JAHV 05 Clinical Protocol (d)

A Randomized, Double-Blind, Placebo-Controlled, Withdrawal, Safety and Efficacy Study of Oral Baricitinib in Patients From 2 Years to Less Than 18 Years Old With Juvenile Idiopathic Arthritis (JIA)

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Confidential Information

Baricitinib (LY3009104)

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1. Synopsis

Title of Study
A Randomized, Double-Blind, Placebo-Controlled, Withdrawal, Safety and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Juvenile Idiopathic Arthritis (JIA).

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, tyrosine kinase 2 [TYK2]) that play an important role in cytokine signal transduction. Baricitinib is a JAK1/JAK2 inhibitor demonstrating selectivity for and balanced 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) (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 rationale for the current study is to evaluate the efficacy and safety profile of oral baricitinib when administered once daily (QD) to pediatric patients with JIA who have had an insufficient response or intolerance to treatment with at least 1 other conventional or biologic disease-modifying antirheumatic drug (DMARD). This includes patients with polyarticular JIA (rheumatoid factor positive or rheumatoid factor negative), extended oligoarticular course JIA, enthesitis-related JIA (ERA), and juvenile psoriatic arthritis (JPsA) as defined by the International League of Associations for Rheumatology (ILAR) criteria. The safety and tolerability data from this study are intended to establish an understanding of the benefit/risk relationship for baricitinib in patients with nonsystemic JIA.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary • To evaluate the efficacy of baricitinib compared to placebo in children with JIA	• Time to disease flare (flare defined as worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria) from the beginning of the double-blind withdrawal (DBW) period to the end of the DBW period
Secondary • To evaluate the efficacy of baricitinib in children with JIA	During the open-label lead-in (OLLI) period: • PedACR30/50/70/90/100 response rates • Changes from baseline in each of the 6 individual components of the PedACR Core Set variables as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by the Childhood Health Assessment Questionnaire (CHAQ) o Acute-phase reactant (high-sensitivity c-reactive protein [hsCRP]) and erythrocyte sedimentation rate (ESR) • Proportion of patients with inactive disease (as defined by Wallace et al. 2011) • Proportion of patients with minimal disease activity (as defined by Consolaro et al. 2012) • Change from baseline in the Physical Summary Score (PhS) and Psychosocial Summary Score (PsS) of the Child Health Questionnaire-Parent Form 50 (CHQ-PF50) • Change from baseline in caregiver burden as measured by the Parental Impact-Time and Parental Impact-Emotion scales of the CHQ-PF50 • Change from baseline in Juvenile Arthritis Disease Activity Score-27 (JADAS-27) • Change from baseline in arthritis-related pain severity as measured by the CHAQ pain severity Visual Analogue Scale (VAS) item

Objectives	Endpoints
• To evaluate the efficacy of baricitinib compared to placebo in children with JIA	During the DBW period: • Proportion of patients with disease flare • PedACR30/50/70/90/100 response rates • Changes from baseline in each of the 6 individual components of the PedACR Core Set variables to the end of the DBW period (due to disease flare or completion) as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by the CHAQ o Acute-phase reactant (hsCRP) and ESR • Proportion of patients with inactive disease (as defined by Wallace et al. 2011) • Proportion of patients with minimal disease activity (as defined by Consolaro et al. 2012) • Proportion of patients in remission (as defined by Wallace et al. 2012) • Change from baseline in JADAS-27 • Change from baseline in the PhS and PsS of the CHQ-PF50 • Change from baseline in caregiver burden as measured by the Parental Impact-Time and Parental Impact-Emotion scales of the CHQ-PF50 • Change from baseline in arthritis-related pain severity as measured by the CHAQ pain severity VAS item
• To assess the efficacy of baricitinib in children with JPsA	• Change in Psoriasis Area and Severity Index (PASI) score during the OLLI period
• To assess the efficacy of baricitinib compared to placebo in children with JPsA	• Change from baseline in PASI score during the DBW period
• To assess the efficacy of baricitinib in children with ERA or JPsA	• Change in Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index during the OLLI period • Change in Juvenile Spondyloarthritis Disease Activity Index (JSpADA) during the OLLI period
• To assess the efficacy of baricitinib compared to placebo in children with ERA or JPsA	• Change from baseline in SPARCC enthesitis index during the DBW period. • Change from baseline in JSpADA during the DBW period
• To evaluate the potential effects of baricitinib on the cellular and humoral immune system	• Change in immunoglobulin levels and peripheral blood immunophenotyping (including T and B cells, T cell subsets, and NK cells) from baseline and at Week 4, Week 12, and Week 44. • Change of IgG titers from pre-vaccination to 4 weeks and 12 weeks post vaccination in patients eligible for vaccination with tetanus, diphtheria, and pertussis (tDaP) and/or pneumococcal conjugate vaccine according to local guidelines.

Objectives	Endpoints
• To characterize baricitinib PK in the JIA population and explore relationships between baricitinib exposure and study endpoints	• Population PK of baricitinib in patients with JIA • Proportions of patients achieving PedACR30/50/70/90/100 response rates by PK exposure • Time to disease flare in patients with JIA by PK exposure • Change in JADAS-27 by PK exposure
• To assess the patient acceptability and palatability of baricitinib tablets and oral suspension	• Assessment of tablet or oral suspension product acceptability and palatability during the OLLI period
• To assess the safety of baricitinib compared to placebo in patients with JIA	• Adverse events including serious adverse events • Permanent discontinuation of investigational product • Temporary interruption of investigation product

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; CHQ-PF50 = Child Health Questionnaire-Parent Form 50; DBW = double-blind withdrawal; ERA = enthesitis-related juvenile idiopathic arthritis; ESR = erythrocyte sedimentation rate; HRQOL = health-related quality of life; hsCRP = high-sensitivity C-reactive protein; IgG = immunoglobulin G; JADAS-27 = Juvenile Arthritis Disease Activity Score-27; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; JSpADA = Juvenile Spondyloarthritis Disease Activity Index; NK = natural killer; OLLI = open-label lead-in; PASI = Psoriasis Area and Severity Index; PedACR = Pediatric American College of Rheumatology; PK = pharmacokinetic(s); SPARCC = Spondyloarthritis Research Consortium of Canada; tDaP = tetanus, diphtheria, and pertussis; VAS = Visual Analogue Scale.

Summary of Study Design

Study I4V-MC-JAHV (JAHV) is a multicenter, randomized, double-blind, placebo-controlled, medication-withdrawal study with a safety/pharmacokinetic (PK) assessment period, an open-label lead-in (OLLI) period, and a double-blind withdrawal (DBW) period in patients with JIA who have had an inadequate response or intolerance to treatment with at least 1 other conventional or biologic DMARD (bDMARD).

Treatment Arms and Duration

The study has a 2-week Safety/PK assessment period, a 12-week OLLI period, and a DBW period of up to 32 weeks.

The Safety/PK assessment period will evaluate if exposure to baricitinib in pediatric patients is consistent with baricitinib exposure in adults. Patients will receive oral baricitinib at a fixed dose by age group QD for approximately 2 weeks. Enrollment will be staggered by age group (12 to <18 years, 9 to <12, 6 to <9 years, and 2 to <6 years), with older groups enrolling before younger groups.

In the OLLI period, patients will receive baricitinib QD at a fixed dose by age group for approximately 12 weeks. Patients who demonstrate disease response improvement of at least 30% in at least 3 of 6 Pediatric American College of Rheumatology (PedACR) core response variables and >30% worsening in not more than 1 of the remaining variables (PedACR30; Giannini et al. 1997) will proceed to the DBW. In the DBW period, patients will be randomized

to either receive placebo or to remain on the same baricitinib dose for up to 32 weeks or until the occurrence of a disease flare (whichever occurs first). Patients who do not achieve PedACR30 will be considered nonresponders; these patients will be given the option of enrolling to the open-label extension (OLE) study.

Disease flare is defined as a worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria from the patient's condition at Visit 9. If either the number of joints with active arthritis or the number of joints with limitation of motion are used in the calculation of flare for a study visit, then a minimum worsening of at least 2 active joints or 2 joints with limitation of motion must be present. An active joint is defined as a joint with swelling or, in the absence of swelling, limitation of motion accompanied by pain on motion and/or tenderness. If either the Physician's Global Assessment of Disease Activity or the Parent's Global Assessment of Well-Being are used in the calculation of flare for a study visit, then a minimum worsening on a visual analogue scale (VAS) (as defined in the SAP) must be present. If ESR or CRP is used in the definition of "flare" and counts towards worsening, then the second value for ESR or CRP used in the calculation must be above the upper limit of normal for ESR (>20 mm/hour) or CRP. .

Patients who complete the DBW period may enroll into a separate OLE study (Study I4V-MC-JAHX [JAHX]). Additionally, patients whose baricitinib dose in safety/PK period is inconsistent with baricitinib 4-mg exposures in adults with rheumatoid arthritis and patients who experience a disease flare during the DBW period will discontinue the study and be offered immediate participation in the OLE.

Patients who do not enroll in the OLE will have a follow-up visit (Visit 801) approximately 28 days after the last dose of the investigational product.

Number of Patients

Approximately 197 patients are planned to enter the OLLI period to allow 128 patients to be randomized into the DBW period (assuming that 65% of the patients meet the PedACR30 criteria at the end of the OLLI period). At least 10 of these patients will have ERA. The nonresponder and dropout rates will be monitored during the OLLI period to adjust the overall sample size to ensure that a minimum of 128 patients are randomized in the DBW. If the PedACR30 response rate during the OLLI period is higher than the assumed rate of 65%, fewer than 197 patients may be required.

Statistical Analysis

The primary endpoint will be the time-to-flare during the DBW period for randomized patients following intent-to-treat principles. Patients who discontinue the DBW period without experiencing a flare will have their data censored. Survival curves will be estimated using the Kaplan–Meier method for all "time-to" variables in the DBW period.

Efficacy and health outcome endpoints will be summarized using descriptive statistics for the OLLI population during the OLLI period. Treatment comparisons will be performed for the DBW population in the DBW period. Continuous data will be summarized in terms of the mean,

standard deviation, minimum, maximum, and median. Continuous efficacy and health outcome variables will be evaluated using an analysis of covariance (ANCOVA) model with treatment, JIA patient category (polyarticular and extended oligoarticular versus ERA and JPsA), prior bDMARD use, baseline ESR category, and baseline score in the model. The last-observation-carried-forward approach will be used to impute missing data.

Categorical data will be summarized as frequency counts and percentages. Categorical efficacy variables will be evaluated using a logistic regression analysis with treatment, JIA patient category (polyarticular and extended oligoarticular versus ERA and JPsA), and prior bDMARD use in the model. The proportions and 95% confidence interval will be reported. Missing data will be imputed using the nonresponder imputation method.

A futility analysis will be conducted using the PedACR30 response rate observed in the first 100 patients who have completed the OLLI phase. The futility analysis will be based on 50% of patients achieving a PedACR30 response rate. The study will stop for futility if <50% of the first 100 patients to complete the OLLI period have a PedACR30 response.

All safety data will be descriptively summarized in each treatment period using corresponding populations. Comparison between baricitinib and placebo will be performed during the DBW period for the DBW population. The Fisher exact test will be used for the adverse events, discontinuations, and other categorical safety data for between-treatment-group comparisons in the DBW period. Continuous vital signs, body weight, and other continuous safety variables, including laboratory variables, will be analyzed using ANCOVA with treatment and baseline values as model covariates.

2. Schedule of Activities

The Schedule of Activities described below should be followed for all participants enrolled in Study JAHV. In the event participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Appendix 8 and consult with the sponsor's representative for additional guidance.

Table JAHV.1. Schedule of Activities for the Safety/PK Cohort

	Safety/PK Cohort Only[a]				
	Screening		Safety/PK[b,c]		
Visit #	**V1**	**V1[a]**	**V2[b] baseline**	**V3**	**V4**
Study Day (Approximately)	**-42 to -1**		**1[d]**	**4**	**14**
Visit Window (Days)				**±3**	
Informed consent and assent[e]	X				
Complete medical history	X				
Immunization record	X		X		X
Demographics	X				
Physical examination[f]	X				
Tanner Staging in patients ≥8 years old (see Section 9.4.6.3)			X		
Symptom-directed physical examination[f]	X		X	X	X
Habits: tobacco and caffeine			X		
Height	X		X		X
Weight	X		X		X
X-ray of wrist/hand/ finger, and knee[g]			X		
Occipital frontal circumference measurement in children 2 years of age			X		X
Vital signs (blood pressure, pulse, temperature)			X	X	X
Inclusion/exclusion criteria review	X		X		
Preexisting conditions	X				
JIA diagnosis (ILAR criteria)	X				
Previous JIA therapy	X				
Uveitis evaluation[h]	X				
Concomitant medications	X		X	X	X
Adverse event	X		X	X	X
Log in IWRS	X		X	X	X
Randomization					
Dispense study drug			X		X
Investigational product returned and compliance assessed[i]					X
Clinical Efficacy					
Joint assessment	X		X	X	X
Physician's Global Assessment of Disease Activity	X		X	X	X
Childhood Health Assessment Questionnaire[j]			X	X	X
CHQ-PF50[j]			X		

	Safety/PK Cohort Only[a]				
	Screening		Safety/PK[b,c]		
Visit #	**V1**	**V1[a]**	**V2[b] baseline**	**V3**	**V4**
Study Day (Approximately)	**-42 to -1**		**1[d]**	**4**	**14**
Visit Window (Days)				**±3**	
EQ-5D-Y[j]			X		
SPARCC Enthesitis Index[k]			X		X
Morning stiffness duration			X		X
Pain Numerical Rating Scale			X		X
Clinical sacroiliitis[k]			X		X
Back mobility (Schober's test)[k]			X		X
PASI[l]			X		X
Product palatability and acceptability			X		
Procedures and Laboratory Tests					
Chest x-ray[m]	X				
Administer PPD/QuantiFERON®-TB Gold/T-SPOT® TB[n]	X				
Read PPD[n]		X			
ECG[o]	X				
hsCRP	X		X	X	X
ESR[p]			X	X	X
HLA-B27					
RF and ACPA	X				
TSH	X				
HIV/HCV[q]	X				
HBV(HBsAg, HBcAb, HBsAb)	X				
HBV DNA[r]	X				
Serum pregnancy test[s]	X				
Urine pregnancy test[s]			X		X
Clinical chemistry[t]	X		X	X	X
Hematology	X		X	X	X
Urinalysis	X		X		
Iron studies (iron, TIBC and ferritin)			X		
Fasting lipid panel[u]			X		
IgA, IgG, IgM			X		
Lymphocyte subsets (T, B, NK, and T- cell subsets)[v]			X		

	Safety/PK Cohort Only[a]				
	Screening		Safety/PK[b,c]		
Visit #	**V1**	**V1[a]**	**V2[b] baseline**	**V3**	**V4**
Study Day (Approximately)	**-42 to -1**		**1[d]**	**4**	**14**
Visit Window (Days)				**±3**	
Antipneumococcal IgG multianalyte Ab assay[w]			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination 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 post vaccination based on the vaccination schedule of each patient		
IGF-1 and IGFBP-3			X		
Gonadal hormones[x]			X		
Exploratory storage samples (RNA, serum, and plasma)			X		
Pharmacogenetic (DNA) collection					
PK sample[y]			X	X	X

Abbreviations: Ab = antibody; ACPA = anti-citrullinated protein antibodies; CHQ-PF50 = Child Health Questionnaire-Parent Form 50; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; eGFR = estimated glomerular filtration rate; EQ-5D-Y = European Quality of Life–5 Dimensions–Youth version; ERA = enthesitis related arthritis; 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; ICF = informed consent form; 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; IWRS = interactive web-response system; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; NK = natural killer; OLLI = open-label lead-in; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic(s); PPD = purified protein derivative; RF = rheumatoid factor; RNA = ribonucleic acid; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; tDaP = tetanus, diphtheria, and pertussis TIBC = total iron-binding capacity; TSH = thyroid-stimulating hormone; V = visit.

a Following completion of the Safety/PK period, patients will advance to the OLLI period.

b Pharmacokinetic samples will be collected as described in Section 9.5.2. Other baseline laboratory samples should be taken before administration of investigational product. Day 1 will be used as the baseline for Safety/PK population. Safety/PK cohort will join the OLLI period at Visit 6.

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. This applies only to patients who do not enter the Open-Label Extension Study.

d This is the first day of taking the investigational product.

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

f 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 any time. Must include an assessment of serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA.

g 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 JAHV at the time of this amendment, 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.

h All patients with active uveitis must be excluded at screening. Signs and symptoms of active uveitis should be monitored.

i At Visit 4, patient will return all investigational products for drug accountability.

j Patient-reported questionnaires will be administered via an on-site eCOA device or paper and is recommended to be completed prior to any clinical examinations.

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

l Only for patients with JPsA.

m 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.

n TB test(s) including 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 72hours 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.)

o An ECG performed within 1 year prior to screening may be used.

p Performed locally. To be drawn prior to dosing early in the visit except for V3.

q 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.

r 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 (for patients in Japan, it is acceptable for sites to draw HBV DNA samples with the test of Visit 1). 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.

s Pregnancy tests prior to first dose of investigational product for females ≥10 years old 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 Visit 2 must be known prior to first dose of investigational product.

t Clinical chemistry will include eGFR (calculated by Bedside Schwartz 2009 formula or the Japanese Society for Pediatric Nephrology formula for patients in Japan).

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

v Patients in the age cohort of age 2 to ≤7 years will not have flow cytometry testing due to blood volume limitations.

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 post vaccination, 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 PK samples will be collected as described in Sections 9.5.2.

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 in Appendix 6.

Table JAHV.2. Schedule of Activities

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
Informed consent and assent[f]	X																
Complete medical history	X																
Immunization record	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Demographics	X																
Physical examination[g]	X																
Tanner Staging in patients ≥8 years old (see Section 9.4.6.3)			X														
Symptom-directed physical examination[g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Habits: tobacco and caffeine			X														
Height	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-ray of wrist, hand, finger, and knee[h]			X														
Occipital frontal circumference			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
measurement in children 2 years of age																	
Vital signs (blood pressure, pulse, temperature)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria review	X		X														
Preexisting conditions	X																
JIA diagnosis (ILAR criteria)	X																
Previous JIA therapy	X																
Uveitis evaluation[i]	X																
Concomitant medications	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
Log in IWRS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization							X										
Dispense study drug[j]			X		X	X	X	X	X	X	X	X	X	X			
Investigational product returned and compliance assessed[k]				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Joint assessment	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
Physician's Global Assessment of Disease Activity	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childhood Health Assessment Questionnaire[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CHQ-PF50[l]			X			X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-Y[l]			X		X	X	X		X	X	X	X	X	X	X	X	X
SPARCC Enthesitis Index[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Morning stiffness duration[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pain Numeric Rating Scale[l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical sacroiliitis[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Back mobility[m] (Schober's test)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Product palatability and acceptability			X				X										
Chest x-ray[o]	X																
Administer PPD/ QuantiFERON®-TB Gold/T-SPOT® TB[p]	X																

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
Read PPD[p]		X															
ECG[q]	X																
hsCRP	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR[r]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HLA-B27								X									
RF and ACPA	X																
TSH	X																
HIV/HCV[s]	X																
HBV (hBsAg, hBcAb, hBsAb)	X																
HBV DNA[t]	X						X			X			X		X	X	X
Serum pregnancy test[u]	X																
Urine pregnancy test[u]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[v]	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
Urinalysis	X		X		X		X			X			X		X	X	X
Iron studies (iron, TIBC and ferritin)			X				X				X				X	X	X
Fasting lipid panel[w]			X				X				X				X	X	X
IgA, IgG, IgM			X		X		X								X	X	X
Lymphocyte subsets			X		X		X								X	X	X

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
(T, B, NK, and T-cell subsets)[x]																	
Antipneumococcal IgG multianalyte Ab assay[y]			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient														
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay[y]			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient														
IGF-1 and IGFBP-3			X				X								X	X	X
Gonadal hormone[z]			X				X								X	X	X
Exploratory storage samples (RNA, serum, and plasma)			X			X	X	X							X		
Pharmacogenetic (DNA) collection					X												
PK sample[aa]			X	X	X	X	X									X	

Abbreviations: Ab = antibody; ACPA = anti-citrullinated protein antibodies; CHQ-PF50 = Child Health Questionnaire-Parent Form 50; DNA = deoxyribonucleic acid; DBW = double-blind withdrawal; ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; eGFR = estimated glomerular filtration rate; EQ-5D-Y = European Quality of Life–5 Dimensions–Youth version; ERA = enthesitis-related juvenile idiopathic arthritis; 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; = hepatitis C virus; HIV = human immunodeficiency virus; HLA-B27 = human leukocyte antigen-B27; hsCRP = high-sensitivity C-reactive protein; ICF = informed consent form; 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; IWRS = interactive web-response system; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; NK = natural killer; OLLI = open-label lead-in; PASI = Psoriasis Area and Severity Index; PedACR30 = Pediatric American College of Rheumatology 30 criteria; PK = pharmacokinetic(s); PPD = purified protein derivative; RF = rheumatoid factor; RNA = ribonucleic acid; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; tDaP = tetanus, diphtheria, and pertussis ; TIBC = total iron-binding capacity; TSH = thyroid-stimulating hormone; V = visit; W = week.

[a] The OLLI period ends on the same day the DBW period begins.

[b] Pharmacokinetic samples will be collected as described in Sections 9.5.2 and 9.5.3. Other baseline laboratory samples should be taken **before** administration of investigational product. Visit 5 (Day 1) will be used as the baseline for OLLI population. Safety/PK cohort will join the OLLI period at Visit 6. The actual study week and study day for the Safety/PK cohort are two weeks longer than that shown due to the additional 2-week safety/PK lead-in assessment period described in Table JAHV.1.

[c] Early termination visit (ETV) occurs if the patient does not have a PedACR30 response rate at Week 12, experiences a flare during the double-blind withdrawal (DBW) (and are not moving to the open-label extension), or terminates participation early. If the ET 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.

[d] 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. This applies only to patients who do not enter the Open-Label Extension Study.

[e] This is the first day of taking the investigational product. .

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

[g] 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.

[h] 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 JAHV at the time of this amendment, 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.

[i] All patients with active uveitis must be excluded at screening. Signs and symptoms of active uveitis should be monitored. Patients with ERA and JPsA may have a higher risk of active uveitis so mandatory evaluation is required at W12 (V9), W44 (V17), ETV, and V801.

[j] Study drug should not be dispensed before review of the Trial Manager report.

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

[l] Patient-reported questionnaires will be administered via an on-site eCOA device or paper and is recommended to be completed prior to any clinical examinations.

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

[n] Only for patients with JPsA.

[o] 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.

p 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. (Note: Exception: Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing but must have a chest x-ray at screening.)

q An ECG performed within 1 year prior to screening may be used.

r Performed locally. To be drawn prior to dosing early in the visit except for V6 and V7.

s 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.

t 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 (for patients in Japan, it is acceptable for sites to draw HBV DNA samples with the test of Visit 1). 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 events.

u Pregnancy tests prior to first dose of investigational product for females ≥10 years old 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 Visit 5 must be known prior to first dose of investigational product.

v Clinical chemistry will include eGFR (calculated by Bedside Schwartz 2009 formula or the Japanese Society for Pediatric Nephrology formula for patients in Japan).

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

x Patients in the age cohort of age 2 to ≤7 years will not have flow cytometry testing due to blood volume limitations.

y 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 post vaccination, and 12 weeks post vaccination.

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

aa PK samples will be collected as described in Sections 9.5.2 and 9.5.3.

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 in Appendix 6.

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) are still poorly understood, but JIA shares 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 similarly observed in RA. Some studies have shown that levels of inflammatory cytokines elevated in adults with RA, such as IL-1β, IL-6, and tumor necrosis factor-alpha (TNFα), are also elevated in the synovial fluid and serum of patients with JIA. These cytokines also correlate with markers of disease activity such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Lepore et al. 1994; Mangge et al. 1995; Rooney et al. 1995, 2000; De Benedetti et al. 1997).

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 (Ravelli and Martini 2007). Pharmacologic interventions that target specific pathways may provide novel therapeutic approaches to disease management for JIA.

The primary treatments in JIA include nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular and systemic corticosteroids, methotrexate (MTX), and other conventional disease-modifying antirheumatic drug (cDMARDs) (Ringold et al. 2013. Biologic agents developed in the past 20 years have improved the treatments available to children with JIA.

Although these biological treatments led to significant improvements, many patients fail to respond and do not achieve long-lasting remission (Hinze et al. 2015).

Inhibition of JAK-STAT signaling by baricitinib can target multiple JIA-associated cytokine pathways and may provide novel therapeutic approaches to disease management. Baricitinib has demonstrated clinical safety and efficacy in patients with RA in 4 completed Phase 3 studies (Taylor et al. 2017; Genovese et al. 2016; Dougados et al. 2017; Fleischmann et al. 2017) and is approved in the European Union, Japan, and other geographical regions for the treatment of adult patients with moderate-to-severe RA. The rationale for the current study is to evaluate the efficacy and safety of baricitinib when administered once daily (QD) to patients with JIA who have had an inadequate response to either conventional or biologic DMARDs (bDMARDs). The safety and tolerability data from this study are intended to inform the benefit/risk relationship for baricitinib in patients with JIA.

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: 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 (Petty et al. 2004).

The prognosis of JIA varies based on the individual patient as well as the distinct disease category. Between 25% and 70% of children with JIA will still have active arthritis 10 years after disease onset; more than 40% will enter adulthood with active arthritis (Lovell 2006). Children with JIA are at risk for significant morbidity in terms of joint damage, impairments in physical function, and reduced health-related quality of life (HRQOL) (Prakken et al. 2011; Gidman et al. 2015).

The goal of JIA treatment is rapid suppression of inflammation to prevent joint damage, maximize physical function, and promote normal growth and development. First-line treatment for patients with nonsystemic JIA includes NSAIDs, corticosteroids, and cDMARDs, but a substantial proportion of patients do not achieve adequate response to these therapies (Ringold et al. 2013; Hinze et al; 2015). Biologic agents approved for RA have improved the treatments available to children with JIA over the past 20 years (Lovell et al. 2000; Ruperto et al. 2010; Brunner et al. 2015), which include etanercept, adalimumab, abatacept, and tocilizumab. Of these, etanercept and adalimumab are TNF-blocking agents that have similar mechanisms of action. Abatacept inhibits T cell production. Tocilizumab is an anti–IL-6 receptor monoclonal antibody. Although these biological treatments have led to clinical improvements, many patients do not respond and do not achieve long-lasting remission (Hinze et al. 2015).

As noted in Section 3.1, the efficacy of baricitinib in adult patients with RA was demonstrated in 4 completed global Phase 3 studies involving patients with moderately to severely active RA.

- Study I4V-MC-JADZ (RA-BEGIN) was a 52-week study that enrolled patients with limited or no prior DMARD exposure (Fleischmann et al. 2017). Patients were randomized to 1 of 3 treatment arms: MTX once weekly (QW [N = 210]), baricitinib 4-mg QD ([N = 159]), or baricitinib 4-mg QD plus MTX QW (N = 215). The primary objective of noninferiority of baricitinib monotherapy to MTX, based on 20% improvement in American College of Rheumatology criteria (ACR20) response at Week 24, was met with a response rate of 77% with baricitinib treatment versus 62% with MTX treatment ($p \leq 0.01$).
- Study I4V-MC-JADV (RA-BEAM) was a 52-week study that enrolled patients who had an inadequate response to prior established MTX therapy (continued as stable background therapy throughout the study) and no previous exposure to bDMARDs (Taylor et al. 2017). Patients were randomized into 1 of 3 treatment arms: placebo QD for 24 weeks followed by a switch to baricitinib 4-mg QD from Week 24 to Week 52 (N = 488), baricitinib 4-mg QD (N = 487), or adalimumab 40-mg every 2 weeks (N = 330). More patients treated with baricitinib met the primary endpoint of an ACR20 response at Week 12 compared to placebo (70% versus 40%, respectively; $p \leq 0.001$). Additionally, an increased ACR20 response rate at Week 12 was observed with baricitinib versus adalimumab (70% versus 61%, respectively; $p = 0.014$).
- Study I4V-MC-JADX (RA-BUILD) was a 24-week study that enrolled patients who had an inadequate response or were intolerant to cDMARD treatment and had no previous exposure to bDMARDs (Dougados et al. 2017). Patients were randomized into 1 of 3 treatment arms: placebo QD (N = 228), baricitinib 2-mg (N = 229), or baricitinib 4-mg (N = 227). More patients treated with baricitinib 4-mg met the primary endpoint of ACR20 response at Week 12 compared to placebo (62% versus 39%, $p \leq 0.001$).
- Study I4V-MC-JADW (RA-BEACON) was a 24-week study that enrolled patients who had an inadequate response or were intolerant to treatment with at least 1 biologic TNF inhibitor (Genovese et al. 2016). Otherwise, no limit was placed on the number or nature of prior bDMARDs. Patients were randomized into 1 of 3 treatment arms: placebo QD (N = 176), baricitinib 2-mg (N = 174), or baricitinib 4-mg (N = 177). Significantly more patients receiving baricitinib at the 4-mg dose than those receiving placebo met the primary endpoint of ACR20 response at Week 12 (55% versus 27%, respectively, $p \leq 0.001$).

Table JAHV.3 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 JAHV.3. 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 12 weeks	≤0.001	≤0.001	≤0.001	ng	≤0.001	≤0.001	≤0.001	≤0.001
ΔmTSS at 24 weeks	NS	≤0.05	≤0.001	ng	ng	ng	n/a	n/a
ΔDAS28-hsCRP at 12 weeks	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001	≤0.001
SDAI remission (≤3.3) at 12 weeks	≤0.01	≤0.001	≤0.001	ng	≤0.001	≤0.001	NS	NS[c]
MJS Duration at 12 weeks	n/a	n/a	≤0.001	ng	≤0.001	ng	n/a	n/a
MJS Severity at 12 weeks	n/a	n/a	≤0.001	ng	≤0.001	ng	n/a	n/a
Worst Tiredness at 12 weeks	n/a	n/a	≤0.001	ng	≤0.05	ng	n/a	n/a
Worst Joint Pain at 12 weeks	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; hsCRP = high-sensitivity C-reactive protein; 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.

Note: ≤0.05 = p≤0.05; ≤0.01 = p≤0.01; ≤0.001 = p≤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.

Therefore, given promising results already observed in completed clinical studies of baricitinib in adults with RA, benefits in efficacy are expected for pediatric patients with JIA. In addition, baricitinib is an orally ingested product, which may be preferable to injectable biologic agents for both patients and caregivers/legal guardians.

3.3. Benefit/Risk Assessment

As summarized in Sections 3.1 and 3.2, 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 HRQOL.

Baricitinib is approved in multiple geographic regions for the treatment of adult patients with moderate-to-severe RA. Juvenile idiopathic arthritis and RA 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 provides evidence for potential efficacy for baricitinib in JIA. Given the results observed in completed baricitinib clinical studies in RA in adult populations and the nature of the pathophysiology of JIA, treating patients with JIA with baricitinib is expected to provide beneficial and therapeutic outcomes to this population.

Section 9.2.2 describes adverse events 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 seen 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, following 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 RA patients 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 (deep vein thrombosis or pulmonary embolism) 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.

Therefore, based on the efficacy of baricitinib demonstrated in a 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.

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

4. Objectives and Endpoints

Table JAHV.4 shows the objectives and endpoints of the study.

Table JAHV.4. Objectives and Endpoints

Objectives	Endpoints
Primary • To evaluate the efficacy of baricitinib compared to placebo in children with JIA	• Time to disease flare (flare defined as worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria) from the beginning of the double-blind withdrawal (DBW) period to the end of the DBW period
Secondary • To evaluate the efficacy of baricitinib in children with JIA	During the open-label lead-in (OLLI) period: • PedACR30/50/70/90/100 response rates • Changes from baseline in each of the 6 individual components of the PedACR Core Set variables as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by CHAQ o Acute-phase reactant (hsCRP) and ESR • Proportion of patients with inactive disease (as defined by Wallace et al. 2011) • Proportion of patients with minimal disease activity (as defined by Consolaro et al. 2012) • Change from baseline in the Physical Summary Score (PhS) and Psychosocial Summary Score (PsS) of the Child Health Questionnaire-Parent Form 50 (CHQ-PF50) • Change from baseline in caregiver burden as measured by the Parental Impact-Time and Parental Impact-Emotion scales of the CHQ-PF50 • Change from baseline in Juvenile Arthritis Disease Activity Score-27 (JADAS-27) • Change from baseline in arthritis-related pain severity as measured by the CHAQ pain severity VAS item.

Objectives	Endpoints
• To evaluate the efficacy of baricitinib compared to placebo in children with JIA	During the DBW period: • Proportion of patients with disease flare • PedACR30/50/70/90/100 response rates • Changes from baseline in each of the 6 individual components of the PedACR Core Set variables to the end of the DBW period (due to disease flare or completion) as follows: o Number of active joints o Number of joints with limited range of motion o Physician's Global Assessment of Disease Activity o Parent's Global Assessment of Well-Being o Physical function as measured by the CHAQ o Acute-phase reactant (hsCRP) and ESR • Proportion of patients with inactive disease (as defined by Wallace et al. 2011) • Proportion of patients with minimal disease activity (as defined by Consolaro et al. 2012) • Proportion of patients in remission (as defined by Wallace et al. 2012) • Change from baseline in JADAS-27 • Change from baseline in the PhS and PsS of the CHQ-PF50 • Change from baseline in caregiver burden as measured by the Parental Impact-Time and Parental Impact-Emotion scales of the CHQ-PF50 • Change from baseline in arthritis-related pain severity as measured by the CHAQ pain severity VAS item
• To assess the efficacy of baricitinib in children with JPsA	• Change in Psoriasis Area and Severity Index (PASI) score during the OLLI period.
• To assess the efficacy of baricitinib compared to placebo in children with JPsA	• Change from baseline in PASI score during the DBW period
• To assess the efficacy of baricitinib in children with ERA or JPsA	• Change in Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index during the OLLI period. • Change in Juvenile Spondyloarthritis Disease Activity Index (JSpADA) during the OLLI period
• To assess the efficacy of baricitinib compared to placebo in children with ERA or JPsA	• Change from baseline in SPARCC enthesitis index at during the DBW period • Change from baseline in JSpADA during the DBW period
• To evaluate the potential effects of baricitinib on the cellular and humoral immune system	• Change in immunoglobulin levels and peripheral blood immunophenotyping (including T and B cells, T cell subsets, and NK cells) from baseline and at Week 4, Week 12, and Week 44 • Change of IgG titers from pre-vaccination to 4 weeks and 12 weeks post vaccination in patients eligible for vaccination with tDaP and/or pneumococcal conjugate vaccine according to local guidelines

Objectives	Endpoints
• To characterize baricitinib PK in the JIA population and explore relationships between baricitinib exposure and study endpoints	• Population PK of baricitinib in patients with JIA • Proportions of patients achieving PedACR30/50/70/90/100 response rates by PK exposure • Time to disease flare in patients with JIA by PK exposure • Change in JADAS-27 by PK exposure
• To assess the patient acceptability and palatability of baricitinib tablets and oral suspension	• Assessment of tablet or oral suspension product acceptability and palatability during the OLLI period
• To assess the safety of baricitinib compared to placebo in patients with JIA	• Adverse events including serious adverse events • Permanent discontinuation of investigational product • Temporary interruption of investigation product
Exploratory □ To evaluate the quality of life (QOL) in children with JIA treated with baricitinib	□ Change from baseline in European Quality of Life-5 Dimensions–Youth version (EQ-5D-Y) scores during the OLLI period
□ To evaluate the QOL in children with JIA treated with baricitinib compared to placebo	□ Change from baseline in EQ-5D-Y scores during the DBW period □ Change from baseline in the individual scales (Global Health; Physical Functioning; Role/Social Limitations-Physical; Role/Social Limitations-Emotional/Behavioral; Bodily Pain/Discomfort; Behavior; Global Behavior Item; Mental Health; Self-Esteem; General Health Perception; Change in Health; Parental-Impact-Time; Parental Impact-Emotion; Family-Activities; Family-Cohesion) as measured by the CHQ-PF50

Abbreviations: CHAQ = Childhood Health Assessment Questionnaire; CHQ-PF50 = Child Health Questionnaire-Parent Form 50; DBW = double-blind withdrawal; ERA = enthesitis-related juvenile idiopathic arthritis; ESR = erythrocyte sedimentation rate; HRQOL = health-related quality of life; hsCRP = high-sensitivity C-reactive protein; IgG = immunoglobulin G; JADAS-27 = Juvenile Arthritis Disease Activity Score-27; JIA = juvenile idiopathic arthritis; JPsA = juvenile psoriatic arthritis; JSpADA = Juvenile Spondyloarthritis Disease Activity Index; NK = natural killer; OLLI = open-label lead-in; PASI = Psoriasis Area and Severity Index; PedACR = Pediatric American College of Rheumatology; PK = pharmacokinetic(s); QOL = quality of life; SPARCC = Spondyloarthritis Research Consortium of Canada; tDaP = tetanus, diphtheria, and pertussis; VAS = Visual Analogue Scale.

5. Study Design

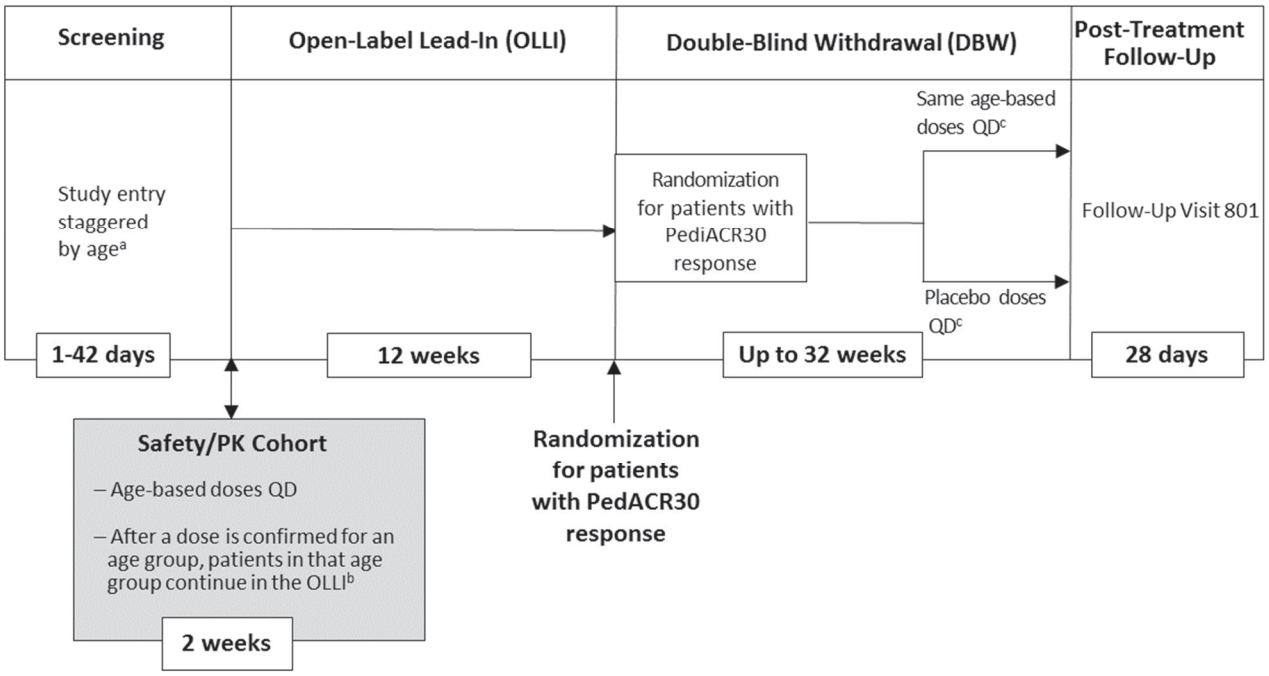
5.1. Overall Design

Study I4V-MC-JAHV (JAHV) is a multicenter, double-blind, randomized, placebo-controlled, medication-withdrawal Phase 3 study in patients with JIA who have had an inadequate response or intolerance to treatment with at least 1 conventional or bDMARD. Study JAHV has a safety/PK assessment period, an open-label lead-in (OLLI) period, and a double-blind withdrawal (DBW) period.

This study will include the following subsets: polyarticular, extended oligoarticular, and enthesitis-related JIA (including juvenile-onset ankylosing spondylitis and JPsA).

Figure JAHV.1 illustrates the study design.

Study governance considerations are described in detail in Appendix 3.



Abbreviations: DBW = double-blind withdrawal; OLE = open-label extension; OLLI = open-label lead-in; PedACR30 = Pediatric American College of Rheumatology 30 criteria; PK = pharmacokinetic(s); QD = once daily.

a Staggered approach to enrollment by age group (12 to <18 years, 9 to <12 years, 6 to <9 years, 2 to <6 years) will be implemented with older groups completing the safety/PK assessment period before younger groups are enrolled.

b Once the PK and safety profiles for an age group are confirmed, subsequent patients in that age group may enroll directly into the OLLI period. If the comparability assessment in the safety/PK period for an age group is inconsistent with baricitinib 4-mg exposures in adults with RA such that baricitinib dosage for the age group needs to be adjusted, the patients on the inconsistent dosage will discontinue the study and may enter the separate OLE study (JAHX).

c Patients who experience a disease flare during the DBW period will discontinue the study and may proceed directly to the separate OLE study (JAHX).

Figure JAHV.1. Study design for Clinical Protocol I4V-MC-JAHV.

Patients who complete the DBW period may enrol into a separate open-label extension (OLE) study (Study JAHX). Additionally, patients whose baricitinib dosage in safety/PK period is inconsistent with baricitinib 4-mg exposures in adults with RA based on comparability assessment for the age group as well as patients who experience a disease flare during the DBW period will discontinue this study and be offered participation in the OLE study (Study JAHX).

The study design allows for treatment with background cDMARDs, oral corticosteroids, and/or NSAIDs at a stable dose (refer to Section 7.7).

5.1.1. Screening and Baseline Periods

The duration of 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 applicable) 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 will need to return within 48 to 72 hours later to read the skin test. Treatments with concomitant JIA therapies during the study is permitted only as described in Section 7.7. Patients will remain on background cDMARDs, oral corticosteroid, NSAIDs, and/or analgesics if patients are on stable doses of these treatments at screening (Sections 6.2 and 7.7). Patients who have previously been treated with bDMARDs are eligible for the study. However, treatment must have been discontinued 4 weeks prior to screening for TNF inhibitors, IL-1 inhibitors, IL-6 inhibitors, or abatacept and 6 months prior to baseline for rituximab.

Investigators should review the vaccination status of their patients and ensure that patients are up to date with all immunizations, and following 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 patients become 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. 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.

5.1.2. Safety/PK Assessment

The Safety/PK assessment period will allow for collection of blood samples to determine if pediatric exposure to baricitinib in a cohort of 5 to 8 pediatric patients in each age group is consistent with baricitinib exposure in adults. Patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 are excluded from the Safety/PK period, as described in Section 6.2.

Patients will receive baricitinib at a fixed dose by age group daily for approximately 2 weeks. At least 5 (maximum of 8) patients will be enrolled in each age group for the JIA study to assess the comparability of their PK and safety profile with that of baricitinib 4-mg in adults with RA. The baricitinib dose will be adjusted as necessary if the comparability assessment demonstrates inconsistency with baricitinib 4-mg in adults with RA and an additional 5 to 8 patients from the respective age group will be enrolled to assess comparability. The next age group may only be enrolled after the PK and safety profiles of the preceding age group are confirmed. Enrollment will be staggered by age group (12 to <18 years, 9 to <12 years, 6 to <9 years, and 2 to <6 years; see Appendix 7 for updated dosing based on the current data) with older age groups enrolling before younger groups.

This study uses "dual assessor" approach to avoid potential unblinding, which includes the Joint Assessor and the Physician Assessor (see Section 9). Each assessment should be evaluated by the same assessor at all study visits including unscheduled and the scheduled final study visit whenever possible.

Patients who complete the Safety/PK assessment period will enter the OLLI period. If the comparability assessment in Safety/PK period for an age group is inconsistent with baricitinib 4-mg exposures in adults with RA and if the baricitinib dosage for the age group is adjusted for an additional comparability assessment, the patients on the inconsistent dosage will discontinue the study and be offered to enroll in the OLE Study JAHX. Patients who choose to enter Study JAHX will have their doses adjusted to the corrected dose. Investigators will be notified of the Safety/PK assessment results and any potential adjustment to dosing.

5.1.3. Open-Label Lead-In Period

In the OLLI period, patients will receive oral baricitinib at a fixed dose by age group daily for approximately 12 weeks from baseline. This study uses "dual assessor" approach to avoid potential unblinding, which includes the Joint Assessor and the Physician Assessor (see Section 9). Each assessment should be evaluated by the same assessor at all study visits including unscheduled and the scheduled final study visit whenever possible.

5.1.4. Double-Blind Withdrawal Period

At Week 12, treatment response (based on PedACR30 criteria) will be reviewed for each patient. Patients who achieve at least a PedACR30 response will be randomized (1:1 ratio) to receive placebo or to remain on the same baricitinib dose for up to 32 weeks (DBW period) or until disease flare, whichever occurs first. Patients who do not achieve PedACR30 will be considered nonresponders; these patients will be given the option of enrolling to the OLE study.

Assessments of disease severity will be performed by the investigator at all study visits including unscheduled and the scheduled final study visit. In this study, to prevent potential unblinding due to observed efficacy or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety at all study visits including unscheduled and the scheduled final study visit. Refer to Section 9 for additional information regarding dual assessment procedures.

The primary efficacy endpoint is time to disease flare (flare defined as worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria) after being randomized to placebo or baricitinib at Week 12 through Week 44. Refer to Section 9 for information regarding the PedACR core criteria.

To assess PedACR30 response at Week 12 for entry to the DBW phase and to diagnose disease flare on-site in a real-time manner, ESR is used as the acute-phase reactant for these measures. The sponsor will provide ESR kits to the site via the central laboratory.

5.1.5. 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 enroll in the OLE study (JAHX) do not need to return for a follow-up visit.

Patients who have received at least 1 dose of investigational product, do not have a PedACR30 response rate at Week 12, experience a flare leading to discontinuation during the DBW (and are not moving to the OLE), or 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 chose 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

Approximately 197 patients will be enrolled with at least 128 patients (at least 10 patients with ERA [including JPsA]) randomized to be evaluated for the primary endpoint in the DBW. The actual number of patients enrolled in the study may be adjusted upward or downward to allow for randomization of 128 patients.

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

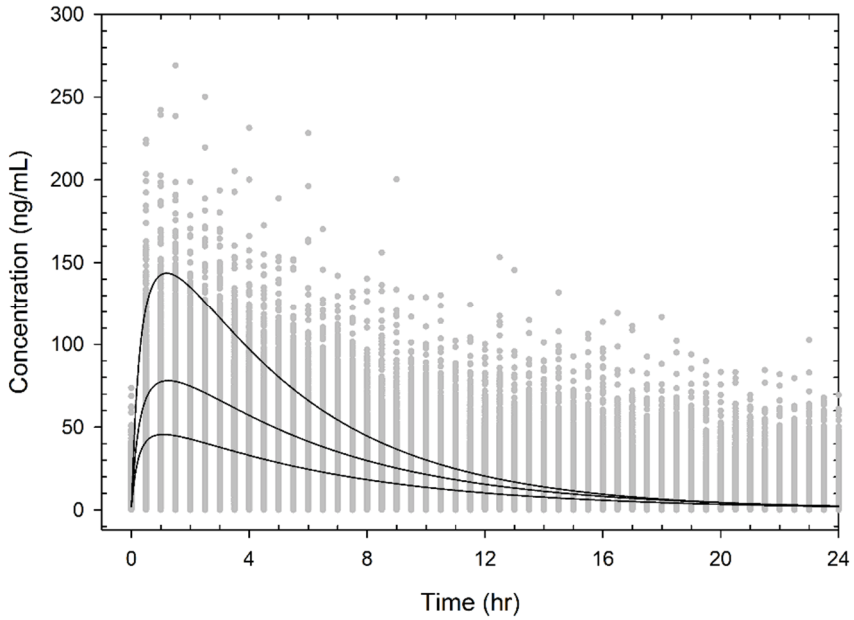
A withdrawal study design, as well as the primary endpoints of such a design (time to disease flare during the DBW period), are well accepted by pediatric rheumatologists and have been used in many other pediatric studies investigating treatments for JIA (Lovell et al. 2000, 2008; Ruperto et al. 2008; Brunner et al. 2015).

A withdrawal design offers all patients open-label treatment for a period of 12 weeks followed by a placebo-controlled randomized phase into which only responders from the OLLI phase are enrolled. This design was selected because it is unethical to expose pediatric patients with JIA to placebo for an extended period of time. This study design minimizes the amount of time patients will be exposed to placebo. The study design also limits placebo exposure to those patients who have already experienced some benefit from the investigational product.

At the first disease flare in the DBW period, patients (receiving either placebo or baricitinib) should be discontinued from Study JAHV and be offered the option to continue treatment with baricitinib in Study JAHX which allows the potential for additional concomitant medication. All patients in the DBW period who have achieved at least a PedACR30 at the end of OLLI period are considered to be responders to baricitinib.

5.5. Justification for Dose

The dose selection for baricitinib in this JIA patient population is informed by the Phase 2 and 3 data in adults with RA who demonstrated a positive benefit/risk profile for the 4-mg QD dose. Predicted concentration-versus-time data in RA patients 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; therefore, these patients will initially be dosed with 4-mg QD dose (Figure JAHV.2; see Appendix 7 for updated dosing based on the current data). In contrast, concentrations in children <9 years would be expected to be toward the higher end of the range seen in adults; therefore this group of patients will initially receive a lower 2-mg QD dose. If the interim analyses after the Safety/PK period demonstrate that the profiles are not comparable with the target PK in adults, adjusted baricitinib doses will be tested until both the PK are found to be comparable with the target profiles in adults.



Abbreviations: PK = pharmacokinetic; QD = once daily; RA = rheumatoid arthritis. 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 RA.

Figure JAHV.2. Comparison of predicted steady-state concentrations of baricitinib in pediatric (solid lines) versus adults (gray dots) receiving 4-mg QD.

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 with onset before the age of 16 years of any of the following forms of JIA as defined by ILAR criteria:

- Polyarticular JIA (positive or negative for RF)
- Extended oligoarticular JIA
- ERA
- JPsA

[3] Have had an inadequate response or intolerance to treatment with ≥1 conventional or bDMARD. Patients must have been treated for at least 12 weeks before inadequate response may be determined.

[4] Patients with polyarticular JIA or extended oligoarticular JIA must have at least 5 active joints at screening and baseline. Those with JPsA must have at least 3 active joints at screening and baseline. Those with ERA must have (a) at least 3 active joints at screening and baseline or (b) involvement of at least 1 sacroiliac joint AND a physician global assessment of at least 3 (on the 21-circle numeric rating scale [NRS]). Active joint is defined as the presence of joint swelling or, in the absence of swelling, joints with limitation of motion plus pain on motion and/or tenderness on palpation.

Informed Consent

[5] Both the child or adolescent and a parent or legal guardian are able to understand and fully participate in the activities of the clinical study and sign their assent and consent, respectively, accordance to local guidelines.

Contraception

[6] 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).

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, post-ovulation methods and withdrawal are not acceptable methods of contraception.

Otherwise, patients and their partners of childbearing 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 childbearing potential.

Women of nonchildbearing 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 have any of the following criteria at screening and/or at baseline as specified below:

Medical Conditions

[7] Have systemic JIA, as defined by ILAR criteria, with or without active systemic features.

[8] Have persistent oligoarticular arthritis as defined by ILAR criteria.

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

[10] Have active anterior uveitis or are receiving concurrent treatment for anterior uveitis (patients with a history of uveitis should not be excluded).

[11] Have active fibromyalgia or other chronic pain conditions that, in the investigator's opinion, would make it difficult to appropriately assess disease activity for the purposes of this study.

[12] 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.

[13] Bone, joint infections within 6 months prior to screening.

[14] Have symptomatic herpes simplex at baseline.

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

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

[17] 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.

[18] 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.

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

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

[21] Have evidence of active TB or latent TB

a. Have evidence of active TB, defined in this study as the following:
   - Positive PPD test (≥5 mm induration between approximately 2 and 3 days 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 they complete at least 4 weeks of appropriate treatment prior to randomization and agree to complete the remainder of treatment 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.

[22] Major surgery within 8 weeks prior to screening or requiring 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.

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

[24] History of a VTE or are considered at high risk of VTE as deemed by the investigator.

[25] Largely or wholly incapacitated, such as being bedridden.

[26] History of lymphoproliferative disease; or have signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; or have primary or recurrent malignant disease.

[27] History of chronic alcohol abuse, IV drug abuse, or other illicit drug abuse within the 2 years prior to screening.

[28] Presence of significant uncontrolled neuropsychiatric disorder, history of a suicide attempt or suicidal ideation, or clinically judged by the investigator to be at risk for suicide.

[29] History of hypogammaglobulinemia.

[30] Body temperature ≥38°C (100.5°F) at baseline.

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

Prior/Concomitant Therapy

[31] Have initiated or changed dosage of concomitant cDMARDs (other than MTX) within 4 weeks prior to screening (such as, but not limited to, hydroxychloroquine, sulfasalazine, gold salts, cyclosporine, or azathioprine). The dose of cDMARDs is expected to remain stable throughout the study and may be adjusted only for safety reasons.

[32] MTX use at doses of >20 mg/m2/week.

If continuing on MTX, must be on a stable dose of □20 mg/m^2/week for the 8 weeks preceding the screening. The dose of MTX is expected to remain stable throughout the study and may be adjusted only for safety reasons.

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

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

[35] Prior treatment with analgesics, including NSAIDs, on an unstable dose within 1 week of baseline.

[36] Prior treatment with any parenteral corticosteroid administered by intra-articular, intramuscular, or intravenous injection within 4 weeks of baseline.

[37] Oral corticosteroid use 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 6 weeks prior to baseline.

[38] 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.

[39] Received any JAK inhibitors (including, but not limited to, tofacitinib or baricitinib) previously.

[40] Received 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.

[41] Patients who are receiving thyroxine as replacement therapy may participate in the study, provided stable therapy has been administered for ≥12 weeks and thyroid-stimulating hormone (TSH) is within the laboratory's reference range.

Exception: Patients who are receiving stable thyroxine replacement therapy who have TSH marginally outside the laboratory's normal reference range may participate if the treating physician has documented that the thyroxine replacement therapy is adequate for the patient.

Diagnostic Assessments

[42] 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/□L (<3.00 x 10^3/□L or <3.00 billion/L)
- Neutropenia (absolute neutrophil count [ANC] <1500 cells/□L) (<1.50 x 10^3/□L or <1.50 billion/L)
- Lymphopenia (lymphocyte count <1000 cells/□L) (<1.00 x 10^3/□L or <1.00 billion/L)
- Thrombocytopenia (platelets <100,000/□L) (<100 x 10^3/□L or <100 billion/L)
- eGFR <40 mL/min/1.73 m^2 are excluded from enrolling in the study (Bedside Schwartz formula 2009 or The Japanese Society for Pediatric Nephrology formula for patients in Japan)
- eGFR <60 mL/min/1.73 m^2 are excluded from the Safety/PK period of the study (Bedside Schwartz formula 2009 or The Japanese Society for Pediatric Nephrology formula for patients in Japan).

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.

[43] 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

[44] 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.

[45] 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.

[46] Previously completed or withdrawn from this study or any other study investigating baricitinib.

Other Exclusions

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

[48] 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.

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

[50] 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 [7] to [11] exclude individuals with conditions that may confound safety or efficacy analyses.
- Exclusion Criteria [12] to [21] exclude individuals who are at an increased risk for infections or infectious complications.
- Exclusion Criteria [22] to [30], and [51] exclude individuals with previous or concomitant medical conditions that increase the risk for their participation in the study.
- Exclusion Criteria [31] to [41] exclude individuals who are taking or who may take JIA medications or treatments that interfere with the ability to assess the safety and efficacy of baricitinib.
- Exclusion Criteria [42] to [43] exclude individuals with laboratory parameters that may increase the risk for their participation in the study.
- Exclusion Criteria [44] to [50] 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 from the previous screening date. Each time rescreening is performed the legal representative must sign a new ICF and the child would sign an assent, as applicable. The individual will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of baricitinib dose, by age (4-mg for children ≥9 years of age and adolescents 12 to <18 years of age and 2-mg for children <9 years of age as the starting dose; see Appendix 7 for updated dosing based on the current data), with placebo in the DBW period. The dosages will be adjusted if the interim analyses after the Safety/PK period demonstrate that the profiles are not comparable with the target PK or safety profiles in adults. Therefore, a 1-mg dose is described in Table JAHV.5 should this be needed.

Baricitinib will be dosed as tablets or oral suspension QD based on the age of the patient at Visit 2 (for patients enrolled in the Safety/PK portion) and at Visit 5 (for all other patients); formulation will not change during the study. Baricitinib should be taken with sufficient water or fluid to allow easy swallowing of the medication. All patients <6 years of age will receive oral suspension. Patients ≥6 to <12 years old have the option of receiving the oral suspension. Patients >12 years old will be supplied tablets. Based on PBPK modeling, initial doses will be 4-mg for adolescents 12 to <18 years old and in children ≥9 to <12 years old, and 2-mg in children <9 years old to produce exposures similar to those in adults after 4-mg QD administration. Refer to Section 5.5 for additional information. Table JAHV.5 shows the treatment regimens.

Table JAHV.5. Treatment Regimens

	Treatments Administered	
Treatment Group	**Safety/PK and OLLI Period**	**DBW Period**
Baricitinib 4-mg	Baricitinib 4-mg oral QD tablet Baricitinib 2-mg/mL oral suspension	Baricitinib 4-mg oral QD tablet Baricitinib 2-mg/mL oral suspension
Baricitinib 2-mg	Baricitinib 2-mg oral QD tablet Baricitinib 2-mg/mL oral suspension	Baricitinib 2-mg oral QD tablet Baricitinib 2-mg/mL oral suspension
Baricitinib 1-mg	Baricitinib 1-mg oral QD tablet Baricitinib 2-mg/mL oral suspension	Baricitinib 1-mg oral QD tablet Baricitinib 2-mg/mL oral suspension
Placebo comparator	N/A	Baricitinib 4-mg placebo oral QD tablet Baricitinib 2-mg placebo oral QD tablet Baricitinib 1-mg placebo oral QD tablet Baricitinib 2-mg/mL placebo oral suspension

Abbreviations: DBW = double-blind withdrawal; eGFR = estimated glomerular filtration rate; N/A = not applicable; OLLI = open-label lead-in; PK = pharmacokinetics; QD = once daily.

Note: Initial doses of baricitinib 4-mg for adolescent patients (12 to <18 years of age) and children ≥9 years of age and baricitinib 2-mg for children <9 years of age will be given. The oral suspension dose may be administered as 4-mg, 2-mg, 1-mg, and 0.5-mg as needed.

Note: Patients with renal impairment or renal immaturity (defined as eGFR <60 mL/min/1.73 m^2) at baseline will have their dose reduced by 50%. Patients receiving the 1-mg dose who have renal impairment or renal immaturity will receive a dose-of 0.5-mg 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 that all unused medication is to be destroyed by the site, as allowed by local law.

Placebo tablets are composed of lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Tablet coating is comprised of polyvinyl alcohol–partially hydrolyzed, titanium dioxide, polyethylene glycol 3350, talc, lecithin (soya), and iron oxide red.

7.1.1. Packaging and Labeling

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

- Tablets containing 4-mg of baricitinib
- Tablets containing 2-mg of baricitinib
- Tablets containing 1-mg of baricitinib
- Placebo tablets to match baricitinib 4-mg tablets, 2-mg tablets, and 1-mg tablets
- Suspension containing 2-mg/mL of baricitinib
- Placebo to match suspension containing 2-mg/mL of baricitinib

Each tablet has a distinctive shape and color: 4-mg versus 2-mg versus 1-mg. Each strength tablet has a matching placebo. Baricitinib oral suspension (containing 2-mg/mL baricitinib) and matching placebo 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.

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

7.2. Method of Treatment Assignment

Patients who enter the PK lead-in period will be assigned a dose based on age. Pharmacokinetic samples will be collected as described in Section 9.5. Doses of subsequent patients who enter the PK lead-in period may be adjusted until a dose is found that produces exposures within the range produced by baricitinib 4-mg in adults with RA. All patients who enter the OLLI period will receive a fixed age-based dose of baricitinib as determined in the PK lead-in period.

Patients who meet the PedACR30 response criteria at the end of the OLLI period will be randomized in a 1:1 ratio (baricitinib age-based dose or matching placebo) to double-blind treatment at Week 12. The randomization will be stratified by history of prior bDMARD use (Yes versus No), the JIA category (polyarticular and extended oligoarticular versus ERA and

JPsA), and predose exposure ESR category (elevated [>20 mm/hour] and not elevated in the polyarticular JIA patients). 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 bottles containing double-blind investigational product to each patient. All patients <6 years of age will receive oral suspension. Patients ≥6 to <12 years old have the option of receiving the oral suspension. Patients >12 years will be supplied tablets only.

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

Refer to Section 5.1.2 for additional information regarding dosing in the Safety/PK assessment and OLLI period.

7.2.1. Selection and Timing of Doses

The doses should be administered at approximately the same time each day. The actual time of doses administered at a visit where a PK sample is collected will be recorded in the patient's electronic case report form (eCRF) according to Section 9.5.

7.3. Blinding

The PK lead-in and OLLI periods of this study are open-label.

The DBW period of this study is double-blind. To preserve the blinding of the study during the DBW period, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. All study assessments will be performed by study personnel who are blinded to the patient's treatment group. Except in clinical circumstances where unblinding is required, the patients, investigators, Lilly study team, and any personnel interacting directly with patients or investigative sites will remain blinded to baricitinib and placebo assignment until after database lock for the DBW period. It is expected that the need for unblinding a patient's treatment prior to database lock for DBW period will be extremely rare. Every effort should be made to preserve the blind unless there is a compelling reason that knowledge of the specific treatment would alter the patient's medical care.

Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a subject's treatment assignment. Emergency unblinding for AEs may be performed through the IWRS. This option may be used only if the patient's well-being requires knowledge of the patient's treatment assignment. All unblinding events are recorded and reported by the IWRS. If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain on the investigational product, the investigator must obtain specific approval from a Lilly clinical research physician for the patient to continue in the study or to discontinue the JAHV study, or to continue treatment with baricitinib in the OLE.

Processes to maintain blinding during the interim analysis conducted by the data monitoring committee (DMC) are described in Section 10.3.11.

7.4. Dosage Modification

The baricitinib dose for an individual patient will not change during the course of this study. However, the baricitinib dose for an age-based cohort may change based on the PK and safety profile of doses evaluated during the PK lead-in period. All patients who complete the PK lead-in period will enter the OLLI period on the dose they received at the start of the PK lead-in period. If the dose is modified for an age group after patients have already entered the OLLI period, they will be discontinued from the study and will be given the option to move to a separate OLE and receive the modified dose. Data from these patients will be censored from statistical analyses of efficacy endpoints in the present study.

The baricitinib dose for patients will be reduced by 50% in those who have renal impairment (defined as eGFR <60 mL/min/1.73 m^2) at baseline. Patients receiving the 1-mg tablet who have renal impairment at baseline will be dose-reduced to 0.5-mg using the oral suspension.

Patients with eGFR <60 mL/min/1.73 m^2 are excluded from the safety/PK assessment period as described in Section 6.2.

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 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 at each visit (except Visit 3) during the treatment period (baseline through Week 44).

Patients treated with baricitinib or placebo 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).

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 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 JIA therapies during the study is permitted only as described below and in Table JAHV.6. The dosages of concomitant treatment may be adjusted only for safety reasons.

- 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 6 weeks prior to baseline and remain on the same dose throughout the study. Patients should not receive other systemic corticosteroids during the study including intra-muscular or intra-articular corticosteroids. Topical, intranasal, intra-ocular, and inhaled corticosteroids are permitted.
- Chronic stable use of MTX is permitted and defined as average dose of ≤20 mg/m^2/week for at least 8 weeks prior to screening and continuation of that dose throughout the study. Local standard of care should be followed for concomitant administration of folic acid.
- Chronic stable usage of cDMARDs (other than MTX) is permitted on stable dose for at least 4 weeks prior to screening and continuation of that dose throughout the study.
- Concomitant usage of >2 cDMARDs (including MTX) are not allowed.
- Chronic stable use of NSAIDs and analgesics is permitted. Patients must be on a stable dose for at least 1 week prior to baseline and increase in dose and/or introduction of new NSAIDs and analgesics are not permitted throughout the study. Dose reductions and/or termination of NSAIDs and analgesics are permitted.

- Patients receiving Organic Anion Transporter 3 (OAT3) inhibitors with a strong inhibition potential, such as probenecid, will have their dose of baricitinib reduced by 50%.

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

- bDMARDs
- Parenteral corticosteroids administered by intramuscular, intra-articular, or intravenous injection
- Live vaccine (within 28 days prior to baseline or are expected to need/receive live vaccine during the course of the study) except booster immunization with attenuated vaccine for MMR or VZV. 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.

Table JAHV.6. Concomitant JIA Therapies

Drug Class	As Needed	Chronic Use	Conditions for Use
MTX[a]	No	Yes	If on MTX, must be on a stable average dose of ≤20 mg/m^2/week for the 8 weeks preceding screening and must continue at that dose throughout the study
cDMARDs other than MTX[a]	No	Yes	If receiving cDMARDs (other than MTX), must be on a stable dose for at least 4 weeks prior to the screening and must continue at that dose throughout the study.
Oral corticosteroids	No	Yes	If receiving oral corticosteroids, daily doses of ≤10 mg/day or 0.2 mg/kg/day prednisone equivalent, whichever is less. Must be on stable dose for at least 2 weeks prior to screening and 6 weeks prior to baseline; the dose must be continued throughout the study.
NSAIDs[b] • including cyclooxygenase-2 inhibitors, e.g., celecoxib	No	Yes	• Must be on stable dose at least 1 week prior to baseline. • Changes in dose, discontinuation and/or introduction of new NSAIDs are only allowed for treatment of an AE.
Analgesics • including local anaesthetics, e.g., lidocaine, and • topical anaesthetics, e.g., EMLA cream.	No	Yes	• Must be on stable dose at least 1 week prior to baseline. • Changes in dose, discontinuation and/or introduction of new analgesics are only allowed for treatment of an AE.

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

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

[b] For use as an anti-inflammatory agent.

7.8. Treatment after the End of the Study

7.8.1. Study Extensions

Patients who complete this study and have a flare during the DBW period may be eligible to participate in the OLE (Study JAHX) if enrollment criteria for the OLE are met.

7.8.2. Special Treatment Considerations

Patients who experience a flare during the DBW period may proceed to Study JAHX if enrollment criteria for Study JAHX are met. Additionally, if the comparability assessment in Safety/PK assessment period for an age group is inconsistent with baricitinib 4-mg exposures in adults with RA and baricitinib dose for the age group is adjusted for an additional comparability assessment, the patient on the inconsistent dosage will discontinue the study and may enter a

separate OLE study (JAHX) and be censored from statistical analyses of efficacy endpoints from the present study.

7.9. Continued Access

After the conclusion of the study, continued access to baricitinib will not be provided unless the patient proceeds to Study JAHX.

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 JAHV.7.

For the abnormal laboratory findings and clinical events (regardless of relatedness) listed in Table JAHV.7, 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 JAHV.7 may be restarted at the discretion of the investigator.

Table JAHV.7. 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 (≥1.00x10^3/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 total bilirubin level (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 JAHV.7) 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.

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

- Pregnancy
- Malignancy
- HBV DNA detected with a value above 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

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).

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 by the DMC 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 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.

In this study, to prevent potential unblinding due to observed efficacy or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety.

The Joint Assessor (or designee) should be a rheumatologist or skilled joint assessor and will be responsible for completing the joint counts for swelling, tenderness, and limited range of motion. Additionally, the Joint Assessor will perform assessment of enthesitis and sacroiliitis (psoriatic arthritis and ERA populations). To ensure consistent joint evaluation throughout the study, individual patients should be evaluated by the same Joint Assessor for all study visits whenever possible. The Joint Assessor will not be involved in patient care and are asked to refrain from discussing disease activity or treatment with the patient, caregiver/legal guardian, principal investigators, or other site personnel. Likewise, the Joint Assessor should not access patient/parent/family-reported forms, Physician's Global Assessment of Disease Activity, or safety assessments.

The Physician Assessor (or designee) should be a pediatric rheumatologist (or medically qualified physician) and will have access to both safety and efficacy data. The Physician Assessor may be the principal investigator. The Physician Assessor will be responsible for completing the Physician's Global Assessment of Disease Activity. The Physician Assessor may delegate other assessments to another appropriately qualified assessor. To ensure consistent assessment throughout the study, this instrument should be completed by the same assessor at all study visits, whenever possible. The Physician Assessor will have access to source documents, laboratory results, and case report forms (CRFs), and will be responsible for making treatment decisions based on a patient's clinical response and laboratory parameters.

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 paediatric 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 keeping 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 Assessments

The primary efficacy assessment is to determine the time to disease flare from Week 12 to the end of the DBW period. Disease flare is defined as a worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria from the patient's condition at the conclusion of the OLLI period. If either the number of joints with active arthritis or the number of joints with limitation of motion are used in the calculation of flare for a study visit, then a minimum worsening of at least 2 active joints or 2 joints with limitation of motion must be evident. If either the Physician's Global Assessment of Disease Activity or the Parent's Global Assessment of Well-Being are used in the calculation of flare for a study visit, then a minimum worsening on a visual analogue scale (as defined in the SAP) must be evident (Brunner et al. 2002, Ruperto et al. 2008). In order to diagnose PedACR30 response at Week 12 and "flare" during the DBW period on-site in a timely manner, ESR is used as the acute phase reactant in PedACR core criteria.

9.1.2. Secondary Efficacy Assessments

Secondary endpoints (assessed at each visit, except Visit 3) are as follows:

- Proportion of patients with disease flare during the DBW period.
- Changes from baseline in each of the 6 individual components of the PedACR core set variables during the OLLI period and during the DBW period
- PedACR30/50/70/90/100 response rates during the OLLI period and during the DBW period.
- Changes from baseline in the Physical Summary Score (PhS) and Psychosocial Summary Score (PsS) of the Child Health Questionnaire-Parent Form 50 (CHQ-PF50) during the OLLI period and during the DBW period.
- Changes from baseline in caregiver burden as measured by the Parental Impact-Time and Parental Impact-Emotion scales of the CHQ-PF50 during the OLLI period and during the DBW period.
- Proportion of patients with inactive disease (as defined by Wallace et al. 2011) during the OLLI period and during the DBW period.
- Proportion of patients in remission (as defined by Wallace et al. 2012) during the DBW period.
- Proportion of patients with minimal disease activity (as defined by Consolaro et al. 2012) during the OLLI period and during the DBW period.
- Change from baseline in JADAS-27 during the OLLI period and during the DBW period.
- Changes from baseline in arthritis-related pain severity as measured by the CHAQ pain severity VAS item during the OLLI period and during the DBW period.
- In patients with JPsA:
    - Change from baseline in PASI score during the OLLI period and during the DBW period.
- In patients with JPsA or ERA:

  - Change from baseline in SPARCC enthesitis index during the OLLI period and during the DBW period.
  - Change from baseline in the JSpADA during the OLLI period and during the DBW period.
- Change in immunoglobulin levels and peripheral blood immunophenotyping (including T and B cells, T cell subsets, and NK cells) from baseline during the OLLI period and during the DBW period.
- Change of IgG titers from pre-vaccination to 4 weeks and 12 weeks post-vaccination in patients eligible for vaccination with tDaP and/or pneumococcal conjugate vaccine according to local guidelines.
- Assessment of tablet or oral suspension product acceptability and palatability at baseline and Week 12.
- Safety variables
  - AEs including SAEs
  - Permanent discontinuation of investigational product
  - Temporary interruption of investigational product

9.1.2.1. PedACR30/50/70/90/100 Assessments

The PedACR30 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%. Pediatric ACR50 and ACR70 improvement criteria are defined as above with improvements of 50% and 70%, respectively.

- 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 9.1.2.7)
- Parent's Global Assessment of Well-Being (Section 9.1.5)
- Physical function as assessed by the Childhood Health Assessment Questionnaire (CHAQ) (Section 9.1.5)
- Acute-phase reactant (hsCRP and ESR)

ACR50, ACR70, ACR90, and ACR100 responses are efficacy measures that are calculated as improvements of at least 50%, 70%, 90% and 100%, respectively, in the PedACR Core Set values listed above.

9.1.2.2. Juvenile Arthritis Disease Activity Score-27

The JADAS-27 score is a validated composite disease activity measure for JIA (Consolaro et al. 2012). Recently, the scoring system was adapted to use the 27-joint count (Bazso et al. 2009), and hsCRP or ESR for the inflammatory marker component (Nordal et al. 2012). The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles.

JADAS-27 score will be determined based on 4 components:

- Physician's Global Assessment of Disease Activity (Section 9.1.2.7)
- Parent's Global Assessment of Well-Being (from CHAQ; Section 9.1.5)
- Number of joints with active disease (27-joint assessment)
- hsCRP or ESR as applicable

9.1.2.3. Disease Activity

Minimal Disease Activity

Minimal disease activity is calculated based on the scores from the Physician's Global Assessment of Disease Activity (Section 9.1.2.7), Parent's Global Assessment of Well-Being (Section 9.1.5), and the number of swollen joints as described in the SAP and Consolaro et al. 2012.

Inactive Disease

Inactive disease is indicated by the presence of all of the following (Wallace et al. 2011):

- No joints with active arthritis based on JADAS-27 (Section 9.1.2.1)
- No fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA as assessed by the investigator
- No active uveitis as assessed by the investigator
- Normal erythrocyte (ESR) or hsCRP (i.e., within normal limits in the local laboratory or, if elevated, not attributable to JIA)
- Physician's Global Assessment of Disease Activity indicating no active disease (best possible score on scale [0]) (Section 9.1.5)
- Duration of morning stiffness ≤15 minutes

Remission

Remission is defined as inactive disease for at least 24 consecutive weeks (Wallace et al. 2012).

9.1.2.4. Psoriasis Area and Severity Index

The PASI combines assessments of the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs). It also assesses the severity of erythema (redness), plaque induration/infiltration (thickness), and desquamation (scaling) in each region, yielding an overall score of 0 (no psoriasis) to 72 (most severe disease [Fredriksson and Pettersson 1978; Mease 2011]).

The head, upper extremities, lower extremities, and trunk are assessed separately and then combined using weighting based on the surface area represented by each area (head = 0.1, upper extremities = 0.2, trunk = 0.3, and lower extremities = 0.4). The degree of erythema, induration, and scale in each area is judged on a 0 to 4 scale, the sum of which represents disease severity. The area of involvement of each area is graded from 0 to 6, depending on the estimated percentage of lesional area (0 = 0%, 1 = 1% to 9%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%). These body scores are multiplied by the disease severity score and the weighting for each body area, yielding a score between 0 and 72. The PASI score will be program-generated.

Further practical details help the assessment: (1) the neck is assessed as part of the head; (2) the axillae and groin are assessed as part of the trunk; (3) the buttocks are assessed as part of the lower limbs; (4) when scoring the severity of erythema, scales should not be removed.

9.1.2.5. Spondyloarthritis Research Consortium of Canada Enthesitis Index

The SPARCC enthesitis index is used to measure the severity of enthesitis, which assesses 16 sites for enthesitis using a score of "0" for no activity or "1" for activity (Maksymowych et al. 2009). The SPARCC enthesitis index is the sum of all site scores (range 0 to 16), with higher scores indicating more severe enthesitis. The sites assessed include medial epicondyle (left/right [L/R]), lateral epicondyle (L/R), supraspinatus insertion into greater tuberosity of humerus (L/R), greater trochanter (L/R), quadriceps insertion into superior border of patella (L/R), patellar ligament insertion into inferior pole of patella or tibial tubercle (L/R), Achilles tendon insertion into calcaneum (L/R), and plantar fascia insertion into calcaneum (L/R).

9.1.2.6. Juvenile Spondyloarthritis Disease Activity Index

The JSpADA is used to evaluate the disease activity of juvenile spondyloarthritis (Weiss et al. 2014). The range of possible scores is 0 to 8, where higher scores indicate more disease activity.

The Juvenile Spondyloarthritis Disease Activity Index scores will be determined by 8 components:

- Active joint count: 0 joints = 0, 1 to 2 joints = 0.5, >2 joints = 1
- Active enthesitis count: 0 entheses = 0, 1 to 2 entheses = 0.5, >2 entheses = 1
- Pain over the past week as assessed using a 0-10 NRS (0 = no pain; 10 = pain as bad as your child can imagine: 0 = 0, 1 to 4 = 0.5, 5 to 10 = 1
- CRP level related to juvenile spondyloarthritis activity: normal = 0, 1 to 2 times normal = 0.5, >2 times normal = 1
- Morning stiffness >15 minutes: Absent = 0, Present = 1
- Clinical sacroiliitis (defined as the presence of ≥2 of the following: tenderness on examination, positive Patrick's test or flexion, abduction and external rotation (FABER) test, and inflammatory back pain): Absent = 0, Present = 1
- Uveitis (any uveitis including acute/symptomatic and chronic/asymptomatic disease): Absent = 0, Present =1
- Back mobility (abnormal back mobility defined as modified Schober's test <20 cm): Normal = 0, Abnormal = 1

9.1.2.7. Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity is used 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. Exploratory Efficacy Assessment

The EQ-5D-Y is a widely used, generic questionnaire that assesses health status "today" (Ravens-Sieberer et al. 2010). The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). This part of the EQ-5D-Y can be used to

generate a health state index score, which is often used to compute a quality-adjusted life years (QALY) for utilization in health economic analyses.

9.1.4. 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 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) to Week 4, 12, and 44 (end of DBW period) will be assessed.

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 are 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.

9.1.5. Health Outcomes

Childhood Health Assessment Questionnaire

The Childhood Health Assessment Questionnaire (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; 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 (Ruperto et al. 2001):

- Parent's Global Assessment of Well-Being
    - This is a component of the PedACR core response set as well as the JADAS-27
    - The instrument is a 0 to 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 to 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.

European Quality of Life-Five Dimensions-Youth (EQ-5D-Y)

The EQ-5D-Y is a widely used, generic questionnaire that assesses health status "today" (The EuroQol Group 2014). It is completed by parents (proxy) for children aged 4 to 7 years; for children aged 8 years and older, the EQ-5D-Y will be self-completed (children aged <4 years will not complete this assessment per developer recommendation); respondents will continue with the version of the instrument they begin the study with even if they change age during the course of the study. The questionnaire consists of 2 parts: the first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 3 possible levels of response (no problems, some problems, or a lot of problems). This part of the EQ-5D-Y can be used to generate a health state index score, which is often used to compute QALY for utilization in health economic analyses. The health state index score is calculated based on the responses to the 3 dimensions, providing a single value on a scale from less than 0 (where zero is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health), with higher scores indicating better health utility.

The second part of the questionnaire consists of a visual analog scale on which the patient rates their perceived health state from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Published studies by EuroQol Group members showed preliminary evidence of the instrument's feasibility, reliability, and validity (Ravens-Sieberer et al. 2010). The scale will be given to the parent/patient by the site investigator and self-completed by the parent/patient while they are at the site. The investigator will be responsible for checking for missing responses.

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 duration. Responses are yes/no.

Patient's Assessment of Pain Numeric Rating Scale (NRS)

The physician will ask the parent/legal guardian to rate their child's worst level of pain over the past week using a 0-10 NRS (0 = no pain; 10 = pain as bad as your child can imagine).

Product Acceptability and Palatability Assessments

The caregiver/legal guardian/patient will be asked to provide responses to questions designed to assess the acceptability and palatability of the formulations, either tablet or oral suspension. The questionnaire for tablet acceptability will assess the subject's ability to swallow the tablet. The questionnaire for suspension acceptability and palatability will assess the subject's experience relating to the taste and smell of the suspension and ease of administering and taking the suspension (Davies and Tuleu 2008; Kozarewicz 2014).

The appropriate questionnaire will be administered at baseline (after initial dose) and Visit 9 (after approximately 12 to 14 weeks of use). The questionnaire will be responded to by parents (proxy) for children aged 2 to 7 years. For children aged 8 years and older, the questionnaire will be self-completed.

9.1.6. Appropriateness of Assessments

All assessments utilized in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

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 their assessment of the potential relatedness of each AE to protocol procedure and/or investigational product, via electronic data entry.

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 in-patient 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 patient has signed the ICF and Assent Form (as applicable) and has 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 as per 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 a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This

24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the electronic data entry system.

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/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 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.

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 9.4.6)
- Venous thromboembolism (deep vein thrombosis and pulmonary embolism)
- Arterial thrombotic events (see Section 9.4.6)

Sites 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 to facilitate process and product improvements.

Patients (or caregivers/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). 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. Patients in the age cohort of age 2 to ≤7 years will not have flow cytometry testing due to blood volume limitations.

Use of local anesthetics (e.g., EMLA cream) consistent with local prescribing information is permitted during the study visit to ease discomfort associated with venipunctures. With the exception of laboratory test results that may unblind the study, 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 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 in Section 2).

Patients who are hBcAb positive and HBV DNA negative (undetectable) at screening will require measurement of HBV DNA at Visit 9, Visit 12, Visit 15, Visit 17, ETV, 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 kinase 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 lab 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.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (refer to Interim Analyses section, Section 10.3.11) can request additional analyses of the safety data.

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 in a blinded manner by Lilly during the clinical study. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to Lilly during the clinical study. If a death or a clinical AE is deemed serious, unexpected, and possibly related to investigational product, only Lilly Global Patient Safety will be unblinded for regulatory reporting and safety monitoring purposes. These measures will preserve the integrity of the data collected during this study and minimize any potential for bias while providing for appropriate safety monitoring.

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, stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary interventions), arterial thromboembolic events, 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 deep vein thrombosis or pulmonary embolism, 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 baseline and postbaseline for the assessment of physical growth according to the Schedule of Activities (Section 2). Height and weight 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 (IGF-BP)-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 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. MRI instead of x-ray), the local addendum should be followed. Otherwise, the current protocol amendment should be followed with regard to knee x-rays.

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).

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 Davies 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.

9.5. Pharmacokinetics

9.5.1. Pharmacokinetic Strategy

The doses for this study were selected based on PK modeling such that the highest dose in an age cohort is expected to produce baricitinib exposure similar to that produced by 4-mg in adult patients with RA. For adolescent patients (aged 12 to <18 years) and children ≥9 years, that dose is expected to be 4-mg QD, whereas in children aged ≥6 to <9 and ≥2 to <6 years the dose is expected to be 2-mg QD.

Before enrolling a majority of patients, the PK in adolescent patients receiving 4-mg QD will be evaluated in a small number of lead-in patients to confirm the suitability of this dose in adolescent patients with JIA. Patients will be dosed QD and serial blood samples will be collected at steady state for analysis of baricitinib concentrations. Refer to Section 9.5.2 for details. The PK in individual patients will be evaluated using noncompartmental methods and will inform dose selection for subsequent adolescent patients. No adolescent patients will be enrolled directly into the OLLI period until the PK in the lead-in patients has been evaluated.

For younger cohorts of PK lead-in patients (aged ≥9 to <12 years, aged 6 to <9 years and aged 2 to <6 years), the same lead-in process will be performed as that for adolescents. The PK lead-in period for patients aged ≥9 to 12 years will complete before the PK lead-in period for patients aged 6 to <9 years can begin, and this one will also complete before the PK lead-in period for patients 2 to <6 years can begin (Section 5.1.2).

For patients enrolled directly into the OLLI period, sparse blood samples for PK analysis will be collected as described in Section 9.5.3. These will be analyzed at the end of the study using population PK methods. Microsampling may be used by patients participating in the Safety/PK period if kits and assays are available for some of the PK sample collections.

9.5.2. Safety/PK Assessment Lead-in Period

A blood sample will be collected at the times indicated in the Schedule of Activities (Section 2). These blood samples will be used to determine the concentrations of baricitinib using a validated bioanalytical method. The timing will be as follows:

- At Day 1, patients will take their investigational product and PK samples will be collected 15 minutes and 1 hour postdose.
- At Day 4, patients will take their investigational product at home. The first blood sampling collected during this visit is collected 2 hours after the dose is taken and includes a microsample and venous blood sample. The second blood sample, which can be collected as a microsample, is collected 4 hours after the dose is taken.
- At Day 14, a PK sample will be collected **BEFORE** the investigational product is taken. Immediately after the PK sample is collected, the patient will take the investigational product. A PK sample will also be collected at each of the following times after the dose is given: 30 minutes and 6 hours.

For visits where PK samples will be collected, the actual date and 24-hour clock time of sample collection, and the date and time of the last 2 doses should be recorded. At Day 4 and Day 14, these 2 doses should be the dose given on the morning of the day of sample collection and the dose given the previous day. This sampling schedule should be followed as closely as possible; however, failure to take PK samples at these specified times will not be considered a protocol violation. If the patient fails to follow the directions for a particular visit, the sample should still be collected at that visit, and the date and 24-hour clock time of sample collection and the date and 24-hour clock time of the 2 doses prior to the sample being drawn should be recorded.

Safety variables (AEs including SAEs, permanent discontinuation of investigative product, temporary interruptions of investigative product) will be assessed throughout this period. Refer to Section 10.3.4 for additional information regarding safety assessments.

9.5.3. OLLI Assessment Period

A venous blood sample will be collected at the times indicated in the Schedule of Activities (Section 2). These blood samples will be used to determine plasma concentrations of baricitinib using a validated bioanalytical method. The timing will be as follows:

- At Visit 5, patients will take their investigational product in the clinic, and PK samples will be collected 15 minutes and 1 hour postdose.
- At Visit 6, patients will be asked to take their investigational product at home prior to visiting the clinic. The clinic visit should be scheduled so that the blood sample collected during this visit is collected 2 to 4 hours after the dose is taken at home.
- At Visit 7, patients will be asked to take their investigational product at home prior to visiting the clinic. The clinic visit should be scheduled so that the blood sample collected during this visit is collected 4 to 6 hours after the oral dose is taken at home.
- For Visit 8 and Visit 9, patients will be asked to not take their investigational product before visiting the clinic and a blood sample will be collected at any time predose on the day of the clinic visits. If the patient has taken the oral dose prior to the visit, the sample may be collected anytime postdose.
- For an early termination visit prior to Visit 9, a sample may be drawn anytime if the last dose of investigational product was taken within the last 48 hours.

Visit 5 samples will not be collected for patients who were in the PK lead-in portion of the study.

For visits at which PK samples will be collected, the actual date and 24-hour clock time of sample collection, and the date and time of the last 2 doses prior to the sample being collected, will be recorded. At Week 2 and Week 4, the 2 previous doses should be the dose taken on the morning of the day of sample collection and the dose taken the day before that. At Week 8 and Week 12, these 2 doses should be the dose given on the morning prior to the day of sample collection and the dose given the day before that.

If the patient fails to follow the directions for a particular visit, the sample should still be collected at that visit. The date and 24-hour clock time of sample collection and the date and time of the 2 doses prior to the sample being collected will be recorded.

Pharmacokinetic samples will be stored at a laboratory facility designated by the sponsor. Pharmacokinetic samples may also be assayed for additional exploratory analyses. Pharmacokinetic results will not be provided to investigative sites. Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following the last patient visit for the study.

9.6. Pharmacodynamics

Refer to Section 10.3.6.

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 samples 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, mechanism of action of baricitinib, and/or research method, or to validate diagnostic tools or assay(s) related to JIA.

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, or for a shorter period if local regulations require. 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

The EQ-5D-Y is being collected in this study to collect data for input into economic models. See Section 9.1.5 for instrument description.

10. Statistical Considerations

10.1. Sample Size Determination

A total of 128 patients will be randomized in a 1:1 ratio to baricitinib or placebo (64 per treatment arm) in the DBW period. This sample size will provide approximately 80% power to detect the difference in time to disease flare between the 2 treatment groups using a 2-sided test with a significance level of 0.05, assuming that the expected percentages of patients experiencing disease flare in the DBW period are 35% for baricitinib and 60% for placebo and that the dropout rate is no greater than 10% in this period.

It is estimated that 197 patients are required to enter the OLLI period to allow 128 patients to be randomized into the DBW period (assuming that 65% of the patients meet the PedACR30 criteria at the end of the OLLI period). The nonresponder and dropout rate will be monitored during the OLLI period to adjust the overall sample size to ensure that a minimum of 128 patients will be randomized in the DBW. If the PedACR30 response rate during the OLLI period is higher than the assumed rate of 65%, fewer than 197 patients may be required.

The above sample size and power estimates are based on nQuery®+nTerim 4.0.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined based on the different treatment period:

Population	Description
Entered population	All participants who sign informed consent.
Safety/PK population	All patients who received at least 1 dose of investigational product in Safety/PK assessment period.
OLLI population	All participants who take at least 1 age-based final dose as confirmed by PK assessments of investigational product in the OLLI period, other than the Safety/PK population.
DBW population	All randomized patients in DBW period following intent-to-treat (ITT) principles.
DBW safety population	All randomized patients in DBW period who receive at least 1 dose of investigational product.
General safety population	All patients who received at least 1 dose of investigational product.

Abbreviations: OLLI = open-label lead-in; DBW = double-blind withdrawal; ITT = intent to treat; PK = pharmacokinetic.

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 statistical analysis plan (SAP) describing the statistical methodologies will be developed by Lilly or its designee.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

The primary endpoint will be the time-to-flare during the DBW period for randomized patients. Patients who discontinue the DBW period without experiencing a flare will have their data censored. Survival curves will be estimated using the Kaplan–Meier method for all "time-to" variables in the DBW period.

Efficacy and health outcome endpoints will be summarized using descriptive statistics for the OLLI population during OLLI period. Treatment comparisons will be performed for the DBW population in the DBW period.

Continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, and median. Continuous efficacy and health outcome variables will be evaluated using an analysis of covariance (ANCOVA) model with treatment, JIA patient category (polyarticular and extended oligoarticular versus ERA and JPsA), prior bDMARD use, and baseline score in the model. The last observation carried forward (LOCF) approach will be used to impute missing data.

Categorical data will be summarized as frequency counts and percentages. Categorical efficacy variables will be evaluated using a logistic regression analysis with treatment, JIA patient category (polyarticular and extended oligoarticular versus ERA and JPsA), and prior bDMARD use in the model. The proportions and 95% confidence interval will be reported. Missing data will be imputed using the nonresponder imputation (NRI) method.

A futility analysis will be conducted using the PedACR30 response rate observed in the first 100 patients complete OLLI phase. The futility analysis will be based on 50% of patients achieving a PedACR30 response rate at the end of OLLI phase. The study will stop for futility if <50% of the first 100 patients to complete the OLLI period have a PedACR30 response.

All safety data will be descriptively summarized in each treatment period using corresponding populations. Comparison between baricitinib and placebo will be performed during the DBW period for the DBW population. The Fisher exact test will be used for the AEs, discontinuations, and other categorical safety data for between-treatment-group comparisons in the DBW period. Continuous vital signs, body weight, and other continuous safety variables, including laboratory variables, will be analyzed using ANCOVA with treatment and baseline value in the model in the DBW population.

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 was approved before the first patient visit in Study JAHV.

Missing Data Imputation

The following methods for imputation of missing data will be used:

1. Nonresponder imputation (NRI): All patients who discontinue the study will be defined as nonresponders for the NRI analysis for categorical variables, such as PedACR30/50/70/90/100, from the time of discontinuation and onward.
2. 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.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

The number of patients along with enrolled, OLLI, DBW, and safety populations will be summarized. Frequency counts and percentages will be presented. All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported along with their reason for discontinuation. Reasons for discontinuation from the study will be summarized.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized descriptively. 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 ACR pediatric JIA core set variables, JADAS, SPARCC (for patients with enthesitis at baseline), and JSpADA.

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 time to disease flare (flare defined as worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria) during the DBW period for the DBW population. If either the number of joints with active arthritis or the number of joints with limitation of motion are used in the calculation of flare for a study visit, then a minimum worsening of at least 2 active joints or 2 joints with limitation of motion must be present. An active joint is defined as a joint with swelling or, in the absence of swelling, limitation of motion accompanied by pain on motion and/or tenderness. If either the Physician's Global Assessment of Disease Activity or the Parent's Global Assessment of Well-Being are used in the calculation of flare for a study visit, then a minimum worsening (as defined in the SAP) on the visual analogue scale (VAS) must be present. If ESR or CRP is used in the definition of "flare" and counts towards worsening, then the second value for ESR or CRP used in the calculation must be above the upper limit of normal for ESR (>20 mm/hour) or CRP. In JAHV, for primary analysis, disease flare definition will only use ESR.

The 6 PedACR core criteria (Gianni et al. 1997) includes:

- 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
- Physical function as assessed by the CHAQ
- Acute-phase reactant (hsCRP and ESR)

Patients who discontinue the DBW period without experiencing a flare will have their data censored. A stratified logrank test across all JIA subtypes will be used as the primary analysis method. Survival curves will be estimated using the Kaplan–Meier method for all "time-to" variables in the DBW period.

10.3.3.2. Secondary Analyses

Secondary efficacy and health outcomes analyses (Table JAHV.8) will be based on the following study periods and study populations:

- OLLI period population: All participants who take at least 1 age-based final dose as confirmed by PK assessments of investigational product in the OLLI period, other than the Safety/PK population. Baseline is defined as Week 0.
- DBW period population: All randomized patients in DBW period following intent-to-treat (ITT) principles.

Table JAHV.8. Secondary Efficacy Endpoint Analyses

Endpoint	Population	Analysis Period	Treatment Comparisons	Analysis Method
Proportion of disease flare	DBW	Week 16 to Week 44	Baricitinib versus placebo	Logistic regression with NRI
PedACR core set variables: change from baseline	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	ANCOVA with LOCF
PedACR30/50/70/90/100 response rates (compare to patient's condition prior to first dose of investigational product)	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	Logistic regression with NRI
PhS and PsS scores (CHQ-PF50): change from baseline	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	ANCOVA with LOCF
Parental Impact –Time/Emotion scores (CHQ-PF50): change from baseline	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	ANCOVA with LOCF
Inactive disease: proportion	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	Logistic regression with NRI
Minimal disease activity: proportion	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	Logistic regression with NRI
Remission: proportion	DBW	Week 28 to Week 44	Baricitinib versus placebo	Logistic regression with NRI
JADAS-27: change from baseline	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	ANCOVA with LOCF
Pain severity VAS (CHAQ): change from baseline	OLLI	Week 2 to Week 12	No comparison	Summary statistics
	DBW	Week 16 to Week 44	Baricitinib versus placebo	ANCOVA with LOCF

Abbreviations: ANCOVA = analysis of covariance; CHQ-PF50 = Child Health Questionnaire-Parent Form 50; DBW = double-blind withdrawal; HRQOL = health-related quality of life; JADAS-27 = Juvenile Arthritis Disease Activity Score 27; LOCF = last observation carried forward; NRI = nonresponder imputation; OLLI = open-label lead-in; PedACR = Pediatric American College of Rheumatology; VAS = visual analog scale.

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 investigation product

- AEs leading to discontinuation
- AEs of special interest
- Laboratory analytes (hematology and chemistry [including ALT and AST], neutrophil counts, and immunological measurements)
- Vital signs

Primary safety analyses will summarize baricitinib and placebo treatment groups for DBW population in DBW period. The Fisher exact test will be used for the AEs, discontinuation, and other categorical safety data for between-treatment-group comparisons in the DBW period. Continuous vital signs, body weight, and other continuous safety variables, including laboratory variables, will be analyzed using ANCOVA with treatment and baseline value in the model.

Summaries of safety data will be presented for baricitinib in OLLI period using OLLI population and throughout the study using general safety population unless otherwise stated.

Sensitivity analysis may be performed when there are patients who did not take investigational product after randomization in DBW. Pharmacokinetic analysis will be conducted using all evaluable PK data in safety/PK population. 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 safety analysis plan. 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 10.3.11.1)
- thrombotic events (such as deep vein thrombosis and pulmonary embolism)

Sites 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 Center 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. Pharmacokinetic/Pharmacodynamic Analyses

In the safety/PK assessment period, plasma concentrations from each group will be analyzed by noncompartmental analysis and/or graphical overlay of PK observations with the anticipated therapeutic concentration range from adult patients with RA. After all PK data have been collected, plasma baricitinib concentration–time data will be pooled and evaluated using population PK methods. A covariate screen of patient and study-specific factors will be included in the analyses based on factors investigated in previous and (if any) ongoing PK analyses and on their relevance to the target population. Exploratory and/or model-based analyses examining the relationships between baricitinib exposure and efficacy and response endpoints will be conducted. Other analyses of efficacy and safety outcome measures may also be assessed as scientifically appropriate and warranted by available data. Details about the analyses to be conducted will be contained in the PK/PD analysis plan.

10.3.6. 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) at Weeks 4, 12, and at the end of DBW period 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.

10.3.7. Health Outcomes

The health outcome measures will be analyzed using methods described for continuous or categorical data as described for efficacy measures in Section 10.3.1. More detailed analytical methods will be described in the SAP.

10.3.8. Product Acceptability and Palatability

Responses from the tablet and suspension acceptability and palatability questionnaires will be summarized categorically (frequency and percentage) by age group, for each visit separately and in aggregate. In addition, general trends from baseline and Week 12 in acceptability and palatability will be analyzed.

10.3.9. Subgroup Analyses

The summary statistical analysis will be conducted for the following subset of patients at each visit.

In the subset of patients with JPsA:

- Change from baseline in PASI score during the OLLI period and during the DBW period.

In the patients with JPsA or ERA:

- Change from baseline in SPARCC index of entheseal assessment during the OLLI period and during the DBW period.
- Change from baseline in JSpADA during the OLLI period and during the DBW period.

10.3.10. Exploratory Analysis

The change from baseline in EQ-5D-Y scores during the OLLI period and during the DBW period will be analyzed using methods described for continuous or categorical data as described for efficacy measures in Section 10.3.3. More detailed analytical methods will be described in the SAP.

10.3.11. Interim Analyses

A DMC will oversee the conduct of all the Phase 3 clinical studies evaluating baricitinib in patients with JIA. 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 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 for studies of patients with JIA 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.

Access to the unblinded interim data will be limited to the statisticians who conduct the interim analyses and the DMC. The statisticians conducting the interim analyses will be independent from the study team. The study team will not have access to the unblinded data. 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 includes, but is 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.

In addition to the DMC members, a limited number of prespecified individuals may gain access to the unblinded PK, safety, and efficacy data (as specified in the unblinding plan) prior to the final database lock to initiate the exploration and/or final population of the PK/PD model development processes. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the database is locked.

Lilly will conduct a futility analysis after 100 patients complete the OLLI period. The study will stop for futility if the observed PedACR30 response rate is <50% in the OLLI period. Due to the open-label feature, there will be no alpha adjustment for futility analysis.

10.3.11.1. 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), venous thrombotic events, arterial thromboembolic events and noncardiovascular deaths. Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the charter.

11. References

Bazso A, Consolaro A, Ruperto N, Pistorio A, Viola S, Magni-Manzoni S, Malattia C, Buoncompagni A, Loy A, Martini A, Ravelli A; Pediatric Rheumatology International Trials Organization. Development and testing of reduced joint counts in juvenile idiopathic arthritis. *J Rheumatol*. 2009;36(1):183-190.

Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. *J Rheumatol*. 2002;29(5):1058-1064.

Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, Lu P, Cuttica R, Keltsev V, Xavier RM, Calvo I, Nikishina I, Rubio-Pérez N, Alexeeva E, Chasnyk V, Horneff G, Opoka-Winiarska V, Quartier P, Silva CA, Silverman E, Spindler A, Baildam E, Gámir ML, Martin A, Rietschel C, Siri D, Smolewska E, Lovell D, Martini A, De Benedetti F; Paediatric Rheumatology International Trials Organisation PRINTO; Pediatric Rheumatology Collaborative Study Group (PRCSG). Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis*. 2015;74(6):1110-1117.

Centers for Disease Control and Prevention. Data table of weight-for-age charts. 2001. Available at: https://www.cdc.gov/growthcharts/html_charts/wtage.htm. Accessed 2019 March 8.

Chavarro JE, Watkins DJ, Afeiche MC, Zhang Z, Sánchez BN, Cantonwine D, Mercado-García A, Blank-Goldenberg C, Meeker JD, Téllez-Rojo MM, Peterson KE. Validity of self-assessed sexual maturation against physician assessments and hormone levels. *J Pediatr.* 2017;186:172-178.e3.

Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C, Pederzoli S, Davì S, Martini A, Ravelli A. Paediatric Rheumatology International Trials Organization. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. *Arthritis Rheum*. 2012;64(7):2366-2374.

De Benedetti F, Ravelli A, Martini A. Cytokines in juvenile rheumatoid arthritis. *Curr Opin Rheumatol.* 1997;9(5):428-433.

Davies E, Tuleu C. Medicines for children: a matter of taste. *J Pediatrics*. 2008;153(5):599-604.

Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, de la Torre I, Gaich C, Rooney T, Schlichting D, de Bono S, Emery P. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95.

Filocamo G, Davì S, Pistorio A, Bertamino M, Ruperto N, Lattanzi B, Consolaro A, Magni-Manzoni S, Galasso R, Camilla Varnier G, Martini A, and Ravelli A. Evaluation of 21-numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. *J Rheumatol*. 2010;37:1534-1541.

Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, Gurbuz S, Dickson C, de Bono S, Schlichting D, Beattie S, Kuo WL, Rooney T, Macias W, Takeuchi T. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis

and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol*. 2017;69(3):506-517.

Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. *Dermatologica.* 1978;157(4):238-244.

Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, Covington MB, Thomas B, Collier P, Favata MF, Wen X, Shi J, McGee R, Haley PJ, Shepard S, Rodgers JD, Yeleswaram S, Hollis G, Newton RC, Metcalf B, Friedman SM, Vaddi K. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol.* 2010;184(9):5298-5307.

Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, Beattie SD, Koch AE, Cardillo TE, Rooney TP, Macias WL, de Bono S, Schlichting DE, Smolen JS. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med.* 2016 31;374(13):1243-1252.

Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum*. 1997;40(7):1202-1209.

Gidman W, Meacock R, Symmons D. The humanistic and economic burden of juvenile idiopathic arthritis in the era of biologic medication. *Curr Rheumatol Rep.* 2015;17:31.

Groot N, Heijstek MW, Wulffraat NM. Vaccinations in paediatric rheumatology: an update on current developments. *Curr Rheumatol Rep*. 2015;7:46.

HealthActCHQ. The CHQ Scoring and Interpretation Manual. Boston, MA: HealthActCHQ, 2013.

Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Koné-Paut I, Fasth A, Minden K, Ravelli A, Abinun M, Pileggi GS, Borte M, Wulffraat NM; EULAR. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis.* 2011;70(10):1704-1712.

Hinze C, Gohar F, Foell D. Management of juvenile idiopathic arthritis: hitting the target. *Nat Rev Rheumatol*. 2015;11(5):290-300.

Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. *Int J Pharm*. 2014;469(2):245-248.

Lepore L, Pennesi M, Saletta S, Perticarari S, Presani G, Prodan M. Study of IL-2, IL-6, TNF alpha, IFN gamma and beta in the serum and synovial fluid of patients with juvenile chronic arthritis. *Clin Exp Rheumatol.* 1994;12(5):561-565.

Lovell DJ. Update on treatment of arthritis in children: new treatments, new goals. *Bull NYU Hosp Jt Dis*. 2006;64(1-2):72-76.

Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, Stein LD, Gedalia A, Ilowite NT, Wallace CA, Whitmore J, Finck BK. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med*. 2000;342(11):763-769.

Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe RK, Weiner LW, Horneff G, Huppertz HI, Olson NY, Medich JR, Carcereri-De-Prati R,

McIlraith MJ, Giannini EH, Martini A; Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med*. 2008;359(8):810-820.

Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, Sampalis J, Conner-Spady B. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis*. 2009;68(6):948-953.

Mangge H, Kenzian H, Gallistl S, Neuwirth G, Liebmann P, Kaulfersch W, Beaufort F, Muntean W, Schauenstein K. Serum cytokines in juvenile rheumatoid arthritis. Correlation with conventional inflammation parameters and clinical subtypes. *Arthritis Rheum.* 1995;38(2):211-220.

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44(235):291–303.

Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.* 1970;45(239):13–23.

Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). *Arthritis Care Res (Hoboken)*. 2011;63(suppl 11):S64-S85.

Nordal EB, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, Lahdenne P, Nielsen S, Peltoniemi S, Straume B, Rygg M. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. *Ann Rheum Dis*. 2012;71(7):1122-1127.

O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis*. 2013;72(suppl 2):ii111-ii115.

O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Ann Rev Med*. 2015;66:311-328.

Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-392.

Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2011;377:2138-3149.

Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet.* 2007;369(9563):767-778.

Ravens-Sieberer U, Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, Egmar AC, Gusi N, Herdman M, Jelsma J, Kind P, Olivares PR, Scalone L, Greiner W. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. *Qual Life Res*. 2010;19(6):887-897.

Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. J Cell Sci. 2004;117(8):1281-1283.

Ringold S, Weiss PF, Beukelman T, DeWitt EM, Ilowite NT, Kimura Y, Laxer RM, Lovell DJ, Nigrovic PA, Robinson AB, Vehe RK. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum.* 2013;65(10):2499-2512.

Rooney M, David J, Symons J, Di Giovine F, Varsani H, Woo P. Inflammatory cytokine responses in juvenile chronic arthritis. *Br J Rheumatol*. 1995;34(5):454-460.

Rooney M, Varsani H, Martin K, Lombard PR, Dayer JM, Woo P. Tumour necrosis factor alpha and its soluble receptors in juvenile chronic arthritis. *Rheumatology (Oxford)*. 2000;39(4):432-438.

Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, Abud-Mendoza C, Burgos-Vargas R, Gerloni V, Melo-Gomes JA, Saad-Magalhães C, Chavez-Corrales J, Huemer C, Kivitz A, Blanco FJ, Foeldvari I, Hofer M, Horneff G, Huppertz HI, Job-Deslandre C, Loy A, Minden K, Punaro M, Nunez AF, Sigal LH, Block AJ, Nys M, Martini A, Giannini EH; Paediatric Rheumatology International Trials Organization and the Pediatric Rheumatology Collaborative Study Group. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheum.* 2010;62(6):1792-1802.

Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, Abud-Mendoza C, Burgos-Vargas R, Gerloni V, Melo-Gomes JA, Saad-Magalhães C, Sztajnbok F, Goldenstein-Schainberg C, Scheinberg M, Penades IC, Fischbach M, Orozco J, Hashkes PJ, Hom C, Jung L, Lepore L, Oliveira S, Wallace CA, Sigal LH, Block AJ, Covucci A, Martini A, Giannini EH; Paediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet*. 2008;372(9636):383-391.

Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L, Tortorelli A, Landgraf JM, Singh G, Martini A, for the Paediatric Rheumatology International Trials Organisation (PRINTO). Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. *Clin Exp Rheumatol.* 2001;19(suppl 23):S1-S9.

Singh G, Athreya B, Fries J, Goldsmith D. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum*. 1994;12:1761-1769.

Sousa S, Duarte AC, Cordeiro I, Ferreira J, Gonçalves MJ, Meirinhos T, Rocha TM, Romão VC, Santos MJ. Efficacy and Safety of Vaccination in Pediatric Patients with Systemic

Inflammatory Rheumatic Diseases: a systematic review of the literature. *Acta Reumatol Port.* 2017;42(1):8-16.

Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr.* 1985;107(3):317-329.

Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich C, Rooney T, Schlichting D, Macias WL, de Bono S, Tanaka Y. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376(7):652-662.

Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N; Childhood Arthritis Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Paediatric Rheumatology International Trials Organisation. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken).* 2011;63(7):929-936.

Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, Szer IS, Ringold S, Brunner HI, Schanberg LE, Sundel RP, Milojevic D, Punaro MG, Chira P, Gottlieb BS, Higgins GC, Ilowite NT, Kimura Y, Hamilton S, Johnson A, Huang B, Lovell DJ; Childhood Arthritis and Rheumatology Research Alliance. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum. 2012;64(6):2012-2021.

Weiss PF, Colbert RA, Xiao R, Feudtner C, Beukelman T, DeWitt EM, Pagnini I, Wright TB, Wallace CA. Development and retrospective validation of the juvenile spondyloarthritis disease activity index. *Arthritis Care Res (Hoboken)*. 2014;66(12):1775-1782.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ACR20	20% 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
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
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
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
CAP	College of American Pathologists
cDMARD	conventional disease-modifying antirheumatic drug
CHAQ	Childhood Health Assessment Questionnaire

Term	Definition
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
DBW	double-blind withdrawal
disease flare	Worsening of 30% or more in at least 3 of the 6 PedACR core criteria for JIA and an improvement of 30% or more in no more than 1 of the criteria from the patient's condition at the conclusion of the OLLI period
disease response	Improvement of 30% or more in at least 3 of 6 PedACR core-response variables without a worsening of greater than 30% in more than 1 variable
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
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.
EQ-5D-Y	European Quality of Life-5 Dimensions–Youth version
ERA	enthesitis-related juvenile idiopathic arthritis
ETV	early termination visit
EULAR	European League Against Rheumatism
GCP	good clinical practice

Term	Definition
hBsAb	hepatitis B surface antibody
hBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
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
Ig	immunoglobulin
IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor-binding protein-3
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.
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.
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.

Term	Definition
IWRS	interactive web-response system
JADAS	Juvenile Arthritis Disease Activity Score
JAK	Janus kinase
JIA	juvenile idiopathic arthritis
JPsA	juvenile psoriatic arthritis
JSpADA	Juvenile Spondyloarthritis Disease Activity Index
LOCF	last observation carried forward
MACE	major adverse cerebro-cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella
MTX	methotrexate
NRI	nonresponder imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OLE	open label extension
OLLI	open-label lead-in
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic(s)
PedACR30	Pediatric American College of Rheumatology 30 responder index
PK	pharmacokinetic(s)
PPD	purified protein derivative
Q2W	once every 2 weeks
QALY	quality-adjusted life years
QD	once daily
QW	once every week
RA	rheumatoid arthritis

Term	Definition
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.
SPARCC	Spondyloarthritis Research Consortium of Canada
STAT	signal transducer and activator of transcription
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.
TNF	tumor necrosis factor-alpha
TSH	thyroid-stimulating hormone
TYK2	tyrosine kinase 2
ULN	upper limit of normal
VAS	visual analogue scale
VTE	venous thromboembolism
VZV	varicella zoster virus

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	Thyroid-stimulating hormone (TSH)
Urobilinogen	Exploratory storage samples (serum, plasma)
Blood	Pharmacogenetic Sample (DNA)
Leukocyte esterase	Pregnancy Test (serum)[h]
Nitrite	Pregnancy Test (urine)[h]
	High sensitivity C-reactive protein (hsCRP)[i]
Lipids[a,b]	Rheumatoid factor
Total cholesterol	QuantiFERON®-TB Gold or T-SPOT®.TB[j]
Low-density lipoprotein	Purified protein derivative (PPD)[j]
High-density lipoprotein	ACPA (Anti-CCP)
Triglycerides	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)[i]
	Baricitinib plasma concentration (PK sample)
	IGF-1
	IGFBP-3
	Gonadal hormone (estradiol for females aged 8 to <18 years, testosterone for males aged 8 to <18 years)

Abbreviations: ACPA = anti-citrullinated protein antibodies; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; hBcAb = hepatitis B core antibody; hBsAb = hepatitis B surface antibody; hBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency 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; NK = natural killer; OLLI = open-label lead-in; PK = pharamacokinetic; PPD = purified protein derivative; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; TIBC = total iron-binding capacity ; TSH = thyroid-stimulating hormone; 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 glucose and lipids will be required at baseline and Week 12 of OLLI. 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 ≤50kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 10 to <25kg: fast for 6 hours prior to laboratory test
- Children <8 years and weighing <10kg: fast for 4 hours prior to laboratory test

These tests may be performed in a nonfasting state at all other visits.

[c] eGFR calculated by Bedside Schwartz 2009 formula or the Japanese Society for Pediatric Nephrology formula for patients in Japan.

[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 childbearing potential at screening only and will be performed centrally; after screening, urine pregnancy test will be performed locally for females of childbearing potential.

[i] Test results of hsCRP and lymphocyte subsets will be blinded after Visit 9, and the test results will not be sent to the study sites.

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

NOTE: 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:

- 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 (as applicable) 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 patient/patient's legal representative willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF and Assent Form (as applicable) 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.

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 (as applicable) 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 (as applicable), including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs and Assent Forms (as applicable) 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 (as applicable)
- 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
- 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 (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 their 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 their 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 his or her 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
- 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 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

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

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; 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. Weight-Based Prioritization Chart for Blood Sampling

Patients with a body weight lower than 30 kg if ≥8 years, or lower than 18 kg if <8 years, 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 JAHV. This prioritization chart uses a conservative estimate for weight, i.e., the third percentile of weight from the CDC Weight-for-age Chart (CDC [WWW]) for the youngest age in an age group.

The laboratory kits used in Study JAHV have been developed to accommodate blood volume limitations. Lilly will use visit- and age-specific laboratory kits for patients ≥8 years old and <8 years old. The kits for patients <8 years old exclude testosterone, estradiol, flow cytometry, and serum and plasma long-term storage samples. Lilly also recommends that purified protein derivative is used for tuberculosis testing instead of Quantiferon Gold or T-Spot in patients aged <8 years who weigh <18 kg. Lilly will provide training to sites along with the prioritization chart of laboratory samples to collect based on patient age and weight.

Weight-Based Prioritization Chart for Blood Sampling

Age	Weight	Excluded Testing – will not be collected
≥8 years	≥30 kg	N/A
	≥27 to <30 kg	• Long-term storage samples: RNA, serum, and plasma
	≥18 to <27 kg	• Long-term storage samples: RNA, serum, and plasma • Flow cytometry
	<18 kg	• Long-term storage samples: RNA, serum, and plasma • Testosterone or estradiol • Flow cytometry
<8 years	≥18 kg	• Long-term storage samples: serum and plasma • Testosterone or estradiol • Flow cytometry
	≥10 to <18 kg	• Long-term storage samples: RNA, serum and plasma • Testosterone or estradiol • Flow cytometry
	<10 kg	• Long-term storage samples: RNA, serum and plasma • Testosterone or estradiol • Flow cytometry • Consult Lilly medical if additional exclusions are required

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

Appendix 7. 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).

Current 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 or JIA-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 physiological-based pharmacokinetics (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 JAHV

An updated summary of dosing for Study JAHV is provided in the table below. Lilly has initiated the following for Study JAHV:

- Lilly enrolled the required patients aged 6 to <9 years in the PK cohort 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, 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 JAHV Dosing Summary

Age Group	Current Status of Enrollment	Baricitinib Dose
12 to <18 years old	Safety/PK completed; OLLI currently enrolling	4 mg
9 to <12 years old	Safety/PK completed; OLLI currently enrolling	4 mg
6 to <9 years old	Safety/PK enrollment completed as of October 2020	2 mg (based on predicted data – to be confirmed with observed data)
2 to <6 years old	Safety/PK to be initiated	2 mg[a]

Abbreviations: OLLI = open-label lead-in; PK = pharmacokinetic;

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

Appendix 8. Provisions for Changes in Study Conduct During Exceptional Circumstances

Exceptional circumstances, such as pandemics or natural disasters, may cause disruptions to the conduct of the study. Examples of such disruptions include limitations in the ability to conduct study procedures or ability to have on-site participant visits.

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 and if permitted by local regulations. These provisions for changes in study conduct are temporary and will be repealed once the restrictions are lifted.** 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.

2. **Remote Assessment and Data Collection**

Patient visit and data collection can be done remotely for OLLI visits following the protocol visit windows. The PI/Sub-I is to document all teleconferences/remote visits in the patient's records. Site facing assessments will be completed on paper (preferably eCOA if the site is able) and patient facing assessments will be conducted in interview format with the PI/SubI or other qualified personnel documenting the patient's responses on paper. Sponsor will provide guidance for performing these assessments (CHQ-PF50, EQ-5D-Y). Patients *cannot* proceed in JAHV past Visit 9 due to the requirement of PedACR30 responder/nonresponder criteria being defined at this visit to determine eligibility for randomization into DBW phase. Because most PedACR components cannot be collected by remote assessment, patients will be terminated from JAHV at Visit 9 and offered enrollment into JAHX (long term extension).

3. Investigational product and ancillary supplies (including participant diaries)

In cases when a patient is unable to come to the 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
- 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 participant'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 AE in the AE eCRF.

For patients unable to access investigator sites, laboratory testing will be conducted at least every 8 weeks in the OLLI and DBW periods. The first collection should be 8 weeks from the patient's last collected central laboratory samples.

Failure to have labs collected within the described ranges above may result in patient termination from the study.

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.

Note: Any results that are obtained from local laboratories will need to be retained by the investigator for their respective patients.

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 the 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 for these select parameters:

- WBC
- ANC
- Lymphocyte count
- Hemoglobin
- Platelet count
- 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 verbal consent for having remote visits and remote dispensing of IP and/or ancillaries prior to implementation of these activities.
- Source document(s) that are generated at an off-site location (e.g., 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 eCRFs. 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 9. Protocol Amendment I4V-MC-JAHV(d) Summary - A Randomized, Double-Blind, Placebo-Controlled, Withdrawal, Safety and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Juvenile Idiopathic Arthritis (JIA)

Overview

Protocol I4V-MC-JAHV—A Randomized, Double-Blind, Placebo-Controlled, Withdrawal, Safety and Efficacy Study of Oral Baricitinib in Patients from 2 Years to Less Than 18 Years Old with Juvenile Idiopathic Arthritis (JIA)—has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

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-JAHV Amendment (d)

*Changes marked only apply if Amendment (c) is in effect. These changes are not applicable in Amendment (d).

Section # and Name	Description of Change	Brief Rationale
Synopsis	• Disease flare improvement defined at Visit 9 instead of baseline • Cohorts adjusted	Clarification
Section 2. Schedule of Activities Appendix 8. Provision 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 additional 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	Baseline assessment of sexual maturity (Tanner Staging) was included based on feedback from regulatory agencies.
Section 2. Schedule of Activities	Height measurements adjusted.	The additional measurements for height were added for additional growth monitoring.

Section # and Name	Description of Change	Brief Rationale
		*Only applicable if Amendment C is in effect
	Addition of weight measurement to Visit 1	To calculate eGFR
	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.
	Addition of language to uveitis footnote	Clarification of study visits and monitoring of active uveitis.
	Addition of footnote related to dispensing of study drug (Table 2)	Requirement for review of Trial Manager report prior to study drug dispensing.
	Deletion of eGFR rows	eGFR is already mentioned in footnote "Clinical chemistry will include eGFR"
	Removed AP positioning from knee X-rays	Not specified
	Added information about imaging required for skeletal maturity. Removed AP positioning.	For clarity
	Added sentence on patients in Japan to specify HBV DNA samples draws in footnote r (Table 1) and footnote t (Table 2).	For clarity
Section 5.1 Overall Design	Cohorts adjusted	For clarity
Section 5.1.2. Safety/PK Assessment Section 5.5. Justification for Dose Section 7.1. Treatments Administered	• Addition of language to reference Appendix 7 for dosing guidance • Cohorts adjusted	• Dosing was updated per protocol requirement after PK analysis of study JAHV. • For clarity
Section 6.2. Exclusion Criteria	• Exclusion Criteria for hypogammaglobinemia adjusted	• IgG, IgM, IgA are not included in screening test.
Section 6.3. Screen Failures	Clarified that rescreening should be at least 4 weeks from the previous screening date.	For clarity
Section 7.7. Concomitant Therapy, Table JAHV.6.	Changes to NSAIDs and analgesics section	Clarification
Section 8.1.3. Discontinuation of Inadvertently Enrolled	Addition of Lilly template language	Clarification of discontinuation of inadvertently enrolled participants and

Section # and Name	Description of Change	Brief Rationale
Patients		safety follow-up. *Only applicable if Amendment C is in effect.
Section 9.4.4. Hepatitis B Virus DNA Monitoring	Weeks were changed to visits	Changed for consistency.
Section 9.4.6.2. Growth Monitoring	Addition of language related to height measurement	Specification of stadiometer as device to be used for height measurement.
	Addition of language on x-rays and country specific addenda	Guidance on previous country specific addenda containing additional imaging.
Section 9.5.1. Pharmacokinetic Strategy	Cohorts adjusted	For clarity
Section 9.5.2. Safety/PK Assessment Lead-in Period	Added sentence in regards to specifying sampling scheduled	For clarity
Appendix 2. Clinical Laboratory Tests	Update of footnote in table for hsCRP	Clarification to sites of test results for hsCRP.
Appendix 6. Weight-Based Prioritization Chart for Blood Sampling	Addition of RNA exclusion for testing for ≥8 years at weight <18 kg	Correction to include RNA in exclusionary testing for ≥8 years at weight <18 kg for long-term storage sample.
Appendix 7. Data-Based Dosing Cohorts	• Addition of Appendix 7 related to data-based dosing cohorts • Changed “will enroll” to “enrolled the required” patients	• Dosing was updated per protocol requirement after PK analysis of Study JAHV. • For clarity.
Appendix 8. Provisions for Changes in Study Conduct During Exceptional Circumstances	• Removed utilizing the lab operating guidance document (included at the end of this proposal form) wording • Laboratory collections adjusted	Clarification

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

1. Synopsis

Treatment Arms and Duration

…

Disease flare is defined as a worsening of ≥30% in at least 3 of the 6 PedACR core criteria for JIA and an improvement of ≥30% in no more than 1 of the criteria from the patient's condition at ~~baseline~~Visit 9. If either the number of joints with active arthritis or the number of joints with limitation of motion are used in the calculation of flare…

2. Schedule of Activities

The Schedule of Activities described below should be followed for all participants enrolled in Study JAHV. In the event participation in this study is affected by exceptional circumstances (such as pandemics or natural disasters), please refer to Appendix 8 and consult with the sponsor's representative for additional guidance.

Table JAHV.1 Schedule of Activities for the Safety/PK Cohort

	Safety/PK Cohort Only[a]				
	Screening		Safety/PK[b,c]		
Visit #	**V1**	**V1[a]**	**V2[b] baseline**	**V3**	**V4**
Study Day (Approximately)	**-42 to -1**		**1[d]**	**4**	**14**
Visit Window (Days)				**±3**	
Tanner Staging in patients ≥8 years old (see Section 9.4.6.3)			X		
Height	X		X		X
Weight	X				
X-ray of wrist, hand, finger, and ~~AP~~ knee[g]			X		
Uveitis evaluation[~~g~~h]	X				
Investigational product returned and compliance assessed[~~h~~i]					X
Clinical Efficacy					
Childhood Health Assessment Questionnaire[~~i~~j]			X	X	X
CHQ-PF50[~~i~~j]			X		
EQ-5D-Y[~~i~~j]			X		
SPARCC Enthesitis Index[~~j~~k]			X		X
Clinical sacroiliitis[~~j~~k]			X		X
Back mobility (Schober's test)[~~j~~k]			X		X
PASI[~~k~~l]			X		X
Procedures and Laboratory Tests					
Chest x-ray[~~l~~m]	X				
Administer PPD/QuantiFERON®-TB Gold/T-SPOT® TB[~~m~~n]	X				
Read PPD[~~m~~n]		X			
ECG[~~n~~o]	X				
ESR[~~o~~p]			X	X	X
HIV/HCV[~~p~~q]	X				
HBV DNA[~~q~~r]	X				
Serum pregnancy test[~~r~~s]	X				
Urine pregnancy test[~~r~~s]			X		X
Clinical chemistry[~~s~~t]	X		X	X	X
~~eGFR~~			~~X~~		
Fasting lipid panel[~~t~~u]			X		
Lymphocyte subsets (T, B, NK, and T- cell subsets)[~~u~~v]			X		

	Safety/PK Cohort Only[a]				
	Screening		Safety/PK[b,c]		
Visit #	**V1**	**V1[a]**	**V2[b] baseline**	**V3**	**V4**
Study Day (Approximately)	**-42 to -1**		**1[d]**	**4**	**14**
Visit Window (Days)				**±3**	
Antipneumococcal IgG multianalyte Ab assay[v,w]			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient		
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay[v,w]			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient		
Gonadal hormones[w,x]			X		
PK sample[x,y]			X	X	X

Abbreviations: ~~AP = anteroposterior~~;

g Semiannual wrist, hand, finger, and ~~AP~~ 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 Study JAHV at the time of this amendment, 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.

~~hg~~ All patients with active uveitis must be excluded at screening. ~~If investigators consider it necessary, evaluation can be added at any visit.~~Signs and symptoms of active uveitis should be monitored.

~~ih~~ At Visit 4, patient will return all investigational products for drug accountability.

~~ji~~ Patient-reported questionnaires will be administered via an on-site eCOA device or paper and is recommended to be completed prior to any clinical examinations.

~~kj~~ Only for patients with enthesitis-related juvenile idiopathic arthritis (ERA) or juvenile psoriatic arthritis (JPsA).

~~lk~~ Only for patients with JPsA.

~~ml~~ 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.

~~nm~~TB test(s) including 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 72hours 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.)

~~on~~ An ECG performed within 1 year prior to screening may be used.

~~po~~ Performed locally. To be drawn prior to dosing early in the visit except for Visit 3.

~~qp~~ 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.

~~rq~~ 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 (for patients in Japan, it is acceptable for sites to draw HBV DNA samples with the test of Visit 1). 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.

~~sr~~ Pregnancy tests prior to first dose of investigational product for females ≥10 years old 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 Visit 2 must be known prior to first dose of investigational product.

~~ts~~ Clinical chemistry will include eGFR (calculated by Bedside Schwartz 2009 formula or the Japanese Society for Pediatric Nephrology formula for patients in Japan).

[u] 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 ≤50kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 10 to <25kg: fast for 6 hours prior to laboratory test
- Children <8 years and weighing <10kg: fast for 4 hours prior to laboratory test

[v] Patients in the age cohort of age 2 to ≤7 years will not have flow cytometry testing due to blood volume limitations.

[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 post vaccination, 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] PK samples will be collected as described in Sections 9.5.2.

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 in Appendix 6.

Table JAHV.2 Schedule of Activities

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
Tanner Staging in patients ≥8 years old (see Section 9.4.6.3)			X														
Height	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-ray of wrist, hand, finger, and ~~AP~~ knee[h]			X														
Uveitis evaluation[~~h~~i]	X																
Dispense study drug[j]			X		X	X	X	X	X	X	X	X	X	X			
Investigational product returned and compliance assessed[~~i~~k]				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Childhood Health Assessment Questionnaire[~~j~~l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CHQ-PF50[~~j~~l]			X			X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-Y[~~j~~l]			X		X	X	X		X	X	X	X	X	X	X	X	X
SPARCC Enthesitis Index[~~k~~m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Morning stiffness			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
duration[f,i,l]																	
Pain Numeric Rating Scale[f,i,l]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical sacroiliitis[f,i,m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Back mobility[f,k,m] (Schober's test)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PASI[f,n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[f,m,o]	X																
Administer PPD/ QuantiFERON®-TB Gold/T-SPOT® TB[f,p]	X																
Read PPD[f,p]		X															
ECG[f,o,q]	X																
hsCRP	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR[f,r]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HLA-B27								X									
RF and ACPA	X																
TSH	X																
HIV/HCV[f,s]	X																
HBV (hBsAg, hBcAb, hBsAb)	X																
HBV DNA[f,t]	X						X			X			X		X	X	X

	Screening		Open-Label Lead-in Period[a]					Double-Blind Randomized Withdrawal Period								Early Termination	Post-Treatment Follow-Up
Visit #	**V1**	**V1a**	**V5[b] baseline**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**ETV[c]**	**V801[d]**
Study Week			**W0**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**Any Week**	
Study Day (Approximately)	**-42 to -1**		**1[e]**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**Any Day**	**28 ± 5 Days after Last Dose**
Visit Window (Days)				**±3**				**±7**									
Serum pregnancy test[su]	X																
Urine pregnancy test[su]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[tv]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
~~eGFR~~			~~X~~														
Fasting lipid panel[uw]			X				X				X				X	X	X
Lymphocyte subsets (T, B, NK, and T-cell subsets)[vx]			X		X		X								X	X	X
Antipneumococcal IgG multianalyte Ab assay[wy]			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient														
Anti-tetanus toxoid IgG, anti-diphtheria toxoid, and anti-pertussis toxoid Ab assay[wy]			At relevant visits for prevaccination, 4 weeks post vaccination, and 12 weeks post vaccination based on the vaccination schedule of each patient														
Gonadal hormone[xz]			X				X								X	X	X
PK sample[yaa]			X	X	X	X	X									X	

Abbreviations: ~~AP = anteroposterior;~~

h Semiannual wrist, hand, finger, and ~~AP~~ 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 Study JAHV at the time of this amendment, 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.

~~h~~i All patients with active uveitis must be excluded at screening. ~~If investigators consider it necessary, evaluation can be added at any visit~~Signs and symptoms of active uveitis should be monitored. Patients with ERA and JPsA ~~should have a uveitis evaluation at W12 (V9), W44 (V17), ETV and V801.~~ may have a higher risk of active uveitis so mandatory evaluation is required at W12 (V9), W44 (V17), ETV, and V801.

j Study drug should not be dispensed before review of the Trial Manager report.

~~i~~k Patients will return all investigational products for drug accountability.

~~j~~l Patient-reported questionnaires will be administered via an on-site eCOA device or paper and is recommended to be completed prior to any clinical examinations.

~~k~~mOnly for patients with enthesitis-related juvenile idiopathic arthritis (ERA) or juvenile psoriatic arthritis (JPsA).

~~l~~n Only for patients with JPsA.

~~m~~oOnly 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.

~~n~~p 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. (Note: Exception: Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing but must have a chest x-ray at screening.)

~~o~~q An ECG performed within 1 year prior to screening may be used.

~~p~~r Performed locally. To be drawn prior to dosing early in the visit except for V6 and V7.

~~q~~s 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.

~~r~~t 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 (for patients in Japan, it is acceptable for sites to draw HBV DNA samples with the test of Visit 1). 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 events.

~~s~~u Pregnancy tests prior to first dose of investigational product for females ≥10 years old 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 Visit 5 must be known prior to first dose of investigational product.

~~t~~v Clinical chemistry will include eGFR (calculated by Bedside Schwartz 2009 formula or the Japanese Society for Pediatric Nephrology formula for patients in Japan).

~~u~~w 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 ≤50kg: fast for 8 hours prior to laboratory test
- Children <8 years and weighing 10 to <25kg: fast for 6 hours prior to laboratory test
- Children <8 years and weighing <10kg: fast for 4 hours prior to laboratory test

~~v~~x Patients in the age cohort of age 2 to ≤7 years will not have flow cytometry testing due to blood volume limitations.

~~w~~y 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 post vaccination, and 12 weeks post vaccination.

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

~~y~~aa PK samples will be collected as described in Sections 9.5.2 and 9.5.3.

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 in Appendix 6.

5.1 Overall Design

...

[a] Staggered approach to enrollment by age group (12 to <18 years,~~6~~ 9 to <12 years, 6 to <9 years, 2 to <6 years) will be implemented with older groups completing the safety/PK assessment period before younger groups are enrolled.

[b] Once the PK and safety profiles for an age group are confirmed, subsequent patients in that age group may enroll directly into the OLLI period. If the comparability assessment in the safety/PK period for an age group is inconsistent with baricitinib 4-mg exposures in adults with RA such that baricitinib dosage for the age group needs to be adjusted, the patients on the inconsistent dosage will discontinue the study and may enter the separate OLE study (JAHX).

[c] Patients who experience a disease flare during the DBW period will discontinue the study and may proceed directly to the separate OLE study (JAHX).

5.1.2 Safety/PK Assessment

…

…Enrollment will be staggered by age group (12 to <18 years, ~~9~~6 to <12 years, 6 to <9 years, and 2 to <6 years; see Appendix 7 for updated dosing based on the current data) with older age groups enrolling before younger groups.

5.5. Justification for Dose

…The modeling predicted that baricitinib concentrations in adolescents 12 to <18 years old and in children ~~6~~9 to <12 years old would be expected to be similar to those in adults; therefore, these patients will initially be dosed with 4-mg QD dose (Figure JAHV.2; see Appendix 7 for updated dosing based on the current data). In contrast, concentrations in children <~~6~~9 years would be expected to be toward the higher end of the range seen in adults;

6.2 Exclusion Criteria

[29] History of hypogammaglobulinemia. ~~or a serum immunoglobulin (Ig)G, IgM, or IgA concentration less than the lower limit of normal of the reference range.~~

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 from the previous screening date. Each time rescreening is performed the legal representative must sign a new ICF and the child would sign an assent, as applicable. The individual will be assigned a new identification number.

7.1. Treatments Administered

This study involves a comparison of baricitinib dose, by age (4-mg for children ≥~~6~~9 years of age and adolescents 12 to <18 years of age and 2-mg for children <~~6~~9 years of age as the starting dose; see Appendix 7 for updated dosing based on the current data), with placebo in the DBW period. The dosages will be adjusted if the interim analyses after the Safety/PK period

demonstrate that the profiles are not comparable with the target PK or safety profiles in adults. Therefore, a 1-mg dose is described in Table JAHV.5 should this be needed.

Baricitinib will be dosed as tablets or oral suspension QD based on the age of the patient at Visit 2 (for patients enrolled in the Safety/PK portion) and at Visit 5 (for all other patients); formulation will not change during the study. Baricitinib should be taken with sufficient water or fluid to allow easy swallowing of the medication. All patients <6 years of age will receive oral suspension. Patients ≥6 to <12 years old have the option of receiving the oral suspension. Patients >12 years old will be supplied tablets. Based on PBPK modeling, initial doses will be 4-mg for adolescents 12 to <18 years old and in children ≥~~6~~9 to <12 years old, and 2-mg in children <~~6~~9 years old to produce exposures similar to those in adults after 4-mg QD administration. Refer to Section 5.5 for additional information. Table JAHV.5 shows the treatment regimens.

Table JAHV.5. Treatment Regimens

Treatment Group	Treatments Administered	
	Safety/PK and OLLI Period	**DBW Period**
Baricitinib 4-mg	Baricitinib 4-mg oral QD tablet Baricitinib 2-mg/mL oral suspension	Baricitinib 4-mg oral QD tablet Baricitinib 2-mg/mL oral suspension
Baricitinib 2-mg	Baricitinib 2-mg oral QD tablet Baricitinib 2-mg/mL oral suspension	Baricitinib 2-mg oral QD tablet Baricitinib 2-mg/mL oral suspension
Baricitinib 1-mg	Baricitinib 1-mg oral QD tablet Baricitinib 2-mg/mL oral suspension	Baricitinib 1-mg oral QD tablet Baricitinib 2-mg/mL oral suspension
Placebo comparator	N/A	Baricitinib 4-mg placebo oral QD tablet Baricitinib 2-mg placebo oral QD tablet Baricitinib 1-mg placebo oral QD tablet Baricitinib 2-mg/mL placebo oral suspension

Abbreviations: DBW = double-blind withdrawal; eGFR = estimated glomerular filtration rate; N/A = not applicable; OLLI = open-label lead-in; PK = pharmacokinetics; QD = once daily.

Note: Initial doses of baricitinib 4-mg for adolescent patients (12 to <18 years of age) and children ≥~~6~~9 years of age and baricitinib 2-mg for children <~~6~~9 years of age will be given. The oral suspension dose may be administered as 4-mg, 2-mg, 1-mg, and 0.5-mg as needed.

Note: Patients with renal impairment or renal immaturity (defined as eGFR <60 mL/min/1.73 m2) at baseline will have their dose reduced by 50%. Patients receiving the 1-mg dose who have renal impairment or renal immaturity will receive a dose-of 0.5-mg using the oral suspension.

7.7. Concomitant Therapy

Table JAHV.6. Concomitant JIA Therapies

Drug Class	As Needed	Chronic Use	Conditions for Use
NSAIDs[b] including cyclooxygenase-2 inhibitors, e.g., celecoxib	No	Yes	Must be on stable dose for at least 1 week prior to baseline. Changes in dose, discontinuation and/or introduction of new analgesics are only allowed for treatment of an AE.
Analgesics including local anaesthetics, e.g., lidocaine, and topical anaesthetics, e.g., EMLA cream.	No	Yes	Must be on stable dose at least 1 week prior to baseline. Changes in dose, discontinuation and/or introduction of new analgesics are only allowed for treatment of an AE. ~~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~~

[b] For use as an anti-inflammatory agent.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a ~~patient~~ participant who did not meet enrollment criteria and was inadvertently enrolled, then the ~~patient~~ participant should be discontinued from ~~the investigational product~~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).

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.

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 in Section 2).

Patients who are hBcAb positive and HBV DNA negative (undetectable) at screening will require measurement of HBV DNA at ~~Week~~ Visit 9, Visit 12, ~~Week 24~~Visit 15, ~~Week 36~~Visit 17, ~~Week 44,~~ ETV, and the follow-up visit, regardless of their hepatitis B surface antibody (hBsAb) status.

9.4.6.2. Growth Monitoring

Height and weight will be measured at baseline and postbaseline for the assessment of physical growth according to the Schedule of Activities (Section 2). Height and weight 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.

…

A semiannual wrist, hand, finger, and ~~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., MRI instead of x-ray), the local addendum should be followed. Otherwise, the current protocol amendment should be followed with regard to knee x-rays.

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).

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 Davies 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.

9.5.1 Pharmacokinetic Strategy

The doses for this study were selected based on PK modeling such that the highest dose in an age cohort is expected to produce baricitinib exposure similar to that produced by 4-mg in adult patients with RA. For adolescent patients (aged 12 to <18 years) and children ≥~~6~~9 years, that dose is expected to be 4-mg QD, whereas in children aged ≥6 to <9 and ~~>~~≥2 to <6 years the dose is expected to be 2-mg QD.

Before enrolling a majority of patients, the PK in adolescent patients receiving 4-mg QD will be evaluated in a small number of lead-in patients to confirm the suitability of this dose in adolescent patients with JIA. Patients will be dosed QD and serial blood samples will be collected at steady state for analysis of baricitinib concentrations. Refer to Section 9.5.2 for details. The PK in individual patients will be evaluated using noncompartmental methods and will inform dose selection for subsequent adolescent patients. No adolescent patients will be enrolled directly into the OLLI period until the PK in the lead-in patients has been evaluated.

For younger cohorts of PK lead-in patients (aged ≥~~6~~9 to <12 years, aged 6 to <9 years and aged 2 to <6 years), the same lead-in process will be performed as that for adolescents. The PK lead-in

period for patients aged ≥~~6~~9 to 12 years will complete before the PK lead-in period for patients aged ~~2~~6 to <~~6~~9 years can begin, and this one will also complete before the PK lead-in period for patients 2 to <6 years can begin (Section 5.1.2).

9.5.2 Safety/PK Assessment Lead-in Period

…

For visits where PK samples will be collected, the actual date and 24-hour clock time of sample collection, and the date and time of the last 2 doses should be recorded. At Day 4 and Day 14, these 2 doses should be the dose given on the morning of the day of sample collection and the dose given the previous day. This sampling schedule should be followed as closely as possible; however, failure to take PK samples at these specified times will not be considered a protocol violation. If the patient fails to follow the directions for a particular visit, the sample should still be collected at that visit, and the date and 24-hour clock time of sample collection and the date and 24-hour clock time of the 2 doses prior to the sample being drawn should be recorded.

11. References

Chavarro JE, Watkins DJ, Afeiche MC, Zhang Z, Sánchez BN, Cantonwine D, Mercado-García A, Blank-Goldenberg C, Meeker JD, Téllez-Rojo MM, Peterson KE. Validity of self-assessed sexual maturation against physician assessments and hormone levels. *J Pediatr.* 2017;186:172-178.e3.

Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44(235):291–303.

Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.* 1970;45(239):13–23.

Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr.* 1985;107(3):317-329.

Appendix 1. Abbreviations and Definitions

Term	Definition
~~AP~~	~~anteroposterior~~
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments

Appendix 2. Clinical Laboratory Tests

i Test results of hsCRP and lymphocyte subsets will be blinded after ~~Week 12~~Visit 9, and the test results will not be sent to the study sites.

Appendix 6. Weight-Based Prioritization Chart for Blood Sampling

Weight-Based Prioritization Chart for Blood Sampling

Age	Weight	Excluded Testing – will not be collected
≥8 years	≥30 kg	N/A
	≥27 to <30 kg	• Long-term storage samples: RNA, serum, and plasma
	≥18 to <27 kg	• Long-term storage samples: RNA, serum, and plasma • Flow cytometry
	<18 kg	• Long-term storage samples: RNA, serum, and plasma • Testosterone or estradiol • Flow cytometry

Appendix 7. 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).

Current 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 or JIA-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 physiological-based pharmacokinetics (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 JAHV

An updated summary of dosing for Study JAHV is provided in the table below. Lilly has initiated the following for Study JAHV:

- Lilly ~~will enroll 5 to 8~~ enrolled the required patients aged 6 to <9 years in the PK cohort 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, 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 JAHV Dosing Summary

Age Group	Current Status of Enrollment	Baricitinib Dose
12 to <18 years old	Safety/PK completed; OLLI currently enrolling	4 mg
9 to <12 years old	Safety/PK completed; OLLI currently enrolling	4 mg
6 to <9 years old	Safety/PK ~~currently enrolling 5 to 8 patients~~ enrollment completed as of October 2020	2 mg (based on predicted data – to be confirmed with observed data)
2 to <6 years old	Safety/PK to be initiated	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 8. Provisions for Changes in Study Conduct During Exceptional Circumstances

Exceptional circumstances, such as pandemics or natural disasters, may cause disruptions to the conduct of the study. Examples of such disruptions include limitations in the ability to conduct study procedures or ability to have on-site participant visits.

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 and if permitted by local regulations. These provisions for changes in study conduct are temporary and will be repealed once the restrictions are lifted.** 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.

2. Remote Assessment and Data Collection

Patient visit and data collection can be done remotely for OLLI visits following the protocol visit windows. The PI/Sub-I is to document all teleconferences/remote visits in the patient's records. Site facing assessments will be completed on paper (preferably eCOA if the site is able) and patient facing assessments will be conducted in interview format with the PI/SubI or other qualified personnel documenting the patient's responses on paper. Sponsor will provide guidance for performing these assessments (CHQ-PF50, EQ-5D-Y). Patients *cannot* proceed in Study JAHV past Visit 9 due to the requirement of PedACR30 responder/nonresponder criteria being defined at this visit to determine eligibility for randomization into DBW phase. Because most PedACR components cannot be collected by remote assessment, patients will be terminated from Study JAHV at Visit 9 and offered enrollment into Study JAHX (long-term extension).

3. Investigational product and ancillary supplies (including participant diaries)

In cases when a participant is unable to come to the 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
- 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 participant'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 AE in the AE eCRF.

For patients unable to access investigator sites, laboratory testing will be conducted at least every 8 weeks in the OLLI and DBW periods. The first collection should be 8 weeks from the patient's last collected central laboratory samples.

Failure to have labs collected within the described ranges above may result in patient termination from the study.

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.

Note: Any results that are obtained from local laboratories will need to be retained by the investigator for their respective patients.

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 the 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 for these select parameters:

- WBC
- ANC
- Lymphocyte count
- Hemoglobin
- Platelet count
- 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 verbal consent for having remote visits and remote dispensing of IP and/or ancillaries prior to implementation of these activities.
- Source document(s) that are generated at an off-site location (e.g., 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 eCRFs. 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.

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