Statistical Analysis Plan Version 2 I4V-MC-JAHW

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

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1. Statistical Analysis Plan: I4V-MC-JAHW: 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

Baricitinib (LY3009104) Juvenile Idiopathic Arthritis-Associated Uveitis or Chronic Anterior Antinuclear Antibody-Positive Uveitis

Study I4V-MC-JAHW (JAHW) is a Phase 3, multicenter, randomized, open-label, parallel, active-controlled study of Baricitinib in patients with Active Juvenile Idiopathic Arthritis-Associated Uveitis or Chronic Anterior Antinuclear Antibody-Positive Uveitis.

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Protocol I4V-MC-JAHW
Phase 3

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3. Revision History

Version 1 of Statistical Analysis Plan (SAP) for Study I4V-MC-JAHW (JAHW) was approved on 16 August 2019 prior to the first patient visit.

Version 2 of SAP JAHW was updated to reflect recent modifications to the Study Protocol based on the EU Paediatric Investigation Plan (PIP) endorsed by the European Medicines Agency Paediatric Committee EMEA-001220-PIP01-11-M08.

Table JAHW.3.1. SAP Version History Summary

Section # and Name	Description of Change	Brief Rationale
Section 4.1. Primary Objective	Updated the primary estimand to include definition specific to the primary variable of interest.	The section is dedicated to the primary objective alone.
Section 4.2 . Secondary Objective	Updated the treatment period Part B details to align is per the latest protocol amendment	As per PIP and Protocol Amendment (e)
Table 4.2	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 and Protocol Amendment (e)
Section 4.3	Removed	As per PIP and Protocol Amendment (e)
Section 5.1. Overall Design	Updated the Study Schema diagram as per the latest protocol Information about overall design added for better clarity	As per PIP and Protocol Amendment (e)

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Determination of Sample Size	Updated the total number of participants for baricitinib and adalimumab arms	As per PIP and Protocol Amendment (e)
Section 5.3. Method of Assignment to treatment	Updated the number of participants to be evaluated for the primary endpoint	As per PIP and Protocol Amendment (e)
Section 6.1.3 Analysis Methods	Removed the line "If the study continues, at the final analysis, the study objective will be successfully met (i.e. a positive study) if at least 20 of the 30 patients are responders."	As per PIP and Protocol Amendment (e)
6.3.Handling of Dropouts or Missing Data	Updated the scope of Modified Non Responder Imputation to only include for primary objective Added Section 6.3.2 Non Responder Imputation method for categorical variables other primary variable.	As per CEC adjudication recommendation
Table JAHW.6.2. Patient Characteristics	Added Prior bDMARD usage Removed the characteristics that were not a part of the previous safety reviews conducted for the study.	
Table 7.1 Secondary Efficacy Endpoint Analyses for Part A	Removed the variables in Table 7.1 as per the changes in Secondary Objectives Section 4.	As per PIP and Protocol Amendment (e)
Table JAHW.8.7. Summary Tables Related to Hematologic Changes	Removed "Listing of patients with treatment-emergent thrombocytosis"	No requirement for this output because of less/no data to display

4. Study Objectives

4.1. Primary Objective

The primary objective of Study JAHW is shown in Table JAHW.4.1.

Table JAHW.4.1. Primary Objective and Endpoint

Objectives	Endpoints
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 0 through Week 24, in the eye most severely affected at baseline.

Abbreviations: JIA-U = juvenile idiopathic arthritis-associated uveitis; SUN = Standardization of Uveitis Nomenclature; ANA = antinuclear antibody.

In compliance with the International Conference on Harmonisation (ICH) E9(R1) guidelines, a study should be clear in defining an estimand framework, which includes 4 attributes:

the population of interest: the patients targeted by the scientific question;
the variable (or endpoint) of evaluation that is obtained for each patient, that is required to address the scientific question;
the population-level summary of the variable, a basis for treatment evaluation; and
the specification of how to account for intercurrent events to reflect the scientific question of interest.

In particular, for Study JAHW, the primary estimand is defined by

Population of interest: the population of interest for Part A of Study JAHW is patients who participate in Study JAHW Part A. Study JAHW patients are patients from 2 years to <18 years old with active juvenile idiopathic arthritis-associated uveitis (JIA-U), or chronic anterior antinuclear antibody (ANA)-positive uveitis. Analysis populations are defined in Section 6.1.1.
Variable (or endpoint) of evaluation: the primary endpoint/variable is listed in Table JAHW.4.1.
Population-level summary: the primary quantity of interest will be the proportion of responders on baricitinib. Details are given in Section 6.7.
Intercurrent event(s) strategy: in Study JAHW Part A, the analysis population will be based on patients who have had, or would have, the chance to complete the visits. In the estimand framework for binary variables, the composite estimand strategy will be applied and modified non-responder imputation will be used for the primary outcome variable (that is, the proportion of responders at Week 24, where response is defined according to the Standardization of Uveitis Nomenclature [SUN] criteria as a 2-step decrease in the

level of inflammation, or a decrease to zero in the eye most severely affected at baseline) to support this strategy.

4.2. Secondary Objectives

The secondary objectives of Study JAHW are grouped according to 2 periods defined in the study design:

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

Baricitinib patients who complete Part A may continue to Part B, the open-label extension (OLE) period of Study JAHW. 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.

In particular, for Study JAHW, the secondary estimand is defined by

Population of interest: the population of interest for Part A of Study JAHW is patients who participate in Study JAHW Part A. The population of interest for Part B is patients who stay in Study JAHW Part B. Study JAHW patients are patients from 2 years to <18 years old with active JIA-U or chronic anterior ANA-positive uveitis. Analysis populations are defined in Section 6.1.1.
Variable (or endpoint) of evaluation: primary and secondary endpoints/variables are listed in Table JAHW.4.1 and Table JAHW.4.2. A full list of endpoints and variables is given in Table JAHW.7.1 and Table JAHW.7.2.
Population-level summary: the summary measure for binary variables will be proportion and the summary measure for continuous variables will be the average.
Intercurrent event(s) strategy: in Study JAHW Part A, for efficacy and health outcomes-related endpoints, the analysis population will be based on patients who have had the chance to complete the visits. In the estimand framework, for binary variables other than the primary outcome variable, the composite estimand strategy will be applied; nonresponder imputation will be applied to variables to support this strategy. The while-on-treatment strategy will be used for continuous variables, and last observation carried forward (LOCF) imputation will be used to support this strategy. For Part B, the analysis population will be based on completers for the specific analysis visit, and this method is referred as the as-observed analysis. The details of the imputation methods for the estimand and intercurrent events are described in Section 6.3. Statistical methods corresponding to each of the efficacy and health outcomes variables are summarized in Table JAHW.7.1, Table JAHW.7.3, Table JAHW.7.3, and Table JAHW.7.4.

The secondary objectives of Study JAHW are described in Table JAHW.4.2.

Table JAHW.4.2. Secondary Objective and Endpoint

Objectives	Endpoints
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 the SUN grade of cells in the anterior chamber through Week 24 in the most severely affected eye Change in the 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. 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 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

Objectives	Endpoints
To evaluate the safety of baricitinib in children with JIA-U or ANA-positive uveitis	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) Adverse events including serious AEs 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	Number of responders at 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 0 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 at 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 patients with inactive anterior uveitis (using SUN definition) in each affected eye through Week 284 Time to inactive anterior uveitis disease (using SUN definition) in each affected eye Number of patients who are able to taper concomitant topical corticosteroids to <2 drops per day and to 0 drops per day. Proportion 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 AEs Permanent discontinuation of investigational product due to AE Temporary interruption of investigational product

Abbreviations: AE = adverse event; ANA = antinuclear antibody; JIA-U = juvenile idiopathic arthritis-associated uveitis; LogMAR = logarithm of the minimum angle of resolution; PediACR = Pediatric American College of Rheumatology; SUN = Standardization of Uveitis Nomenclature.

5. Study Design

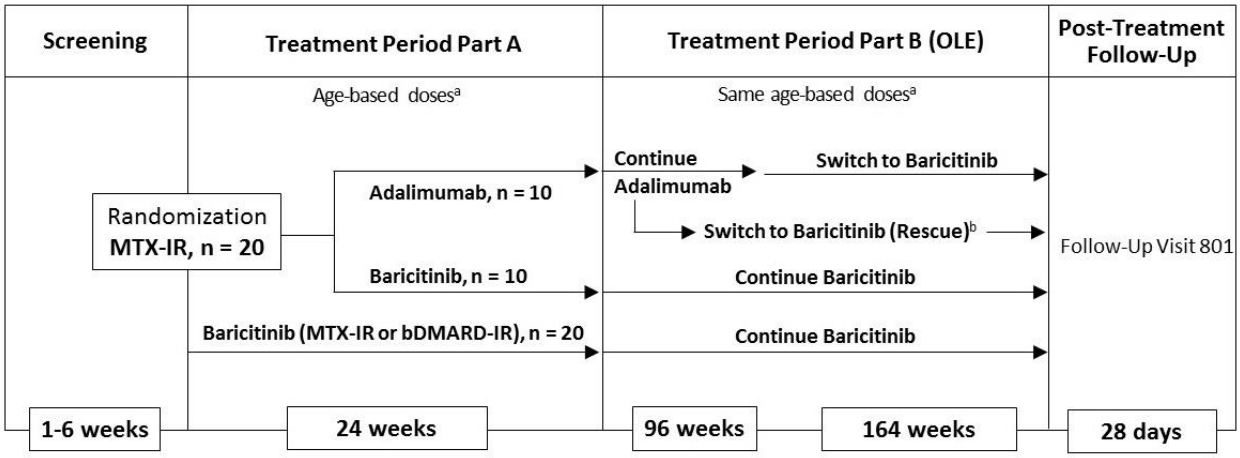
5.1. Summary of Study Design

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 methotrexate (MTX). Study JAHW will be conducted in 2 parts. Part A will include the screening period and treatment period (open-label treatment) with baricitinib and adalimumab up to Week 24. Part B (the OLE) will provide treatment for up to 5 years after Part A.

In the original Study JAHW design (Figure JAHW 5.1), patients who received baricitinib during Part A continued to receive baricitinib during Part B. Patients who received 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, Protocol JAHW and the study design have been modified (Figure JAHW.5.2). Patients currently assigned to baricitinib who have completed the primary endpoint as a responder will continue receiving baricitinib until the end of Study JAHW, or discontinuation from the study. The 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 Study JAHW after Week 24.

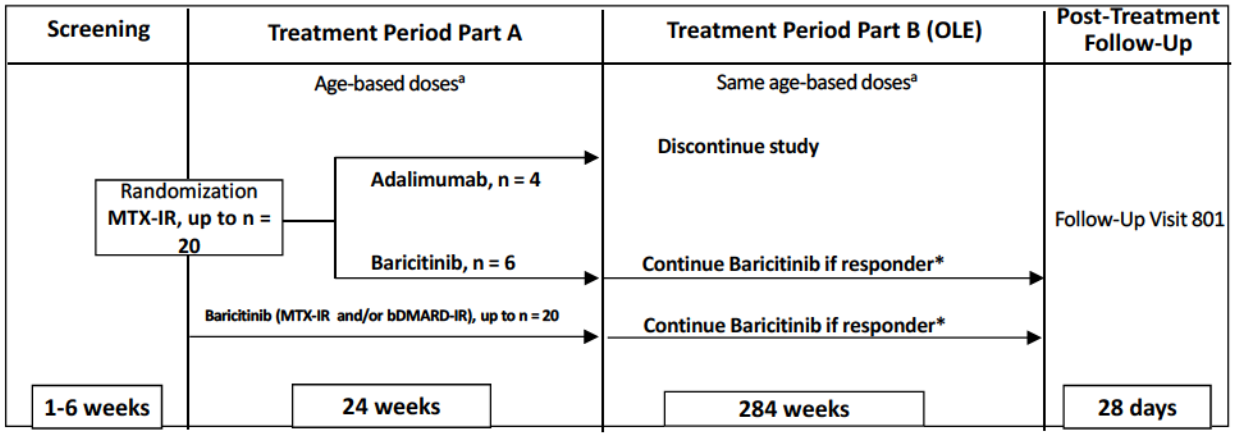
Figure JAHW 5.1 illustrates the study design from the previous amendment (d).



Abbreviations: bDMARD = biologic disease-modifying antirheumatic drug; IR = inadequate response or intolerance to; MTX = methotrexate; n = number of patients; 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.

Figure JAHW 5.1 Study design for Clinical Protocol I4V-MC-JAHW (d).

Figure JAHW.5.2 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.
* 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.

Figure JAHW.5.2. Study design for Clinical Protocol I4V-MC-JAHW (e).

5.2. Determination of Sample Size

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-inadequate response [IR] and biologic disease-modifying antirheumatic [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 CCI , Study JAHW will be able to detect a true baricitinib treatment response rate of >CCI with >CCI probability. The observed response rate of CCI is based on the assumption that 20 out of 30 patients in the baricitinib arm will achieve the primary endpoint. CCI [redacted]

Since the original sample size was determined, Study JAHW 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.

5.3. Method of Assignment to Treatment

Patients will receive the final age-based dose of baricitinib selected in the pharmacokinetic (PK) assessment period of Study JAHV (Section 5.3.1). Pharmacokinetic data from Study JAHV will be provided by age cohort (12 to <18 years, 6 to <12 years, and 2 to <6 years). 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 the 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.

5.3.1. 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 PK modeling, this is expected to be 4 mg for patients ≥6 to <18 years of age and 2 mg for patients <6 years of age, in order to produce exposures similar to those in adults after 4-mg once-daily (QD) administration.

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 summary of product characteristics [SmPC]).

6. A Priori Statistical Methods

6.1. General Considerations

This plan describes *a priori* statistical analyses for efficacy, health outcomes, and safety that will be performed.

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly). The statistical analyses will be performed using SAS® Version 9.4 or a more recent version.

Not all displays described in this SAP will necessarily be included in the clinical study report (CSR). Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in this SAP and not included in the CSR would be available upon request.

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 0 in the eye most severely affected at baseline, measured by the SUN criteria (Jabs et al. 2005). CCI [redacted]

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 "less severely affected eye" and "more severely affected eye" are defined by the baseline SUN grade for each patient with a higher SUN grade indicating more severity.

Efficacy and health outcomes 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 (SD), minimum, maximum, and median. Categorical data will be summarized as frequency counts and percentages.

All safety data will be descriptively summarized.

6.1.1. Analysis Populations

For purposes of analysis, the following populations are defined as shown in Table JAHW.6.1.

Table JAHW.6.1. Treatment Period Populations

Population	Description
Modified Intent-to-Treat population	The mITT population is defined as patients who take at least 1 dose of investigational product in part A.
As-observed population	The as-observed population is defined as the patients who complete the analysis visit as scheduled in part B.
Safety population	The safety population is defined as all patients who receive at least 1 dose of investigational product and who do not discontinue from the study for the reason 'Lost to Follow-up' at the first postbaseline visit.

Abbreviation: mITT = modified intent to treat.

Unless otherwise specified, the efficacy and health outcomes analyses will be conducted on the modified intent-to-treat (mITT) analysis set in Part A. For the efficacy and health outcomes analyses in Part B, the analyses will be conducted on as-observed data. Safety analyses will be carried out on the safety population.

In the rare situation where a patient is lost to follow-up at the first postbaseline visit but some safety data exist (e.g., unscheduled laboratory assessments) after the first dose of study drug, a listing of the data or a patient profile will be provided.

6.1.2. Definition of Baseline and Postbaseline Measures

Baseline

The baseline for change from baseline endpoints will be the baseline of Treatment Period Part A (visit at which the patient receives the first dose of investigational product).

Postbaseline

Postbaseline measurements are collected after the study drug administration.

6.1.3. Analysis Methods

The primary analysis is to evaluate efficacy of baricitinib in patients with active JIA-U or chronic ANA-positive uveitis. 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 0 in the eye most severely affected at baseline.

Bayesian posterior probability analysis will be used as the primary analysis for Study JAHW Part A. Bayesian analyses will be conducted both at interim and the end of Study JAHW (if the study is not stopped earlier).

Two interim analyses will be performed to potentially stop Study JAHW early due to futility when 10 and 20 patients have completed 24 weeks of treatment, respectively. CCI

[redacted]

CCI [redacted]

Given the proposed overall sample size and timing of interim analyses, the above Bayesian decision rules can be translated to correspond to the following:

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

All safety data will be descriptively summarized by treatment groups and analyzed using the safety population. Vital signs, body weight, and other safety variables, including laboratory variables, will be summarized by treatment groups.

Efficacy and health outcomes endpoints will be presented per Table JAHW.7.1 and Table JAHW.7.3.

6.2. Adjustments for Covariates

No statistical inference based on hypothesis testing is planned. Thus, there is no need to adjust for covariates.

6.3. Handling of Dropouts or Missing Data

Intercurrent events (ICH E9[R1]) are events which occur after the treatment initiation and preclude observation of a variable or affect how it should be interpreted. Examples of such events include treatment discontinuation due to death or adverse events (AEs) and loss to follow-up. This section describes 3 missing data imputation methods for handling intercurrent events. Part A utilizes modified nonresponder imputation (mNRI) and nonresponder imputation (NRI) for categorical variables and LOCF for continuous variables. As-observed analysis is used in Part B, thus the patient analysis in Part B will be based on completer of analysis visit only; no missing data imputation method will be applied for Part B.

6.3.1. Modified Nonresponder Imputation (mNRI)

An mNRI method can be justified based on the composite strategy (ICH E9[R1]) for handling intercurrent events. In a composite strategy with 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 makes them a nonresponder.

For Study JAHW, this definition is modified such that, if either one of (i) or (ii) criteria fails, the patient data will be reviewed by the Clinical Endpoints Committee (CEC) for further responder evaluation.

The primary efficacy outcome variable, that is, the proportion of responders at Week 24 where 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, will be imputed using mNRI. Patients will be considered a nonresponder for the mNRI analysis if they do not meet the clinical response criteria or are entirely missing the visit at the analysis time due to lack of efficacy. If the primary efficacy outcome variable data are missing for reasons other than this, available preceding data from patients with missing data will be reviewed by an independent and external 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.

6.3.1.1. Nonresponder Imputation (NRI)

An NRI imputation method can be justified based on the composite strategy (ICH E9R1) for handling intercurrent events. In a composite strategy with 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 variables, excluding the primary outcome variable, 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.

6.3.2. Last Observation Carried Forward (LOCF)

According to ICH E9(R1), the while-on-treatment strategy could be applied based on the last postbaseline value at or before the visit of interest while the patient was still on the study drug.

All continuous endpoints will be imputed using the LOCF methodology after censoring those who discontinued the study drug. For patients who permanently discontinue study treatment or discontinue from Study JAHW for any reason at any time, the last nonmissing postbaseline observation on or prior to discontinuation will be carried forward to subsequent time points for evaluation.

6.3.3. As-observed Analysis

For Part B of Study JAHW, the population of interest is formed by patients who complete through the analysis time as assigned. Thus, the as-observed analysis will be used for Part B. Therefore, this estimand is conditional and targets the effect of treatment conditional on completion of treatment through the time point of interest.

Only data observed at the time of interest are relevant and included in the analyses. There is no need to deal with missing data, as the population consists only of patients with observed data.

6.4. Multicenter Studies

This study will be conducted by multiple investigators at multiple sites. As the summaries of these data are descriptive in nature, no adjustments for site differences will be made.

6.5. Multiple Comparisons/Multiplicity

No multiplicity control measures will be used.

6.6. Patient Disposition

An overview of patient populations will be summarized by treatment group. Frequency counts and percentages of patients excluded prior to first dose by primary reason for exclusion will be provided for patients who failed to meet study entry requirements during screening.

Patient disposition will be summarized using the mITT population. Frequency counts and percentages of patients who complete the study treatment visits or discontinue early from Study JAHW, along with whether they completed follow-up or did not complete follow-up, will be summarized separately by treatment group for patients along with their reason for study discontinuation. Frequency counts and percentages of patients who complete the treatment or discontinue treatment early will also be summarized separately by treatment group for patients, along with their reason for treatment discontinuation.

A listing of patient disposition will be provided for all randomized patients, with the extent of their participation in Study JAHW and the reason for discontinuation. A listing of all randomized patients with their treatment assignment will also be provided.

6.7. Patient Characteristics

Patient characteristics, including demographics and baseline characteristics, will be summarized descriptively by treatment group for the mITT population. Historical illnesses and pre-existing conditions will be summarized descriptively by treatment group for the safety population. Descriptive statistics including number of patients (n), mean, SD, minimum, 1st quartile, median,

3rd quartile, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures. A listing of patient demographics will also be provided for the mITT population. No formal statistical comparisons will be made among treatment groups unless otherwise stated.

Table JAHW.6.2 describes the specific variables and how they will be summarized.

Table JAHW.6.2. Patient Characteristics

Variable	Continuous Measure Summary	Categorical Summary
Age [a]	Yes	12 to <18 years, 9 to <12 years, 6 to <9 years and 2 to <6 years
Sex	No	Male, Female
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple
Geographic region	No	By Country
Height (cm)	Yes	None
Weight (kg)	Yes	<20kg, 20 to < 30 kg, ≥30kg
BMI[b]	Yes	Underweight (<18.5 kg/m^2), Normal (≥18.5 and <25 kg/m^2), Overweight (≥25 and <30 kg/m^2), Obese (≥30 and <40 kg/m^2), Extremely obese (≥40 kg/m^2)
Alcohol use	No	Never, Current, Former
Tobacco use	No	Never, Current, Former
Prior JIA-U therapy	No	Never used, Ever used
Prior MTX use	No	Never used, Ever used
Prior bDMARD-IR use	No	Never used, Ever used
Duration of uveitis diagnosis (years)[a]	Yes	0 to <2 years, 2 to <5 years, 5 to <10 years, ≥10 years
Age at uveitis onset (years)[a]	Yes	12 to <18 years, 9 to <12 years, 6 to <9 years and 0 to <6 years
Type of uveitis	No	Active JIA-U, chronic anterior ANA-positive uveitis
Baseline number of active joints	Yes	None
Baseline number of joints with limited range of motion	Yes	None
Baseline Physician's Global Assessment of Disease Activity	Yes	None
Baseline Parent's Global Assessment of Well-Being	Yes	None
Baseline CHAQ Physical Function	Yes	None
Baseline ESR	Yes	
Baseline Juvenile Arthritis Disease Activity Score (JADAS)-27	Yes	None

Abbreviations: ANA = Anterior Antinuclear Antibody; bDMARD = biological disease-modifying antirheumatic drug; BMI = body mass index; CHAQ = Childhood Health Assessment Questionnaire;; ESR = erythrocyte sedimentation rate; JADAS-27 = Juvenile Arthritis Disease Activity Score-27; JIA-U = juvenile idiopathic arthritis-associated uveitis; MTX = methotrexate.

[a] In case the date of birth is missing, age in years will be calculated as length of the time interval from the imputed date of birth (15th of birth month collected in the electronic case report form to the informed consent date).

[b] BMI will be calculated as: $BMI\ (kg\ /\ m^2) = Weight\ (kg)\ /(Height\ [m])^2$.

6.8. Treatment Compliance

Treatment compliance with investigational product will be summarized for each treatment period with corresponding population. Patients will be considered compliant for each treatment period if they miss <20% of the expected doses (unless the patient's investigational product was withheld by the investigator for safety reasons). The proportions of patients compliant will be summarized.

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.

Compliance for baricitinib:

Compliance to baricitinib in the period of interest will be calculated as follows:

$$\text{Compliance} = \frac{\text{total number of tablets (or weight of suspension) dispensed} - \text{total number of tablets (or weight of suspension)returned}}{\text{expected number of total tablets (or weight of suspension)}}$$

where

Total number of tablets (or weight of suspension) dispensed: sum of tablets (or weight of suspension) dispensed in the period of interest prior to Visit *x*;

Total number of tablets (or weight of suspension) returned: sum of the tablets (or weight of suspension) returned in the period of interest prior to and including Visit *x*;

Expected number of tablets (or weight of suspension): number of days in the period of interest×number of tablets (or weight of suspension) taken per day = [(date of visit – date of first dose + 1) – number of days of temporary drug interruption] ×number of tablets (or weight of suspension) taken per day

If a patient has dose interrupted for safety reasons during the period, the total number of days drug was withheld will be deducted from the expected total # of tablets (or weight of suspension) used.

Compliance for injections (adalimumab):

Compliance to adalimumab the period of interest will be calculated as follows:

$$\frac{\text{actual total \# of syringes used}}{\text{Expected total \# of syringes used}} \times 100$$

Where:

Expected total number of syringes used = integer of [(total number of days in the period of interest)/14] + 1.

Actual total # of syringes used = total # of syringes dispensed – total # of syringes returned.

For patients with drug interruptions, the expected number of syringes used will be calculated for the period before and after interruption in the period of interest separately, then the sum of the two will be the expected total for the period of interest.

6.9. Previous and Concomitant Therapy

Summaries of previous and concomitant medications will be based on the safety population. Patients may continue to receive concomitant treatments for JIA-U. At screening, previous and current JIA-U treatments are recorded for each patient. A summary of previous medications used for JIA-U, including zoster immunization and the tuberculosis vaccine and medications that were discontinued after screening and before the first dose of study drug in the previous study, will be presented using frequency counts and percentages by preferred medication name. Concomitant therapy will be recorded at each visit and will be classified similarly. An additional summary for previous medications used for JIA-U will be presented with the reason of discontinuation.

Concomitant therapy for the treatment period is defined as therapy that starts before or during the treatment period and ends during the treatment period or is ongoing (has no end date or ends after the treatment period). Should there be insufficient data to make this comparison (for example, the concomitant therapy stop year is the same as the treatment start year, but the concomitant therapy stop month and day are missing), the medication will be considered as concomitant for the treatment period.

Summaries of previous medications will be provided for the following categories:

previous JIA-U therapies including reason for discontinuation

Summaries of concomitant medications will be provided for the following categories:

concomitant medications for JIA-U

concomitant medications for non-JIA-U

The drug class may considered in concomitant medication summaries are: MTX, conventional synthetic (cs)DMARDs other than MTX, mycophenolate mofetil, topical steroid eye drops, oral corticosteroids, intra-articular corticosteroid joint injections, intraocular corticosteroid injections, systemic corticosteroids (other than oral and intra-articular), analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).

The previous use of bDMARDs will be summarized in previous JIA-U therapies.

7. Efficacy Analyses

The general methods used to summarize efficacy data, including the definition of baseline value for assessments, are described in Section 7.1.

Efficacy will generally be analyzed through Week 24 (Part A) and through Week 284 (Part B), and patients will be analyzed according to the investigational product to which they were received at Week 0 (Visit 3):

Table JAHW.7.1 includes the descriptions and derivations of the primary and secondary efficacy outcomes.

Table JAHW.7.2 provides the detailed analyses including analysis type, method and imputation, population, time point, and comparisons for efficacy outcomes.

Table JAHW.7.3 includes the descriptions and derivations of secondary health and quality-of-life outcomes.

Table JAHW.4.1 provides the detailed analyses including analysis type, method and imputation, population, time point, and comparisons for health and qualify-of-life endpoints.

7.1. Primary Outcome and Methodology

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 Study JAHW 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

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

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

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

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

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

Table JAHW.7.1. Description and Derivation of Secondary Efficacy Outcomes for Part A

Measure	Description	Variable	Derivation / Comment	Definition of Missing
SUN grade	SUN grade of cells in the anterior chamber	▪ SUN grade of cells in the anterior chamber in the most severely affected eye ▪ SUN grade of cells in the anterior chamber in the less severely affected eye (if applicable)	Change from baseline: observed SUN grade – baseline SUN grade	Missing if baseline or observed value is missing.
		▪ In patients with bilateral uveitis disease at baseline: Proportion of 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.	Change from baseline: observed SUN grade – baseline SUN grade≤ -2 in most severely affected eye at baseline (or both eyes if the inflammation grade is the same in both eyes) and ≤ -1 in the less severely affected eye at baseline	Missing if baseline or observed value is missing or if the patient does not have bilateral uveitis disease at baseline.
LogMar test	Visual acuity is measured by age-appropriate LogMar test in each eye	▪ LogMAR test score	Change from baseline: observed LogMAR test score – baseline LogMAR test score	Missing if baseline or observed value is missing.
Vitreous haze	Slit-lamp examination is used for assessment of vitreous haze	▪ Vitreous haze in each affected eye	Change from baseline: observed vitreous haze – baseline vitreous haze	Missing if baseline or observed value is missing.
Grade of flare	Flare will be assessed using a slit-lamp, and graded using the SUN grading scheme	▪ Grade of flare in the anterior chamber in each affected eye	Change from baseline: observed grade of flare – baseline grade of flare	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
Inactive anterior uveitis disease status	Inactive anterior uveitis disease status is ascertained using the SUN criteria.	▪ Proportion of eyes with inactive anterior uveitis	Proportion of eyes with inactive anterior uveitis is calculated by the number of eyes that achieve inactive disease status divided by the total number of affected eyes.	Missing if disease activity is missing
		▪ Time to inactive anterior uveitis disease status	Date when inactive anterior uveitis disease status attained in each affected eye – Baseline date	Missing if either date of attaining inactive anterior uveitis disease status is missing or baseline date is missing
Concomitant topical corticosteroid tapering status	Steroid tapering is recommended as outlined in the protocol for patients eligible for tapering.	▪ Proportion of patients who are able to taper concomitant topical corticosteroids	Proportion of patients who are able to taper concomitant topical corticosteroids is calculated by dividing the number of patients who were able to taper concomitant topical corticosteroids to <2 drops per day and to 0 drops per day by the total number of patients who were eligible to be tapered at baseline.	Missing if the tapering status is missing

Measure	Description	Variable	Derivation / Comment	Definition of Missing
PediACR 30/50/70/90/100	The PediACRX consists of the 6 core criteria listed below. The definition of improvement is ≥X% improvement from baseline in at least 3 of the 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 Parent's Global Assessment of Well-Being (CHAQ) Physical function as assessed by the CHAQ Acute-phase reactant: hsCRP	▪ Proportion of patients who achieve PediACR 30/50/70/90/100 response	Calculated as the number of subjects who achieve PediACRX divided by number of subjects assessed for PediACRX; where X = 30/50/70/90/100	Missing if all the PediACR core criteria for JIA are missing or baseline is missing;

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; hsCRP = high-sensitivity C-reactive protein; JIA = juvenile idiopathic arthritis; LogMAR = logarithm of the minimum angle of resolution; PediACR = Pediatric American College of Rheumatology; SUN = Standardization of Uveitis Nomenclature.

Table JAHW.7.2. Secondary Efficacy Endpoint Analyses for Part A

Measure	Endpoint	Analysis Method	Handling of Missing Data
SUN grade of cells in the anterior chamber in the most severely affected eye	Change from baseline	Summary statistics	LOCF
SUN grade of cells in the anterior chamber in the less severely affected eye (if applicable)	Change from baseline	Summary statistics	LOCF
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	NRI
Visual acuity by age-appropriate LogMAR test in each eye	Change from baseline	Summary statistics	LOCF
Vitreous haze in each affected eye	Change from baseline	Summary statistics	LOCF
Grade of flare in the anterior chamber in each affected eye	Change from baseline	Summary statistics	LOCF
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	Summary statistics	LOCF
Proportion of number of eyes with inactive anterior uveitis disease status in each affected eye	Proportion of affected eyes	Summary statistics	NRI

Measure	Endpoint	Analysis Method	Handling of Missing Data
	Time to inactive disease status	Time-to flare will be summarized graphically by treatment group using Kaplan-Meier estimates.	censoring
Concomitant topical corticosteroid tapering status, for patients eligible for corticosteroid tapering	Proportion of patients	Summary statistics	NRI
PediACR 30/50/70/90/100	Proportion of responders	Summary statistics	NRI

Abbreviations: LOCF = last observation carried forward; LogMAR = logarithm of the minimum angle of resolution; NRI = nonresponder imputation; PediACR = Pediatric American College of Rheumatology; SUN = Standardization of Uveitis Nomenclature.

Table JAHW.7.3. Description and Derivation of Health Outcomes and Quality-of-Life Measures for Part A

Measure	Description	Variable	Derivation / Comment	Definition of Missing
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 Disease Activity.	Change from baseline: observed Patient Uveitis-related Disease Activity – baseline Patient Uveitis-related Disease Activity	Missing if baseline or observed value is missing.
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 Uveitis-related Improvement	Patient uveitis related improvement score at analysis visit	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
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 Disease Activity score	Change from baseline: observed Patient Arthritis Disease Activity – baseline Patient Arthritis Disease Activity	Missing if baseline or observed value is missing.
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").	▪ Patient Arthritis Improvement score	Patient Arthritis Improvement score at analysis visit	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Definition of Missing
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 Disease Activity score	Change from baseline: observed Ophthalmologist Uveitis-related Disease Activity – baseline Ophthalmologist Uveitis-related Disease Activity	Missing if baseline or observed value is missing.
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").	▪ Ophthalmologist Uveitis-related Improvement score	Change from baseline: observed Ophthalmologist Uveitis-related Improvement – baseline Ophthalmologist Uveitis-related Improvement	Missing if baseline or observed value is missing.

Table JAHW.7.4. Secondary Efficacy Endpoint Analyses for Part A

Measure	Endpoint	Analysis Method	Handling of Missing Data
Patient Uveitis-related Disease Activity	Change from baseline	Summary statistics	LOCF
Patient Uveitis-related Improvement	Change from baseline	Summary statistics	LOCF
Patient Arthritis Disease Activity	Change from baseline	Summary statistics	LOCF
Patient Arthritis Improvement	Change from baseline	Summary statistics	LOCF
Ophthalmologist Uveitis-related Disease Activity	Change from baseline	Summary statistics	LOCF
Ophthalmologist Uveitis-related Improvement	Change from baseline	Summary statistics	LOCF

Abbreviation: LOCF = last observation carried forward.

7.2. Secondary Efficacy Analyses

Secondary efficacy analyses (Table JAHW.7.1) 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 analyses for Part B will be summarized in descriptive statistics.

7.3. Health Outcomes/Quality-of-Life Analyses

Health outcomes and quality-of-life related analyses for Part A are listed in in Section 4.2 and Table JAHW.7.3.

7.4. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

PK, pharmacodynamic (PD) and biomarker analyses to address secondary and exploratory objectives of this study will be described by Lilly in separate PK/PD and biomarker analysis plans.

7.5. 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 tetanus-diphtheria-acellular pertussis (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.

8. Safety Analyses

The planned safety analyses are consistent with compound-level standards, which are based on various sources, including company standards, internal and external subject matter experts, and cross-industry initiatives (e.g., white papers produced by a PHUSE Computational Science Working Group [a collaboration with FDA and PHUSE], published in the PHUSE Deliverables Catalog). Descriptions of the safety analyses are provided in this SAP; however, some details are in compound-level safety standards.

For Study JAHW, the following treatment groups and summary for each study period and analysis population are described below in Table JAHW.8.1.

Table JAHW.8.1. Summary of Safety Analysis Population, Baseline and Postbaseline

Population for safety analysis	Part A safety population		Long-term safety population	
	Bari	Ada	Bari	Ada
Treatment period	Part A		Part A+B	
Postbaseline definition	Start with first dose of study treatment, end until treatment period plus up to 30 days off-drug follow-up time	Start with first dose of study treatment, end until treatment period plus up to 30 days off-drug follow-up time.	First day of Bari administration up to data cut for ongoing patients or up to 30 days after the last dose of Bari as long as the patient is in the program.	First day of Ada administration up to data cut for ongoing patients or up to the first dose of Bari or end of study participation as long as the patient is in the program.
Baseline for LLT used in defining treatment-emergence	Screening period up to date of first dose of study treatment.			

Abbreviations: Ada = adalimumab; Bari = baricitinib; LLT = Lowest Level Term.

8.1. Extent of Exposure

Duration of exposure (in days) to study drug will be summarized for each treatment period with corresponding safety population, which is defined in Table JAHW.8.1.

Total patient years (PY) of exposure will be reported for overall duration of exposure. Descriptive statistics (n, mean, SD, minimum, 1st quartile, median, 3rd quartile and maximum) will be provided for patient-days of exposure, and the frequency of patients falling into different

exposure ranges will be summarized. Exposure ranges will generally be reported in weeks using the following as a general guide:

For Part A safety analysis population (see Table JAHW.8.1)

- ≥4 weeks, ≥8 weeks, ≥16 weeks, ≥ 24 weeks
- >0 to <4 weeks, ≥4 weeks to <8 weeks, ≥8 weeks to <16 weeks , ≥16 weeks to <24 weeks

For long-term safety analysis population (see Table JAHW.8.1):

- Every 24 weeks or semi-annually

Overall exposure will be summarized in total PY which is calculated according to the following formula:

PYE = sum of duration of exposure in days (for all patients in treatment group) / 365.25

8.2. Adverse Events

The planned summaries for AEs are provided in Table JAHW.8.2 and are described more fully in compound-level safety standards and in the AE-related PHUSE white paper (Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Document [PHUSE resources pageWWW]).

Table JAHW.8.2. Summary Tables Related to Adverse Events

Analysis	Population or Analysis Set[a]
An overview table, with the number and percentage of subjects who experienced a TEAE, SAE, death, discontinued from study treatment due to an AE	A, L
The number and percentage of subjects with TEAEs using MedDRA Preferred Term nested within System Organ Class	A, L
The number and percentage of subjects with TEAEs using MedDRA Preferred Term (without regard to System Organ Class)	A, L
The number and percentage of subjects with TEAEs by maximum severity using MedDRA Preferred Term	A, L
The number and percentage of subjects with TEAEs using MedDRA Preferred Term for the common TEAEs (occurred in ≥1% of treated subjects before rounding of the percentage)	A, L
The number and percentage of subjects who experienced a SAE (including deaths and SAEs temporally associated or preceding deaths) during the treatment period using MedDRA Preferred Term nested within System Organ Class	A, L
A listing of SAEs	Enrolled
The number and percentage of subjects who permanently discontinued from study treatment due to an adverse event (including adverse events that led to death) during the treatment period using MedDRA Preferred Term nested within System Organ Class	A, L

Abbreviations: AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = Serious Adverse Event; TEAE = Treatment Emergent Adverse Event.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term period.

8.3. Clinical Laboratory Evaluations

The planned summaries for clinical laboratory evaluations are provided in Table JAHW.8.3 and are described more fully in compound level safety standards and in the laboratory-related PHUSE white papers (PHUSE Computational Science Deliverables Catalog WWW; PHUSE Computational Science Deliverables Catalog WWW).

Table JAHW.8.3. Summary Tables Related to Clinical Laboratory Evaluations

Analysis	Population or Analysis Set[a]
Spaghetti plots for observed values	A, L
Listing of abnormal findings for laboratory analyte measurements, including qualitative measures	Enrolled

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.4. Vital Signs, Growth and Other Physical Findings

The planned summary analyses and by-patient listing for vital signs (systolic blood pressure [BP], diastolic BP, pulse) and other physical findings (weight, body mass index [BMI], temperature, height, head circumference) will be provided for the safety population and are summarized in Table JAHW.8.4. The reference limits for pulse/heart rate (P/HR) and blood pressure parameter will align with Lilly cardiovascular safety advisory committee's guidance "Reference Limits for PR/HR, BP, Orthostasis, & ECG Parameters" CCI [redacted]

Table JAHW.8.4. Summary Tables Related to Vital Signs

Analysis	Population or Analysis Set[a]
Spaghetti plots for observed values	A, L
Listing of abnormal finding in pulse/heart rate and blood pressure.	Enrolled

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

The reference limits for abnormal finding in pulse/heart rate and blood pressure is listed in Table JAHW.8.5.

Table JAHW.8.5. Reference Limits for Blood Pressure, Pulse/Heart Rate

Age (years)		Systolic BP, mm Hg (supine or sitting forearm at heart level)	Diastolic BP, mm Hg (supine or sitting forearm at heart level)	Pulse/HR bpm (supine or sitting)
Infant <2	Low High[a]	≤70 and decrease ≥15 ≥108 and increase ≥15	≤35 and decrease ≥10 ≥74 and increase ≥10	<70 and decrease ≥25 >190 and increase ≥25
Child 2-4	Low High[a]	≤75 and decrease ≥15 ≥110 and increase ≥15	≤40 and decrease ≥10 ≥76 and increase ≥10	<60 and decrease ≥25 >160 and increase ≥25
Child 5-9	Low High[a]	≤80 and decrease ≥15 ≥119 and increase ≥15	≤45 and decrease ≥10 ≥78 and increase ≥10	<60 and decrease ≥25 >150 and increase ≥25
Child 10-12	Low High[a]	≤85 and decrease ≥20 ≥126 and increase ≥20	≤50 and decrease ≥10 ≥82 and increase ≥10	<60 and decrease ≥25 >140 and increase ≥25
Adolescent >13	Low High[a]	≤90 and decrease ≥20 ≥129 and increase ≥20	≤50 and decrease ≥10 ≥86 and increase ≥10	<50 and decrease ≥15 >120 and increase ≥15
Adult ≥18	Low High[a]	≤90 and decrease ≥20 ≥129 and increase ≥20	≤50 and decrease ≥10 ≥90 and increase ≥10	<50 and decrease ≥15 >100 and increase ≥15

Abbreviations: BP = blood pressure; HR = heart rate.

[a] The high limit values shown in this table correspond to 95th percentile for the age group under the 2017 ACC/AHA Task Force on Clinical Practice Guidelines revised criteria for hypertension. Values higher than 95th percentile are consistent with Stage 1 or Stage 2 hypertension. Under some circumstances it may be appropriate to conduct analyses considering only the change from baseline reference limit.

Source: Flynn et al. 2017; Whelton et al. 2018.

Standardized Growth

Weight, height, BMI and head circumference data will be merged to the Centers for Disease Control and Prevention (CDC) standard growth data (released in 2000) by age and gender in order to compare patients' growth with the standard. Z-score and standardized percentile of weight, height, and BMI at each visit will be calculated and compared to the 2000 CDC growth charts.

The z-score and percentile calculations are based on algorithms and data provided by the National Center for Health Statistics. The data are provided in the CDC website (CDC resources page WWW).

The summaries will be provided and patients' mean of the parameter of interest will be plotted versus investigational product exposure time. By-patient listings of actual measures will be provided if needed.

8.5. Special Safety Topics, including Adverse Events of Special Interest

In addition to general safety parameters, safety information on specific topics of special interest will also be presented. Additional special safety topics may be added as warranted. The topics outlined in this section include the protocol-specified adverse events of special interest (AESI).

In general, for topics regarding safety in special groups and circumstances, patient profiles and/or patient listings, where applicable, will be provided, when needed, to allow for medical review of the time course of cases/events, related parameters, patient demographics, study drug treatment, and meaningful concomitant medication use. In addition to the safety topics for which provision or review of patient data are specified, these will be provided when summary data are insufficient to permit adequate understanding of the safety topic.

The analysis and summary will be provided for each treatment period with the corresponding population, where the detailed definition of the population and baseline can be found in Section 8 and Table JAHW.8.1.

8.5.1. Abnormal Hepatic Tests

Hepatic labs include alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBL), and serum alkaline phosphatase (ALP). When criteria are met for subgrotic evaluations, investigators will complete a follow-up hepatic safety eCRF. The planned summaries are provided in Table JAHW.8.6.

Table JAHW.8.6. Summary Tables Related to Hepatic Safety

Analysis	Population or Analysis Set[a]
ALT and AST: The percentages of patients with a measurement greater than or equal to 3 times (3X), 5 times (5X), and 10 times (10X) the central lab ULN for all patients with a post-baseline value and for subsets based on various levels of baseline value.	A, L
TBL: The percentages of patients with a measurement greater than or equal to 2 times (2X) the central lab ULN will be summarized for all patients with a post-baseline value and for subsets based on various levels of baseline value.	A, L
ALP: The percentages of patients with a measurement greater than or equal to 1.5 times (1.5X) the central lab ULN will be summarized for all patients with a post-baseline value and for subsets based on various levels of baseline value.	A, L
Plot of maximum post-baseline ALT vs. maximum post-baseline total bilirubin.	Safety population
Patient profiles including demographics, disposition, information collected on the hepatic-safety CRF (where applicable) and a display of study drug exposure, adverse events, medications, blood pressure, heart rate, and the liver-related measurements over time will be provided for patients with information collected on the hepatic-safety CRF and any additional patients meeting ALT or AST measurement greater than or equal to 5X ULN (on a single measurement) or ALP measurement greater than or equal to 2X ULN (on a single measurement).	Safety population

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate transaminase; CRF = case report form; TBL = total bilirubin; ULN = upper limit of normal.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.5.2. Hematologic Changes

Hematologic changes will be defined based on clinical laboratory assessments. Common Terminology Criteria for Adverse Events (CTCAEs) will be applied for laboratory tests potentially related to myelosuppressive events. The planned summaries are provided in Table JAHW.8.7. and are described more fully in compound-level safety standards.

Table JAHW.8.7. Summary Tables Related to Hematologic Changes

Analysis	Population or Analysis Set[a]
Shift tables showing the number and percentage of patients based on baseline to maximum will be created, with baseline depicted by the most extreme CTCAE grade during the baseline period. With each shift table, a summary displaying the number and percentage of patients who decreased, increased, or stayed the same in CTCAE grade category will be presented.	A, L
The percentages of patients with treatment-emergent shifts at any time will be summarized, based on any increase to CTCAE Grade 1 or above, Grade 2 or above, Grade 3 or above, and Grade 4 or above.	A, L
The percentages of patients with treatment-emergent thrombocytosis will be summarized, defined as an increase in platelet count from a maximum baseline value ≤600 billion/L to any postbaseline value >600 billion/L.	A, L

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.5.3. Lipids Effects

Lipids effects will be assessed through analysis of elevated total cholesterol, elevated low-density lipoprotein (LDL) cholesterol, decreased and increased high-density lipoprotein (HDL) cholesterol, and elevated triglycerides. The planned summaries are provided in Table JAHW.8.8. and are described more fully in compound-level safety standards.

Table JAHW.8.8. Summary Tables Related to Lipids Effects

Analysis	Population or Analysis Set[a]
Shift tables showing the number and percentage of patients based on baseline to maximum will be created, with baseline depicted by the most extreme NCEP-based level during the baseline period. With each shift table, a summary displaying the number and percentage of patients who decreased, increased, or stayed the same in NCEP-based level will be presented.	A, L
The percentages of patients with treatment-emergent shifts at any time will be summarized, based on increases to various levels of NCEP-based categories.	A, L
The percentages of patients with treatment-emergent potential hyperlipidemia will be summarized using a predefined MedDRA list of PTs that is a subset of the narrow scope PTs in the MedDRA SMQ "Dyslipidemia."	A, L

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities;
NCEP = National Cholesterol Education Program; PT = Preferred Term; SMQ = Standardised MedDRA Query.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

Categorical analyses will be performed using Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (2011) as shown in Table JAHW.8.9.

Table JAHW.8.9. Acceptable, Borderline-High, and High Plasma Lipid, Lipoprotein, and Apolipoprotein Concentrations for Children and Adolescents

Category	Low (mg per dL)[a]	Acceptable (mg per dL)	Borderline-high (mg per dL)[a]	High (mg per dL)[a]
total cholesterol	--	<170	170 to 199	≥200
LDL cholesterol		<110	110 to 129	≥130
Non-HDL cholesterol		<120	120 to 144	≥145
Apolipoprotein B		<90	90 to 109	≥110
Triglycerides				
0 to 9 years of age		<75	75 to 99	≥100
10 to 19 years of age		<90	90 to 129	≥130
HDL Cholesterol	<40	>45	40 to 45	
Apolipoprotein A-1	<115	>120	115 to 120	

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.

[a] Low cut point for HDL cholesterol and apolipoprotein A-1 represent approximately the 10th percentile. The cut points for high and borderline-high represent approximately the 95th and 75th percentiles, respectively.

8.5.4. Renal Function Effects

Effects on renal function will be assessed through analysis of elevated creatinine. The planned summaries are provided in Table JAHW.8.10. and are described more fully in compound-level safety standards.

Table JAHW.8.10. Summary Tables Related to Effects on Renal Function

Analysis	Population or Analysis Set[a]
Shift tables showing the number and percentage of patients based on baseline to maximum will be created, with baseline depicted by the most extreme CTCAE grade during the baseline period. With each shift table, a summary displaying the number and percentage of patients who decreased, increased, or stayed the same in CTCAE grade category will be presented.	A, L
The percentages of patients with treatment-emergent shifts at any time will be summarized, based on any increase to CTCAE Grade 1 or above, Grade 2 or above, Grade 3 or above, and Grade 4 or above.	A, L

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.5.5. Elevations in Creatine Phosphokinase (CPK)

The planned summaries are provided in Table JAHW.8.11. and are described more fully in compound-level safety standards.

Table JAHW.8.11. Summary Tables Related to Effects on CPK

Analysis	Population or Analysis Set[a]
Shift tables showing the number and percentage of patients based on baseline to maximum will be created, with baseline depicted by the most extreme CTCAE grade during the baseline period. With each shift table, a summary displaying the number and percentage of patients who decreased, increased, or stayed the same in CTCAE grade category will be presented.	A, L
The percentages of patients with treatment-emergent shifts at any time will be summarized, based on any increase to CTCAE Grade 1 or above, Grade 2 or above, Grade 3 or above, and Grade 4 or above.	A, L
Treatment-emergent adverse events potentially related to muscle symptoms may also be analyzed based on reported AEs. The Muscle Symptoms special search category is a predefined MedDRA search criteria list that contains the narrow scope terms from the Rhabdomyolysis/myopathy SMQ plus selected terms from the Musculoskeletal SOC	A, L

Abbreviations: AE = adverse event; CPK = creatine phosphokinase;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L=Long-term.

8.5.6. Infections

Infections will be defined using all the PTs from the Medical Dictionary for Regulatory Activities (MedDRA) Infections and Infestations System Organ Class (SOC). The MedDRA terms used to identify infections considered to be opportunistic infections (OIs) are based on Winthrop and colleagues (Winthrop et al. 2015) and are listed in the compound-level safety standards. The list contains narrow (more specific) and broad (less specific) PTs.

The planned summaries are provided in Table JAHW.8.12. and are described more fully in compound-level safety standards.

Table JAHW.8.12. Summary Tables Related to Infections

Analysis	Population or Analysis Set[a]
The number and percentage of patients with treatment-emergent infections, serious infections, and infections resulting in permanent study drug discontinuation will be summarized using MedDRA PTs.	A, L
The number and percentage of patients with TEAEs of infections by maximum severity will be summarized using MedDRA PTs.	A, L
Listing of patients experiencing TEAE infections will be provided. The listing will include patient demographics, treatment group, treatment start and stop dates, infectious PT event, event start and stop dates, total leukocytes, total lymphocytes, absolute neutrophils, event seriousness, and event outcome	Enrolled
Summary of OIs based on MedDRA PTs	A, L
A summary table of herpes zoster will be provided, including event maximum severity, seriousness, whether resulting in temporary study drug interruption, whether resulting in study drug discontinuation, whether treated with antiviral medication, and event outcome. The incidence rate adjusted for observation time will also be provided.	A, L
The summary table of herpes simplex will include event maximum severity, seriousness, whether resulting in temporary study drug interruption, whether resulting in study drug discontinuation, and whether treated with antiviral medication. The EAIR will also be provided.	A, L
A listing of patients with detectable HBV DNA will be provided	Enrolled

Abbreviations: DNA=deoxyribonucleic acid; EAIR = exposure-adjusted incidence rate; HBV = hepatitis B virus; MedDRA = Medical Dictionary for Regulatory Activities; OI = opportunistic infection; PT = Preferred Term; TEAE = treatment-emergent adverse event.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.5.7. Allergic Reactions and Hypersensitivities

A search for relevant events related to allergic reaction and hypersensitivity will be performed using the following SMQs:

Anaphylactic reaction SMQ (20000021)

Hypersensitivity SMQ (20000214)

Angioedema SMQ (20000024)

Events that satisfy the queries will be listed, by temporal order within patient ID, and will include SOC, PT, SMQ event categorization including detail on the scope (narrow or broad), reported AE term, AE onset and end dates, severity, seriousness, outcome, etc.

The summaries described in Table JAHW.8.13. will be created if there are sufficient numbers of events to warrant further examination beyond the listing specified above.

Table JAHW.8.13. Summary Tables Related to Allergic Reactions/Hypersensitivities

Analysis	Population or Analysis Set[a]
The percentages of patients with TEAEs will be summarized using MedDRA Preferred Term for any narrow or algorithmic term in the compound-level safety standard from any one of the 3 SMQs (each SMQ and SMQs combined)	A, L
The percentages of patients with TEAEs will be summarized using MedDRA Preferred Term for any broad term (each SMQ separately)	A, L

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.5.8. Major Adverse Cardiovascular Events and Other Cardiovascular Events

Major Adverse Cardiovascular Events (MACE) and other cardiovascular events will be adjudicated by an independent, external adjudication committee. All confirmed events after adjudication will be used for the analysis. The planned summary is provided in Table JAHW.8.14..

Table JAHW.8.14. Summary Tables Related to MACE and Other Cardiovascular Events

Analysis	Population or Analysis Set[a]
A listing of the events sent for cardiovascular adjudication will be provided to include data concerning the MedDRA PT related to the event, the seriousness of the event, and the event outcome, along with the adjudicated result.	Enrolled

Abbreviations: MACE = Major Adverse Cardiovascular Event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.5.9. Venous and Pulmonary Artery Thromboembolic Events

Venous thromboembolic (VTE) events will be adjudicated by an independent, external adjudication committee. Venous and pulmonary artery thromboembolic events will be classified as deep vein thrombosis (DVT), pulmonary embolism (PE), or other peripheral venous thrombosis. All confirmed events after adjudication will be used for the analysis.

The planned summary is provided in Table JAHW.8.15.

Table JAHW.8.15. Summary of Tables Related to VTE Events

Analysis	Population or Analysis Set[a]
A listing of the VTE events sent for adjudication will be provided to include data concerning the MedDRA PT related to the event, the seriousness of the event, and the event outcome, along with the adjudicated result.	Enrolled

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; VTE = venous thromboembolic.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

Arterial Thrombosis (ATE) Events

Arterial thromboembolic (ATE) events will be adjudicated by an independent, external adjudication committee.

The planned summary is provided in Table JAHW.8.16.

Table JAHW.8.16. Summary of Tables Related to ATE Events

Analysis	Population or Analysis Set[a]
A listing of the ATE events sent for adjudication will be provided to include data concerning the MedDRA PT related to the event, the seriousness of the event, and the event outcome, along with the adjudicated result.	Enrolled

Abbreviations: ATE = Arterial Thromboembolic; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term.

[a] Analysis Sets are abbreviated as follows: A = Part A safety population, L = Long-term.

8.5.10. Malignancies

Malignancies will be identified using terms from the Malignant tumors SMQ. Malignancies excluding nonmelanoma skin cancers (NMSC) and NMSC will be reported separately. All the cases identified by the Malignant tumors SMQ will be assessed through medical review to determine *confirmed* NMSC cases.

The planned summary is provided in Table JAHW.8.17.

Table JAHW.8.17. Summary Tables Related to Malignancies

Analysis	Population or Analysis Set
Listing of all malignancy cases, with an NMSC flag.	Enrolled

Abbreviations: NMSC = nonmelanoma skin cancers.

8.5.11. Gastrointestinal Perforations

Potential gastrointestinal (GI) perforations will be identified using terms from the GI perforations SMQ. Potential GI perforations identified by the SMQ search will be provided as a listing for internal review by the medical safety team. Each case will be assessed to determine whether it is a GI perforation. All confirmed events after medical review will be used for the listing. The planned summary is provided in Table JAHW.8.18.

Table JAHW.8.18. Summary Tables Related to Gastrointestinal Perforations

Analysis	Population or Analysis Set
Listing of all gastrointestinal perforations cases.	Enrolled

9. Protocol Violations

Protocol deviations will be tracked by the clinical team, and their importance will be assessed by key team members during protocol deviation review meetings. Out of all important protocol deviations (IPDs) identified, a subset occurring during the treatment period with the potential to affect the primary efficacy analyses will be noted.

The categories and subcategories of important protocol deviations, the source of identification for the deviation, and the statistical programming guidance for the clinical study report (CSR) are included in the JAHW Trial Issue Management Plan document.

The number and percentage of patients having IPD(s) will be summarized within category and subcategory of deviation by treatment groups. Individual patient listings of IPDs will be provided.

10. Interim Analyses and Data Monitoring

A Data Monitoring Committee (DMC) will oversee the conduct of this trial. 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. Data Monitoring Committee membership will include, at a minimum, specialists with expertise in rheumatology, statistics, and other appropriate specialties.

The DMC will be authorized to review unblinded results of analyses by treatment group prior to final database lock, including study discontinuation data, AEs including SAEs, clinical laboratory data, vital sign data, etc. The DMC may recommend continuation of Study JAHW, as designed; temporary suspension of enrollment; or the discontinuation of a particular dose regimen or 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 Study JAHW. However, Study JAHW will not be stopped for positive efficacy results. Hence, no alpha is spent. Details of the DMC, including its operating characteristics, are documented in the Baricitinib Pediatric Joint DMC charter.

Analyses for the DMC will include listings and/or summaries of the following information:

patient disposition, demographics, and baseline characteristics

exposure

AEs, to include the following:

- TEAEs
- SAEs, including deaths
- selected special safety topics

clinical laboratory results

vital signs

growth parameters (for example, height, weight, assessment of bone age)

All listings will include patient ID. Summaries will include TEAEs, SAEs, special topics AEs, and treatment-emergent high and low laboratory and vital signs in terms of counts, percentages and incidence rates, where applicable. For continuous analyses, box plots of laboratory analytes will be provided by time point.

The DMC may request efficacy data if they feel there is value and to confirm a reasonable benefit/risk profile for ongoing patients in the studies. Further details are given in the DMC charter.

10.1. Interim Analysis Plan

Two interim analyses will be performed to potentially stop Study JAHW early due to futility when 10 and 20 patients have completed 24 weeks of treatment, respectively. The analysis

population for interim analysis will be reviewed and determined based on the CEC meeting. At each interim analysis, the posterior probability of the treatment response rate being lower than 40% will be calculated and Study JAHW will be stopped if this probability is more than 75%. The detailed calculation related to interim analysis decision is documented in Section 6.1.

11. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include a summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AE are summarized: by treatment group, by MedDRA PT.

An AE is considered 'Serious' whether or not it is a TEAE.
An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:

- the number of participants at risk of an event
- the number of participants who reported each event term
- the number of events are reported.

Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that are reported in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

Similar methods will be used to satisfy the European Clinical Trials Database (EudraCT) requirements.

12. Unblinding Plan

Study JAHW is a open-label study with no comparison between treatment groups. The efficacy and safety analyses will focus on baricitinib patients only. The adalimumab patients' efficacy and safety data will be summarized using descriptive statistics. No formal statistical analyses will be conducted comparing baricitinib and adalimumab. Therefore, no unblinding plan is required.

13. Annual Report Analyses

Annual report analyses, such as for the Development Safety Update Report (DSUR), will be documented in a separate document.

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