitinib in patients with JIA or JIA-uveitis. These data confirmed the recommended baricitinib dose of 4 mg QD for pediatric patients with JIA or JIA-uveitis aged 12 to <18 years.

Ages 6 to <12

The PK and safety data from the 8 pediatric patients aged 9 to <12 years support continued dosing with the 4-mg QD dose of baricitinib in patients with JIA, JIA-uveitis, or ANA positive uveitis in this age group. The observed concentrations of baricitinib in the middle age group (9 to <12 years old) were consistent with:

- the anticipated efficacious exposure level in adult patients with RA receiving baricitinib 4 mg QD,
- model-predicted mean concentrations in pediatric patients aged 9 to <12 years with JIA receiving baricitinib 4 mg QD.

The population of patients recruited at global investigative sites did not include any patients 6 to <9 years of age. The PBPK prediction suggested that a dose of 2 mg QD is likely to produce exposure in this age group more aligned with the mean adult exposure.

Next Steps for Study JAHW

An updated summary of dosing for Study JAHW is provided in the table below.

Lilly has initiated the following for Study JAHV to confirm dosing:

- Lilly has enrolled the cohort aged 6 to <9 years in the PK cohort in JAHV to receive a dose of 2 mg baricitinib in order to conduct a safety/PK analysis and to confirm the dose for this age group.
- Once the PK analysis is completed in the patients aged 6 to <9 years in JAHV, the PBPK model will be updated accordingly for the patients aged 2 to <6 years (the youngest age cohort) to verify the appropriate starting dose for the safety/PK evaluation. These patients will proceed into the Open-Label Lead-In period after the safety/PK assessment.

Updated Study JAHW Dosing Summary

Age Group	Baricitinib Dose
12 to <18 years old	4 mg
9 to <12 years old	4 mg
6 to <9 years old	2 mg (based on predicted data – to be confirmed with observed data)
2 to <6 years old	2 mg[a]

Abbreviations: OLLI = open-label lead-in; PK = pharmacokinetic; QD = once daily.

[a] To be confirmed after evaluating data from patients aged 6 to <9 years.

Appendix 9. Provisions for Changes in Study Conduct During Exceptional Circumstances

There may be times of exceptional circumstances, such as pandemics or natural disasters, which may cause disruptions to the conduct of the study. Possible disruptions are limitations in the ability to conduct study procedures or ability to have on-site visits occur by participants.

To mitigate the risk of participants missing visits, to allow participants to safely continue in the study, and to maintain the data integrity of the study in the case of an exceptional circumstance, **sites may implement changes to the conduct of the study on a case-by-case basis following sponsor's written approval (if permitted by local regulations).** Good Clinical Practice compliance and minimization of risks to study integrity are important considerations. Ensuring the safety of study participants is the prevailing consideration.

Additional written guidance will be provided by the sponsor in the event written approval is granted for changes in study conduct.

The following changes in study conduct captured in this appendix will not be considered protocol deviations. Missing data will be captured as protocol deviation(s).

1. **Remote visit (telephone/telemedicine)**

Telephone or technology-assisted virtual visits (telemedicine) to complete appropriate assessments are acceptable if in-person site visits are not possible. 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 in source document and eCRF. The site must discuss with the patient and ensure consent to the proposed remote operational plan. This communication should be documented in the patient's records.

Examples of assessments that may be completed via telephone/telemedicine visit include the following:

- AEs and product complaints
- concomitant medications
- review of study participant diary (including study drug compliance)

2. **Remote Assessment and Data Collection**

Patient visit and data collection can be done remotely for treatment period A and treatment period B. The PI/Sub-I is to document all teleconferences/remote visits in the patient's records. Site facing assessments can be completed on paper (preferably eCOA if the site is able) and patient facing assessments will be conducted in interview format with the qualified personnel documenting the patient's responses on paper. Sponsor will provide guidance for performing these assessments (CHQ-PF50, EQ-5D). For ophthalmology assessments, PI should direct patient care based on symptom-directed physical examination. Ophthalmology assessments are required to be completed every 8 weeks.

3. Investigational product and ancillary supplies

In cases when a patient is unable to come to site to receive trial supplies during a normal on-site visit, the site should work with the sponsor to determine appropriate actions to receive trial supplies. This may include a participant coming to the site to receive trial supplies only from site staff without full completion of a visit, a participant-approved designee coming to the site to receive trial supplies on a participant's behalf, or delivery to a participant's home.

The following requirements must be met:

- sponsor approves the alternative method of delivery, taking local regulatory requirements into consideration
- participant consents to alternate method of delivery as defined by local regulations
- 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.
- when delivering supplies to a patient's home:
    - participant consent must include provision of any personal information
    - site should ensure oversight of the shipping process to ensure accountability and product quality (i.e., storage conditions and intact packaging upon receipt)
- additional instructions should be provided to the participant on how to return any unused or completed trial supplies.

4. Local laboratory option

In exceptional circumstances, to ensure patient safety and with the sponsor's prior written approval, local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with local regulations. Clinically significant laboratory findings must be recorded as an adverse event in the AE eCRF.

For patients unable to access investigator sites, laboratory testing will be obtained and collected at least every 8 weeks in treatment period A and every 12 weeks in treatment period B. The first collection should be 8 weeks or 12 weeks, respectively, from the patient's last collected central laboratory samples.

When collecting local labs, sites should store records from the labs including results, address, certification (College of American Pathologists/Clinical Laboratory Improvement Amendments, [CAP/CLIA]) status, and reference ranges. The PI/Sub-I should sign and date review of local labs per normal process and follow-up with the patient as needed. Local labs may be sent to the patient as this is standard process in clinical care.

The laboratory measures listed below are the **minimum** required in order to monitor patient safety and determine temporary or permanent discontinuation of IP. Additionally, investigators should include any symptom-based laboratory testing based on their interactions with their patients. As stated in the protocol, investigators are responsible for monitoring the overall health of their patients.

The investigators should request the following laboratory analyses:

- WBC
- ANC
- Lymphocyte count
- Platelet count
- Hemoglobin
- ALT, AST, total bilirubin, INR
- ESR
- Urine pregnancy

These laboratory results will allow the investigators to follow both the temporary and permanent discontinuation criteria as provided in the protocol (Section 8.1.1, Temporary Interruption of Investigational Product and Section 8.1.2, Permanent Discontinuation from Investigational Product).

5. Documentation

a. Changes to study conduct

Changes to study conduct will be documented as the following:

- Sites will need to identify and document the details of how all participants, visits, methods, and activities conducted were affected by exceptional circumstances. All dispensing/shipment records of IP and relevant communications, including delegation, should be filed with site trial records.
- The site should document the participant's consent for having remote visits and remote dispensing of IP, ancillaries, and diaries, prior to implementation of these activities.
- Source document(s) that are generated at participant's home should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

b. Missing data and other protocol deviations

The study site should capture specific explanations for any missing data and other protocol deviations in source documents and eCRF. While protocol deviations may be unavoidable in an

exceptional circumstance, documentation of deviations and missing data will be important for data analysis and reporting.

Details of changes in analyses to specifically accommodate exceptional circumstances will be further described in the study SAP.

6. Informing ethical review boards (ERBs)

The sponsor and study investigators will notify ERBs as soon as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study participants, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation.

Appendix 10. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [d]: 07-Nov-2020

Overall Rationale for the Amendment

The overall changes and rationale for the changes made to this protocol are described in the following table. Editorial revisions with no impact on protocol design or implementation were also made. These revisions are not noted in this protocol amendment summary except where contained in a section with substantive changes.

Amendment Summary for Protocol I4V-MC-JAHW Amendment (d)

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis Section 4. Objectives and Endpoints	Addition of footnote for endpoints in Secondary Part A	Clarification of response definition for Secondary Endpoints related to bilateral uveitis disease SUN criteria.
Section 2. Schedule of Activities Appendix 9. Provisions for Changes in Study Conduct During Exceptional Circumstances	Addition of provisional language for participation in the study during exceptional circumstances such as the COVID-19 pandemic	This language and appendix describe the types of changes to study conduct that will be possible during exceptional circumstances. These changes to study conduct will only be implemented with approval from the sponsor and if permitted by local regulations.
Section 2. Schedule of Activities Section 9.4.6.3. Tanner Stage Scale Section 11. References	Addition of baseline Tanner Staging Scale	Baseline assessment of sexual maturity (Tanner Staging) was included based on feedback from regulatory agencies.
Section 2. Schedule of Activities	Addition of x-ray procedure	Imaging procedures were included or increased in frequency based on feedback from regulatory agencies for additional monitoring of bone growth and assessment of symptomatic areas of bones/joints.
	Height measurements were added for all study visits	The additional measurements for height were added for additional growth monitoring.
	• Height schedule changed to Initial Protocol design • Added Weight in V1 Screening • Adjusted footnote f in Table JAWH.1. to include imaging requirements and specify ± timing for	• Error in previous amendment. • For Clarity. *Only applicable if Amendment (c) is in effect. These changes are not present in Amendment (b).

	consent/assents • Removed positioning wording "AP" for hand and knee X-rays in both column cell and footnote f • Adjusted footnote d in Table JAWH.2. to include imaging requirements and specify ± timing for consent/assents	
5.1. Overall Design, Figure JAHW.1	Updated study figure in Treatment Period Part B (OLE) with change from 96 to 74 weeks for adalimumab	Study figure was updated to clarify number of weeks on adalimumab during Treatment Period Part B (OLE).
5.5. Justification of Dose	Updated Cohorts	For Clarity. *Only applicable if Amendment (c) is in effect. These changes are not present in Amendment (b).
5.5. Justification for Dose 7.1. Treatments Administered 7.2. Method of Treatment Assignment 7.2.1. Selection and Timing of Doses	Addition of language to reference Appendix 8 for dosing guidance	Dosing was updated per protocol requirement after PK analysis of study JAHV.
7.2. Method of Treatment Assignment 7.2.1. Selection and Timing of Doses 7.4 Dosage Modification	Updated Cohorts	For Clarity. *Only applicable if Amendment (c) is in effect. These changes are not present in Amendment (b).
8.1.3. Discontinuation of Inadvertently Enrolled Patients	Addition of Lilly template language	Clarification of discontinuation of inadvertently enrolled participants and safety follow-up. *Only applicable if Amendment C is in effect.
9.4.6.2. Growth Monitoring	• Addition of language related to height measurement • Added screening	• Specification of stadiometer as device to be used for height measurement. • Error in previous amendment. *Only applicable if Amendment (c) is in effect. These changes are not present in Amendment (b).
	Addition of language on x-rays and country specific addenda	Guidance on previous country specific addenda containing additional imaging.
Appendix 2. Clinical Laboratory Tests	Removal of footnote in table for hsCRP	Clarification to sites of unblinding of test results for hsCRP.

Appendix 8. Data-based Dosing Cohorts	• Addition of Appendix 8 related to data-based dosing cohorts • Updated enrollment Status	• Dosing was updated per protocol requirement after PK analysis of study JAHV. • For Clarity. *Only applicable if Amendment (c) is in effect. These changes are not present in Amendment (b).
Appendix 9. Provisions for Changes in Study Conduct During Exceptional Circumstances	• Added collection period of 12 weeks • Removed C-SRRS assessments • Laboratory collections adjusted	• For clarity. • Not applicable. • For clarity. *Only applicable if Amendment (c) is in effect. These changes are not present in Amendment (b).

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