Protocol I4V-MC-JADY (i)

# A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis

NCT01885078

Approval Date: 10-Dec-2019

# 1. Protocol I4V-MC-JADY(i)
# A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis

## Confidential Information



Baricitinib (LY3009104)

Study I4V-MC-JADY is a Phase 3, multicenter, outpatient long-term safety and efficacy extension study. Patients who completed a Phase 2 or Phase 3 baricitinib RA trial may be eligible to enter this trial.

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Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly: 13 December 2012
Amendment (a) Electronically Signed and Approved by Lilly: 14 February 2013
Amendment (b) Electronically Signed and Approved by Lilly: 28 May 2013
Amendment (c) Electronically Signed and Approved by Lilly: 31 May 2013
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on approval date provided below.

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# 2. Synopsis

## Study Rationale

Baricitinib (LY3009104) is an oral Janus kinase 1 (JAK1)/Janus kinase 2 (JAK2) selective inhibitor representing a potentially effective therapy for treatment of patients with moderately to severely active rheumatoid arthritis (RA). The rationale for the current study is to evaluate the safety profiles and durability of effect of 2-mg and 4-mg baricitinib doses when administered once daily (QD) over an extended time period to patients with RA who have completed a previous Phase 2 or Phase 3 study of baricitinib. The safety and tolerability data from this study are intended to inform the current understanding of the benefit-risk relationship for baricitinib in patients with RA.

**Clinical Protocol Synopsis:** Study I4V-MC-JADY

<table>
<tr><td colspan="2">Name of Investigational Product:<br>Baricitinib (LY3009104)</td></tr>
<tr><td colspan="2">Title of Study: A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis</td></tr>
<tr><td>Number of Planned Patients/Subjects:<br>Entered: approximately 2400–3500<br>Planned Enrollment: 2400–3500<br>Completed: 1200–1700</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="2">Length of Study: 10 years<br>Planned first patient visit: May 2013 Planned last patient visit: July 2024</td></tr>
<tr><td colspan="2">Objectives: The primary objective of the study is to evaluate the long-term safety and tolerability of baricitinib in patients who have completed a previous baricitinib RA study. Safety and tolerability assessments will include:<br>• Treatment-emergent adverse events (TEAEs), adverse events of special interest, and serious adverse events (SAEs)<br>• Temporary investigational product interruptions and permanent investigational product discontinuations<br>• Vital signs and laboratory evaluations (including chemistry and hematology)<br><br>The secondary objective(s) of the study are:<br>To evaluate in patients initially randomized to receive baricitinib in the originating study, the effect of long-term administration of baricitinib as assessed by:<br>• Proportion of patients who maintain an ACR20, ACR50, and ACR70 response through each 12 months of treatment<br>• Proportion of patients who maintain a Disease Activity Score modified to include the 28 diarthrodial joint count (DAS28)-high sensitivity C-reactive protein (hsCRP) ≤3.2, DAS28-erythrocyte sedimentation rate (ESR) ≤3.2, DAS28-hsCRP <2.6, and DAS28-ESR <2.6; Clinical Disease Activity Index (CDAI) ≤10 and CDAI ≤2.8; Simplified Disease Activity Index (SDAI) ≤11 and SDAI ≤3.3; ACR/EULAR remission according to the Boolean-based definition; and Health Assessment Questionnaire–Disability Index (HAQ-DI) improvement ≥0.22 and ≥0.3 from Month 6 (of the originating study) through each 12 months of treatment<br>• Change from baseline of originating study through each 12 months of treatment up to 5 years in structural joint damage as measured by modified Total Sharp Score (mTSS) (van der Heijde method)</td></tr>
</table>

- Proportion of patients with mTSS change ≤0 from baseline of originating study through each 12 months of treatment up to 5 years
- Change from baseline of originating study through each 12 months of treatment up to 5 years in joint space narrowing and bone erosion score
- Change from baseline in duration of morning stiffness through each 12 months of treatment
- Change from baseline through each 12 months of treatment in European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) scores
- Evaluation of healthcare resource utilization through each 12 months of treatment
- To determine if treatment with baricitinib 2 mg QD maintains the low disease activity level achieved with the 4-mg QD dose (i.e., step-down dosing) on the following outcomes:
    - Proportion of patients who maintain a CDAI score of ≤10 from Studies JADV, JADW, and JADX after 3 months of treatment with baricitinib 2 mg QD and with patients continuing treatment with the 4-mg QD dose
    - Time to relapse (where relapse is defined as a CDAI score >10 from Studies JADV, JADW, and JADX) after randomization to the baricitinib 2-mg and 4-mg QD doses

Similar analyses will be conducted on patients who initiated treatment with baricitinib as rescue therapy at some time during the originating study.

The exploratory objective(s) of the study are:

- To determine if treatment with baricitinib 2 mg QD maintains the low disease activity level or remission achieved with the 4-mg QD dose (i.e., step-down dosing) on the following outcomes:
    - Proportion of patients who maintain a CDAI score of ≤2.8 from Study JADZ after 3 months of treatment with baricitinib 2 mg QD and with patients continuing treatment with the 4-mg QD dose
    - Time to relapse after randomization to the baricitinib 2-mg and 4-mg QD doses where relapse is defined as:
        - a CDAI score >2.8 from Study JADZ
        - loss of CDAI categorization at randomization (a CDAI score >2.8 if CDAI score at randomization is ≤2.8 or a CDAI score > 10 if CDAI score at randomization is >2.8 and ≤10)
        - having been rescued
- To describe the clinical course of patients initiating baricitinib at the time of enrollment in Study JADY as assessed by DAS28-hsCRP, DAS28-ESR, and CDAI at 3, 6, 12, and at each 12 months of treatment allocation in the originating study
    - From placebo in Study JADW or JADX to baricitinib in Study JADY
    - From MTX in Study JADZ to baricitinib in Study JADY
    - From adalimumab in Study JADV to baricitinib in Study JADY
- To describe the clinical course of patients switching from MTX + baricitinib in Study JADZ to baricitinib monotherapy in Study JADY as assessed by DAS28-hsCRP, DAS28-ESR, and CDAI at 3, 6, 12, and at each 12 months of treatment

**Study Design**: Study I4V-MC-JADY (JADY) is a Phase 3, multicenter, long-term extension study evaluating the safety and efficacy of baricitinib (2 mg QD and 4 mg QD) in patients with rheumatoid arthritis for up to 84 months. Patients who completed an originating study (Study JADA, JADZ, JADV, JADX, JADW, or JAGS) may be eligible for enrollment into Study JADY. Patients from future baricitinib RA studies may also be enrolled into Study JADY. Planned enrollment will be approximately 2400 to 3500 patients.
This study will consist of 3 parts: a screening period that will occur during the last visit of the originating study; Part A: treatment period lasting up to 84 months from enrollment into Study JADY; and Part B: posttreatment follow-up period.
Patients will receive baricitinib 4 mg QD or baricitinib 2 mg QD.

**Diagnosis and Main Criteria for Inclusion and Exclusions:** Male or female patients at least 18 years of age who have been diagnosed with RA and have completed the final study visit in a previous baricitinib RA study

**Investigational Product, Dosage, and Mode of Administration or Intervention:** Patients who have completed Study JADV, JADZ, JADX, JADW, or JAGS will be assigned to blinded baricitinib treatment (2 mg QD or 4 mg QD), and all patients who have completed Study JADA will be assigned to receive open-label baricitinib 4 mg QD. Patients with renal impairment at baseline of the originating study (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 $m^2$) will only be eligible for dosing with baricitinib 2 mg QD. Baricitinib tablets will be administered orally.

Planned Duration of Treatment: 84 months
Screening period: 1 day (should occur during the last visit of the originating study. However, in particular circumstances, this duration may be extended after consultation with the sponsor.)
Treatment period: 84 months
Follow-up period: 28 days

**Reference Therapy, Dose, and Mode of Administration or Comparative Intervention:** Patients originating from Study JADV, JADZ, JADX, JADW, or JAGS and who were not previously rescued will receive either a 4-mg or 2-mg matching placebo tablet to maintain the blind of the step-down.

Criteria for Evaluation:
Efficacy:
The following efficacy measures will be assessed in this study:

- ACR20, ACR50, and ACR70 indices
- Hybrid ACR (bounded) response measure
- DAS28-ESR and DAS28-hsCRP
- EULAR28
- mTSS (includes joint space narrowing score and bone erosion score)
- HAQ-DI
- Simplified Disease Activity Index (SDAI)
- CDAI
- ACR/EULAR remission (according to the Boolean-based definition)

Safety:
The following safety measures will be assessed in this study:

- adverse events (AEs)
- Adverse events of special interest
- SAEs
- suspected unexpected serious adverse reactions (SUSARs)
- concomitant medications
- physical examinations
- vital signs (blood pressure and pulse) and physical characteristics
- standard laboratory tests (including hematology, clinical chemistry, urinalysis, lipid profile, eGFR, iron studies, hsCRP, and ESR)

Adverse events of special interest or laboratory results of special interest will include:

- severe or opportunistic infections
- myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia
- thrombocytosis
- elevations in alanine aminotransferase or aspartate aminotransferase (>3 times the upper limit of normal [ULN]) with total bilirubin (>2 times the ULN)

Patients with these laboratory-value-specified events will be identified using the same criteria for the interruption of investigational product with the exception of anemia, which will be identified using the same criteria for the discontinuation of investigational product, and thrombocytosis, which will be defined as a platelet count >600,000/μL.

Health Outcomes:

The following health outcome measures will be administered in this study:

- duration of morning joint stiffness
- EQ-5D-5L
- Quick Inventory of Depressive Symptomatology Self-Rated-16 ($QIDS\text{-}SR_{16}$)
- healthcare resource utilization

Statistical Methods:

Sample Size: It is expected that 80% of patients will complete Study JADV, JADZ, JADX, JADW, JADA, or JAGS; therefore, planned enrollment for JADY will be approximately 2400 to 3500 patients.

Analysis Population: The efficacy and health outcome analyses will be conducted on an intention-to-treat (ITT) basis. The ITT analysis set will include all data from all enrolled patients treated with at least 1 dose of the investigational product in Study JADY. The ITT population will be subcategorized based on baricitinib exposure in the originating study and whether the patient required rescue therapy. Analysis of structural progression (van der Heijde mTSS) will be conducted on the ITT population using patients with available baseline (from the originating study) and at least 1 postbaseline x-ray assessment (collected in JADY). Safety analyses will be performed on the safety population, defined as all enrolled patients who received at least 1 dose of the investigational product in Study JADY.

Missing Data Imputation:

1. Nonresponder imputation (NRI): All patients who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the NRI analysis for categorical variables, such as ACR20/50/70, from the time of discontinuation and onward. Patients who are eligible for rescue therapy starting at 3 months (all studies except JADZ) or at any time point (JADZ) will be analyzed as nonresponders after rescue therapy and onward. Enrolled patients without available data at a postbaseline visit will be defined as nonresponders for the NRI analysis at that visit. The time period used for the NRI analysis will be defined in the statistical analysis plan (SAP) and in the integrated efficacy analysis plan (IEAP).
2. Linear extrapolation method: The linear extrapolation method will be used for analysis of the structural progression endpoint (van der Heijde mTSS) to impute missing data. The time period used for the linear extrapolation method will be defined in the SAP.
3. Multiple imputation: Methods other than linear extrapolation that include multiple imputation will be employed for analysis of the structural progression endpoint (van der Heijde mTSS) to impute missing data. Details will be provided in the SAP and IEAP.
4. Modified last observation carried forward (mLOCF): For all continuous measures including safety endpoints, the mLOCF will be a general approach to impute missing data unless otherwise specified. For patients who are eligible for rescue therapy starting at 3 months (all studies except JADZ) or at any time point (JADZ), the last nonmissing observation at or before rescue will be carried forward to subsequent time points for evaluation. For all other patients discontinuing from the study or the study treatment for any reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to subsequent time points for evaluation. If the postbaseline observation is missing, then it will not be included in the analysis even if the baseline observation is not missing. The time period used for the mLOCF method will be defined in the

SAP and IEAP.

5. Supportive methods to the NRI and mLOCF will be used.

Efficacy Analyses: Change from baseline of originating studies to postbaseline visits in JADY in mTSS will be summarized by treatment and analyzed using a t-test. Within-treatment changes from baseline along with 95% confidence interval (CI) will be assessed using the t-test. The linear extrapolation method as described above will be used to impute missing mTSS. Mixed model for repeated measures (MMRM) will also be used to analyze structural progression data and other continuous endpoints. Joint space narrowing and bone erosion score analysis will follow the same model specification described for mTSS. Proportion of patients with mTSS change ≤0 from baseline of originating studies to postbaseline visits in JADY, the proportion of patients maintaining a CDAI score ≤10, CDAI score ≤2.8, DAS28-hsCRP ≤3.2, DAS28-ESR ≤3.2, DAS28-hsCRP <2.6, DAS28-ESR <2.6, SDAI ≤11, SDAI ≤3.3; HAQ-DI improvement from baseline (of originating studies) of ≥0.22 and ≥0.3; ACR20/50/70 response; and ACR/EULAR remission (according to the Boolean-based definition) at applicable visits in JADY will be summarized by treatment and study cohort. The 95% CI for single proportion will be provided using the Wilson Score method (Wilson 1927; Newcombe 1998). Categorical repeated measure analyses such as pseudo-likelihood-based mixed effects model for repeated measures (categorical MMRM) will be explored. The Kaplan Meier method will be used to assess durability of effect using time to relapse by treatment group. Cox regression model might be explored for time to relapse. Graphical presentations of median time to relapse will be provided. Mean change from baseline to postbaseline visits in continuous efficacy variables (including DAS28-C-reactive protein [CRP] and DAS28-ESR) will be summarized. The t-test will be used to summarize within-group changes from baseline. Within treatment changes from baseline will be assessed by the t-test along with 95% CI.

Safety: All safety data will be descriptively summarized by cohort and treatment group (step-down) and analyzed using the safety population. Treatment-emergent AEs (TEAEs) are defined as AEs that first occurred or worsened in severity on or after the first dose of study treatment in JADY. The number and percentage of TEAEs will be summarized using MedDRA (Medical Dictionary for Regulatory Activities) for each system organ class and each preferred term by cohort and treatment group (step-down). TEAEs will also be summarized by relationship to treatment and by severity within each cohort and treatment group (step-down). SAEs and AEs that lead to investigational product discontinuation will also be summarized by cohort and treatment group (step-down). Fisher exact test will be used for statistical comparisons. Change from baseline in quantitative clinical chemistry will be analyzed using analysis of covariance (ANCOVA) with treatment (or cohort) and baseline value in the model or the t-test where applicable. Categorical variables, including the incidence of abnormal values and incidence of adverse events of special interest, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures and analyzed by treatment (or cohort). Change from baseline to postbaseline in vital signs, QIDS-SR16, and body weight will be analyzed using ANCOVA with treatment (or cohort) and baseline value in the model or the t-test where applicable.

Health Outcomes: Health outcome measures will be analyzed using methods described for the continuous or categorical data as described for the efficacy measures. More details are provided in the IEAP.

Planned Analyses: Several analyses for regulatory purposes, such as safety updates (including the 120-day safety update), regulatory responses, yearly analyses for disclosure purposes, and a 2-year and a 5-year analysis of x-ray (radiographic progression of structural joint damage) data for publication purposes and/or to provide to regulatory agencies are planned for this study. The first analysis is planned after all of the Phase 3 original studies (JADV, JADZ, JADX, or JADW) are analyzed and a final analysis after all patients complete the study.

Unblinding details will be specified in the unblinding plan section of the SAP.

Interim Analyses: A DMC oversaw the conduct of all the Phase 3 clinical trials evaluating baricitinib in patients with RA. The DMC consisted of members external to Lilly. This DMC followed the rules defined in the DMC charter, focusing on potential and identified risks for this molecule and for this class of compounds. DMC membership included, at a minimum, specialists with expertise in rheumatology, statistics, and other appropriate specialties. This DMC for studies of patients with RA was coordinated with the DMC(s) for other ongoing studies of baricitinib in other indications, and this coordination did not alter the number and timing of the interim analyses.

Access to the unblinded interim data was limited to the statisticians who conducted the interim analyses and the DMC. The statisticians conducting the interim analyses were independent from the study team. The study team did not have access to the unblinded data. Study sites received information about interim results ONLY if they needed to know for the safety of their patients.

The DMC reviewed study discontinuation data, AEs including SAEs, clinical laboratory data, vital sign data, and so on. The DMC recommended continuation of the study, as designed. The DMC reviewed efficacy data to investigate the benefit/risk relationship in the context of safety observations for ongoing patients in the study. The study was not stopped for positive efficacy results, and there was no planned futility assessment. Hence, there was no alpha adjustment for these interim analyses. Details of the DMC and interim safety analyses were documented in a DMC charter and DMC analysis plan, and all documentation is archived in the sponsor trial master file.

Besides DMC members, a limited number of preidentified individuals may gain access to the safety data, as specified in the unblinding plan, prior to the final database lock, to initiate the exploration for safety data (e.g., neutropenia, anemia). 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.

The DMC fulfilled the responsibilities of the Charter and have been disbanded. Ongoing safety monitoring is being conducted by the Global Patient Safety and RA-BEYOND Study team according to company policy.

# 3. Table of Contents

## A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis

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# 4. Abbreviations and Definitions

| Term | Definition |
|---|---|
| **ACR** | American College of Rheumatology |
| **ACR20** | 20% improvement in American College of Rheumatology criteria |
| **ACR50** | 50% improvement in American College of Rheumatology criteria |
| **ACR70** | 70% improvement in American College of Rheumatology criteria |
| **adverse event (AE)** | Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and 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. |
| **ALT** | alanine aminotransferase |
| **ANCOVA** | analysis of covariance |
| **anti-CCP** | anticyclic citrullinated peptide |
| **AST** | aspartate aminotransferase |
| **audit** | a systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s) |
| **blinding** | A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the patient(s) being unaware, and double-blinding usually refers to the patient(s), investigator(s), monitor(s), and in some cases, select sponsor personnel being unaware of the treatment assignment(s). |
| **case report form (CRF)** | sometimes referred to as clinical report form: an electronic form for recording study participants' data during a clinical study, as required by the protocol |
| **CDAI** | Clinical Disease Activity Index |
| **cDMARD** | conventional disease-modifying antirheumatic drugs |
| **CI** | confidence interval |
| **clinical research physician** | Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician or other medical officer. |

| Term | Definition |
|---|---|
| **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. |
| **compliance** | adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements |
| **COX-2** | cyclooxygenase-2 |
| **CRP** | C-reactive protein |
| **DAS** | Disease Activity Score |
| **DAS28** | Disease Activity Score modified to include the 28 diarthrodial joint count |
| **DMARD** | disease-modifying antirheumatic drug |
| **DMC** | data monitoring committee |
| **DVT** | deep vein thrombosis |
| **efficacy/ effectiveness** | Efficacy is the ability of a treatment to achieve a beneficial intended result.<br>Effectiveness is the measure of the produced effect of an intervention when carried out in a clinical environment. |
| **eGFR** | estimated glomerular filtration rate |
| **end of study (trial)** | the date of the last visit or last scheduled procedure shown in the study schedule for the last active patient in the study |
| **enroll/randomize** | The act of assigning a patient to a treatment. Patients who are enrolled/randomized in the trial are those who have been assigned to a treatment. |
| **enter** | The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives. |
| **ePRO** | electronic patient-reported outcome |
| **EQ-5D-5L** | European Quality of Life-5 Dimensions-5 Level |
| **ESR** | erythrocyte sedimentation rate |
| **ethical review board (ERB)** | a board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected |
| **EULAR** | European League Against Rheumatism |

| Term | Definition |
|---|---|
| **EULAR28** | European League Against Rheumatism Responder Index based on the 28-joint count |
| **FSH** | follicle-stimulating hormone |
| **GCP** | good clinical practice |
| **HAQ-DI** | Health Assessment Questionnaire–Disability Index |
| **HBcAb** | hepatitis B core antibody |
| **HBsAb** | hepatitis B surface antibody |
| **HBV DNA** | hepatitis B virus deoxyribonucleic acid |
| **HDL** | high-density lipoprotein |
| **hsCRP** | high-sensitivity C-reactive protein |
| **IB** | Investigator's Brochure |
| **$IC_{50}$** | inhibitory concentration of 50% |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IEAP** | integrated efficacy analysis plan |
| **IL-6** | interleukin-6 |
| **intention to treat (ITT)** | 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 (i.e., 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. |
| **interim analysis** | an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked |
| **investigator** | A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. |
| **IVRS** | interactive voice-response system |
| **IWRS** | interactive web-response system |
| **JAK** | Janus kinase |
| **JAK1** | 1 of 4 identified members of the family of Janus kinases |

| Term | Definition |
|---|---|
| **JAK2** | 1 of 4 identified members of the family of Janus kinases |
| **JAK3** | 1 of 4 identified members of the family of Janus kinases |
| **LDL** | low-density lipoprotein |
| **legal representative** | an individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical trial |
| **LS** | least squares |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MI** | myocardial infarction |
| **mLOCF** | modified last observation carried forward |
| **MMRM** | mixed model for repeated measures |
| **month** | a period of 28 days |
| **mTSS** | modified Total Sharp Score |
| **MTX** | methotrexate |
| **MTX-IR** | patients who have had an inadequate response to methotrexate |
| **NRI** | nonresponder imputation |
| **NSAID** | nonsteroidal anti-inflammatory drug |
| **patient** | a study participant who has the disease or condition for which the investigational product is targeted |
| **PE** | pulmonary embolism |
| **PK** | pharmacokinetic(s) |
| **PPD** | purified protein derivative |
| **PSAP** | program safety analysis plan |
| **QD** | once daily |
| **QIDS-SR$_{16}$** | Quick Inventory of Depressive Symptomatology Self-Rated-16 |
| **RA** | rheumatoid arthritis |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |

| Term | Definition |
|---|---|
| **SC** | subcutaneous |
| **screening** | 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 |
| **SD** | standard deviation |
| **SDAI** | Simplified Disease Activity Index |
| **SJC** | swollen joint count |
| **STAT** | signal transducers and activators of transcription |
| **subject** | An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient. |
| **SUSARs** | suspected unexpected serious adverse reactions |
| **TB** | tuberculosis |
| **TJC** | tender joint count |
| **TNF** | tumor necrosis factor |
| **TNF-α** | tumor necrosis factor-alpha |
| **treatment-emergent adverse event (TEAE)** | any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms [TESS]) |
| **TYK2** | tyrosine kinase 2, 1 of 4 identified members of the family of Janus kinases |
| **ULN** | upper limit of normal |
| **V1** | central compartment volume of distribution |
| **VAS** | visual analog scale |
| **VTE** | venous thromboembolic event (deep vein thrombosis or pulmonary embolism) |

# A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis

# 5. Introduction

## 5.1. Background

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease. The disease has variable expression and outcome ranging from mild, limited disease to severe disease associated with progressive joint destruction, significantly compromised quality of life, and reduced survival (Smolen and Steiner 2003; Colmegna et al. 2012). Substantial comorbidity can be seen outside of the musculoskeletal system, with excess cardiovascular risk, dyslipidemia, and propensity for infection partially related to the need for treatment with immunomodulatory agents (Curtis et al. 2007; Kitas and Gabriel 2011).

Management of RA has improved substantially in recent years. In addition to reduction of signs and symptoms, improvement of physical function, and inhibition of structural damage, better patient outcomes and clinical remission are now considered achievable goals. Therefore, the current recommended primary target for treatment of RA should be a state of clinical remission (Smolen et al. 2010; Felson et al. 2011). There are several definitions for clinical remission based on composite scores (commonly including: tender joint counts [TJCs]/swollen joint counts [SJCs], level of acute phase reactants, and assessment of a patient or physician global response). These scores include the Disease Activity Score (DAS), DAS modified to include the 28 diarthrodial joint count (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and a Boolean definition as recently proposed jointly by American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) (Felson et al. 2011). The current focus on arresting disease activity results from an understanding that persistent joint inflammation leads to progressive joint destruction manifested by cartilage loss, erosive damage to juxta-articular bone, and resultant functional impairment; that erosive bone changes occur within months of disease onset; and that early and aggressive treatment increases the likelihood of disease control (Klareskog et al. 2009; Colmegna et al. 2012).

Despite a variety of approved agents for RA, complete or sustained disease remission is unusual. Conventional disease-modifying anti-rheumatic drugs (cDMARDs) have been used with some success. Patients often receive 1 or more of these medications (e.g., methotrexate [MTX], sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, gold salts, and cyclosporine), typically in combination with low-dose oral or intra-articular glucocorticoids. In addition to cDMARDs, biological agents that block or antagonize critical inflammatory mediators, T cells, or B cells can reduce pain and swelling and provide joint protection against structural damage. The efficacy of these biologics, particularly in combination with MTX, has been shown to have a clinically important effect on the signs and symptoms of RA (Fleischmann 2005); however, a majority of patients do not go into remission or achieve a 50% improvement in ACR criteria (ACR50) in a clinical trial setting. During treatment with tumor necrosis factor-alpha (TNF-α)

antagonists, approximately 30% of patients fail to achieve a 20% improvement in ACR criteria (ACR20; primary failure), and more patients lose efficacy during therapy (secondary failure; Rubbert-Roth and Finckh 2009). Achieving remission is the first treatment hierarchical objective of the Treat to Target RA recommendations (Smolen et al. 2010). As RA is a chronic condition, patients are usually treated with long-term cDMARDs and/or biologics. Therefore, there is interest in assessing whether doses can be decreased slowly once disease activity has been controlled. For patients who do achieve remission or low disease state, the EULAR recommendations for the management of RA is to consider tapering ± withdrawal of background cDMARDs (Smolen et al. 2017).

Members of the Janus kinase (JAK) family of protein tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2 [TYK2]) play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with a number of chronic inflammatory conditions, including RA. Many of the pro-inflammatory cytokines implicated in the pathogenesis of RA, including interleukin-6 (IL-6) and interferon-gamma, use cell signaling that involves the JAK/signal transducers and activators of transcription (STAT) pathways. Inhibition of JAK/STAT signaling can target multiple RA-associated cytokine pathways and thereby reduce inflammation, cellular activation, and proliferation of key immune cells as demonstrated with other JAK inhibitors (Williams et al. 2008; Kremer et al. 2009).

## 5.2. Benefit/Risk

Baricitinib is an orally available, selective JAK inhibitor with excellent potency and selectivity for JAK1 (inhibitory concentration of 50% [$IC_{50}$] = 5.9 nM) and JAK2 ($IC_{50}$ = 5.7 nM) and less potency for JAK3 ($IC_{50}$ ≥400 nM) or TYK2 ($IC_{50}$ = 53 nM) (Fridman et al. 2010). Baricitinib is being developed for treatment of patients with moderately to severely active RA who are either intolerant to MTX treatment or who have had an inadequate response to DMARDs, either conventional or biologic. Three completed Phase 2 studies, four completed Phase 3 studies, and one ongoing Phase 3 study (Study I4V-CR-JAGS [JAGS]) have evaluated the clinical utility of baricitinib as treatment for patients with active RA. In the Phase 2 study (I4V-MC-JADC [JADC], conducted by Incyte Corporation), administration of baricitinib at doses of 4, 7, or 10 mg daily for up to 24 weeks resulted in improved signs and symptoms in patients with an inadequate response to DMARDs, including biologics. A relatively flat dose response was observed for the efficacy parameters, with the 4-mg dose performing as well as the 7- and 10-mg doses. The proportions of patients who were ACR responders generally decreased in the off-treatment follow-up period (from Week 24 to Week 28).

In another Phase 2 study (I4V-MC-JADA [JADA]), administration of baricitinib at doses of 1, 2, 4, and 8 mg daily for up to 12 weeks with continued administration of the 2-, 4-, and 8-mg doses for up to 24 weeks resulted in improved signs and symptoms in patients with an inadequate response to MTX. The observed treatment effect in the 4- and 8-mg dose groups was similar, confirming the flat dose response observed in Study JADC. The treatment effect in these dose groups was larger than that observed in the 1- and 2-mg dose groups. The 1- and 2-mg dose groups offered some clinical effectiveness relative to placebo treatment. Patients completing

24 weeks of treatment could enter the extension period of Study JADA that provided treatment for up to an additional 24 months.

The primary efficacy objective (based on ACR20) was met in each completed Phase 3 study, and most major (gated) secondary objectives were also met. Baricitinib also demonstrated significant improvements compared to comparators (placebo, MTX, adalimumab) with respect to relevant domains of efficacy. Across measures, improvements were generally seen with baricitinib from the earliest weeks of treatment (in many instances as early as Week 1) and sustained through the duration of each study. Baricitinib demonstrated statistically significant inhibition of radiographic progression of structural joint damage in each of the three completed studies which incorporated this measure. For additional details regarding efficacy, see Section 6.3 of Investigator's Brochure (IB).

Consistent with prior cumulative data, baricitinib continued to be well-tolerated through 52 and 128 weeks of treatment. The data were consistent with the safety profile observed in the first 24 weeks and, in particular, the data do not demonstrate new signals for events occurring after long-term administration of baricitinib. There were few discontinuations, and no new signals of concern with regard to overall adverse events (AEs), serious adverse events (SAEs), infections, malignancies, cardiovascular events, or other aspects of clinical safety.

The safety profile for baricitinib has been informed by results from nonclinical and clinical studies evaluating a wide range of doses (up to 40 mg once daily [QD]). There are potential risks recognized for baricitinib that will be followed carefully in the Phase 3 development program. The potential risks for baricitinib include increased AEs due to increased exposures in patients with renal impairment, myelosuppression, increased infections (including opportunistic infections and herpes zoster), increased cardiovascular events due to changes in lipids, fetal malformations, emergence of malignancies previously contained by the immune system, and pharmacologic interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and baricitinib to decrease the capacity of the kidneys to respond to hemodynamic changes.

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), had been determined to be an important potential risk for baricitinib. Based on the 2019 updated review of reported events from clinical trials and spontaneous postmarketing cases, as well as the evolving external landscape acknowledging an association with JAK inhibitors as a class, DVT and PE are proposed to be considered as adverse drug reactions (ADRs) in baricitinib labeling for United States, Europe, Canada, and Japan. Globally, labels for baricitinib carry the following warning and precaution: "Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib. Baricitinib should be used with caution in patients with risk factors for DVT/PE. If clinical features of DVT/PE occur, interrupt baricitinib, evaluate promptly, and institute appropriate treatment."

More information about the known and expected benefits, risks, and reasonably anticipated AEs may be found in the investigator's brochure (IB). Information on AEs expected to be related to

the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on SAEs expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate periodically during the course of the study and may be found in Section 6 (Effects in Humans) of the IB. For additional details regarding risks, see Section 6.2 of the IB.

Study I4V-MC-JADY (JADY) is a Phase 3 long-term extension (up to 84 months) study investigating the efficacy and safety of baricitinib in patients with RA. Patients who have completed a Phase 2 or Phase 3 study of baricitinib (i.e., an originating study) are eligible for enrollment into Study JADY. Originating studies include but are not limited to Studies JADA, JADZ, JADV, JADX, JADW, and JAGS:

- Study I4V-MC-JADA (JADA), as described above, is a Phase 2b, double-blind, placebo-controlled study investigating the efficacy and safety of baricitinib doses of 1, 2, 4, and 8 mg QD in patients with active RA despite ongoing MTX therapy. Study JADA consists of a 12-week double-blind treatment period, a 12-week blinded extension period, and 2 optional 52-week open-label extension periods. At the time of study completion, all patients in Study JADA will be receiving baricitinib 4 mg QD.
- Study I4V-MC-JADZ (JADZ) is a Phase 3, double-blind, active-controlled study investigating the efficacy and safety of baricitinib (4 mg QD) administered as monotherapy or in combination with MTX, during a 52-week treatment period, in patients with early RA who have had limited or no treatment with DMARDs. MTX, administered as monotherapy and titrated to the highest tolerated dose specified in the protocol, serves as the active comparator. At the time of study completion, all patients in Study JADZ will be receiving baricitinib 4 mg QD, MTX (at highest tolerated dose), or the combination of baricitinib plus MTX.
- Study I4V-MC-JADV (JADV) is a Phase 3, double-blind, placebo- and active-controlled study investigating the efficacy and safety of baricitinib (4 mg QD) in patients with active RA who have had an inadequate response to MTX (MTX-IR). The study is 52 weeks in duration and includes assessment of structural joint damage. As tumor necrosis factor (TNF) inhibitors are the most commonly used biologic class of therapies for the treatment of moderately to severely active RA in MTX-IR patients, Humira® (adalimumab) was selected as an appropriate active comparator to baricitinib. At the time of study completion, all patients in Study JADV will be receiving either baricitinib 4 mg QD or adalimumab.
- Study I4V-MC-JADX (JADX) is a Phase 3, double-blind, placebo-controlled study investigating the efficacy and safety of baricitinib (2 mg QD or 4 mg QD) administered with background cDMARD(s), during a 24-week treatment period, in patients with active RA who have had an inadequate response to cDMARDs. At the time of study completion, all patients in Study JADX will be receiving baricitinib 2 mg QD, baricitinib 4 mg QD, or placebo.

- Study I4V-MC-JADW (JADW) is a Phase 3, double-blind, placebo-controlled study investigating the efficacy and safety of baricitinib (2 mg QD or 4 mg QD) administered with background cDMARD(s), during a 24-week treatment period, in patients with active RA who have had an inadequate response to biologic DMARDs. At the time of study completion, all patients in Study JADW will be receiving baricitinib 2 mg QD, baricitinib 4 mg QD, or placebo.
- Study I4V-CR-JAGS (JAGS) is a Phase 3, double-blind, placebo-controlled study investigating the efficacy and safety of baricitinib (4 mg QD) administered with background MTX, during a 52-week treatment period, in patients with moderately to severely active RA who have had an inadequate response to MTX therapy. At the time of study completion, all patients in Study JAGS will be receiving baricitinib 4 mg QD.

Given the continuing unmet medical need in patients with moderately to severely active RA, the efficacy of baricitinib demonstrated in Phase 2 studies, and the acceptable safety profile for baricitinib observed through exposures to date, continued administration of baricitinib in this extension of the ongoing Phase 3 studies is appropriate.

# 6. Objectives

## 6.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of baricitinib. Safety and tolerability assessments will include:

- Treatment-emergent adverse events (TEAEs), adverse events of special interest, and serious adverse events (SAEs)
- Temporary investigational product interruptions and permanent investigational product discontinuations
- Vital signs and laboratory evaluations (including chemistry and hematology)

## 6.2. Secondary Objectives

To evaluate in patients initially randomized to receive baricitinib in the originating study, the effect of long-term administration of baricitinib as assessed by:

- Proportion of patients who maintain an ACR20, ACR50, and ACR70 through each 12 months of treatment
- Proportion of patients who maintain a Disease Activity Score modified to include the 28 diarthrodial joint count (DAS28)-high sensitivity C-reactive protein (hsCRP) ≤3.2, DAS28-erythrocyte sedimentation rate (ESR) ≤3.2, DAS28-hsCRP <2.6, and DAS28-ESR <2.6; Clinical Disease Activity Index (CDAI) ≤10 and CDAI ≤2.8; Simplified Disease Activity Index (SDAI) ≤11 and SDAI ≤3.3; ACR/EULAR remission according to the Boolean-based definition; and Health Assessment Questionnaire–Disability Index (HAQ-DI) improvement ≥0.22 and ≥0.3 from Month 6 (of the originating study) through each 12 months of treatment
- Change from baseline of originating study through each 12 months of treatment up to 5 years in structural joint damage as measured by modified Total Sharp Score (mTSS) (van der Heijde method)
- Proportion of patients with mTSS change ≤0 from baseline of originating study through each 12 months of treatment up to 5 years
- Change from baseline of originating study through each 12 months of treatment up to 5 years in joint space narrowing and bone erosion score
- Change from baseline in duration of morning stiffness through each 12 months of treatment
- Change from baseline through each 12 months of treatment in European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) scores
- Evaluation of healthcare resource utilization through 12 months of treatment
- To determine if treatment with baricitinib 2 mg QD maintains the low disease activity level achieved with the 4-mg QD dose (i.e., step-down dosing) on the following outcomes:

- Proportion of patients who maintain a CDAI score of ≤10 from Studies JADV, JADW, and JADX after 3 months of treatment with baricitinib 2 mg QD and with patients continuing treatment with the 4-mg QD dose
- Time to relapse (where relapse is defined as a CDAI score >10 from Studies JADV, JADW, and JADX) after randomization to the baricitinib 2-mg and 4-mg QD doses

Similar analyses will be conducted on patients who initiated treatment with baricitinib as rescue therapy at some time during the originating study.

## 6.3. Exploratory Objectives

- To determine if treatment with baricitinib 2 mg QD maintains the low disease activity level or remission achieved with the 4-mg QD dose (i.e., step-down dosing) on the following outcomes:
  - Proportion of patients who maintain a CDAI score of ≤2.8 from Study JADZ after 3 months of treatment with baricitinib 2 mg QD and with patients continuing treatment with the 4-mg QD dose
  - Time to relapse after randomization to the baricitinib 2-mg and 4-mg QD doses where relapse is defined as:
    - a CDAI score >2.8 from Study JADZ
    - loss of CDAI categorization at randomization (a CDAI score >2.8 if CDAI score at randomization is ≤2.8 or a CDAI score > 10 if CDAI score at randomization is >2.8 and ≤10)
    - having been rescued
- To describe the clinical course of patients initiating baricitinib at the time of enrollment in Study JADY as assessed by DAS28-hsCRP, DAS28-ESR, and CDAI at 3, 6, 12, and at each 12 months of treatment by initial treatment allocation in the originating study
  - From placebo in Study JADW or JADX to baricitinib in Study JADY
  - From MTX in Study JADZ to baricitinib in Study JADY
  - From adalimumab in Study JADV to baricitinib in Study JADY
- To describe the clinical course of patients switching from MTX + baricitinib in Study JADZ to baricitinib monotherapy in Study JADY as assessed by DAS28-hsCRP, DAS28-ESR, and CDAI at 3, 6, 12, and at each 12 months of treatment

# 7. Investigational Plan

## 7.1. Summary of Study Design

### *7.1.1. Design Overview*

Study I4V-MC-JADY (JADY) is a Phase 3, multicenter, long-term extension study evaluating the safety and efficacy of baricitinib (2 mg QD and 4 mg QD) in patients with RA. Patients who completed an originating study (Study JADA, JADZ, JADV, JADX, JADW, or JAGS) may be eligible for enrollment into Study JADY. Patients from future baricitinib RA studies may also be enrolled into Study JADY. Planned enrollment will be approximately 2400 to 3500 patients.

Study JADY will consist of 3 parts:

- Screening: Screening should occur during the last visit of the originating study. However, in particular circumstances, this duration may be extended after consultation with the sponsor.
- Part A: treatment period lasting up to 84 months from enrollment into Study JADY
- Part B: posttreatment follow-up period of 28 days.

Patients may continue to receive the background non-investigational, open-label cDMARD, NSAID, corticosteroid, and other analgesic therapies they were receiving at completion of the originating study. If, after final analysis of the Phase 2 and Phase 3 studies, it is determined that either dose of baricitinib does not have a positive benefit/risk profile, then that dose arm may be discontinued and all patients transferred to the remaining dose arm. However, patients with renal impairment at baseline of the originating study will not receive doses higher than 2 mg baricitinib QD.

### *7.1.2. Treatment Duration, Treatment Assignment, and Maintenance of Study Blind in Study JADY*

As Studies JADA, JADZ, JADV, JADX, JADW, and JAGS vary in duration; patients enrolling in Study JADY will enter the study at different visits. Timing of assessments in Study JADY is described in terms of 28-day months of treatment since randomization in the originating study. This study construct allows the activities required at each visit to be the same for all patients enrolled in Study JADY regardless of the originating study.

- Patients completing Studies JADX and JADW will have had approximately 6 months of treatment with investigational product (baricitinib or placebo) and will enter Study JADY at Visit 1.
- Patients completing Studies JADV, JADZ, and JAGS will have had approximately 12 months of treatment with investigational product (baricitinib, adalimumab [JADV], or MTX [JADZ]) and will enter Study JADY at Visit 4.
- Patients completing Study JADA will have had approximately 30 months of treatment with baricitinib and will enter Study JADY at Visit 11.

Studies JADA, JADZ, JADV, JADX, JADW, and JAGS also vary by whether patients are receiving open-label baricitinib or blinded investigational product at the time of study completion. Therefore, treatment assignments and blinding in Study JADY vary depending on the originating study. In all cases, however, patients and investigators will remain blind as to their original (initial) blinded treatment assignment in the originating study.

- Patients completing Study JADA will have been receiving open-label baricitinib 4 mg QD and will receive open-label baricitinib 4 mg QD in Study JADY.
- Patients enrolled in Studies JADW and JADX were initially randomized to baricitinib 2 mg QD, 4 mg QD, or placebo and had the option of rescue therapy beginning at Week 16. Patients completing these studies without requiring rescue therapy are still blinded to treatment allocation. To maintain the study blinds, these patients will receive blinded therapy in Study JADY. Patients who had been receiving baricitinib 2 mg QD will receive the 2-mg dose in Study JADY. Patients who had been receiving either baricitinib 4 mg QD or placebo will receive the 4-mg dose. Patients who received rescue therapy during Studies JADW and JADX will be receiving baricitinib 4 mg QD at study completion. These patients will continue to receive baricitinib 4 mg QD in Study JADY. Patients with renal impairment will receive baricitinib 2 mg QD.
- Patients enrolled in Study JADV were initially randomized to baricitinib 4 mg QD, adalimumab 40 mg subcutaneous (SC) Q2 weeks, or placebo (both placebo tablet and SC injection). Patients had the option of rescue therapy beginning at Week 16. Patients initially randomized to placebo received baricitinib 4 mg QD beginning at Week 24. Patients completing the study without rescue therapy are still blinded to treatment allocation. To maintain the study blind and to avoid administering a SC placebo injection for an extended period, these patients will receive baricitinib 4 mg QD, and adalimumab investigational product (i.e., adalimumab and matching adalimumab placebo) will be discontinued. Patients who had received rescue therapy during Study JADV will be receiving open-label 4 mg QD baricitinib at study completion. These patients will continue to receive baricitinib 4 mg QD in Study JADY. Patients with renal impairment will receive baricitinib 2 mg QD.
- Patients enrolled in Study JADZ were initially randomized to baricitinib 4 mg QD, MTX monotherapy, or baricitinib plus MTX. Patients had the option of rescue therapy beginning at Week 24. Patients completing the study without rescue therapy are still blinded to treatment allocation. To maintain the study blind, these patients will receive baricitinib 4 mg QD and MTX investigational product (i.e., MTX or matching MTX placebo) will be discontinued. Patients who had received rescue therapy during Study JADZ will be receiving open-label baricitinib 4 mg QD and open-label MTX at study completion. These patients will continue to receive baricitinib 4 mg QD, and open-label MTX will be discontinued. Patients with renal impairment will receive 2 mg baricitinib QD.

- Patients enrolled in Study JAGS were initially randomized to baricitinib 4 mg QD or placebo. At Week 24, all patients entered the open-label period and received a dose of baricitinib 4 mg QD. Patients will continue to receive baricitinib 4 mg QD in Study JADY. Patients with renal impairment will receive baricitinib 2 mg QD.

### *7.1.3. Baricitinib Dose Titration*

An exploratory objective of this study is to evaluate the effectiveness of a reduced dose of baricitinib (step-down from baricitinib 4 mg QD to baricitinib 2 mg QD) in patients who achieve a sustained (at least 3 months in JADY) low disease activity level (CDAI score ≤10; for patients originating in Studies JADV, JADX, JADW, and JAGS) or a sustained remission (CDAI score ≤2.8; for patients originating in Study JADZ). Patients achieving these disease activity criteria will be randomized following a 1:1 ratio allocation to continue baricitinib 4 mg QD or receive the 2-mg QD dose in a blinded fashion. Patients eligible for randomization to step-down must have received at least 15 months of treatment with baricitinib 4 mg QD and have not received rescue therapy in the originating study or JADY. Patients from Study JADA are not eligible for participation in step-down dosing.

If a patient experiences worsening of disease symptoms (either CDAI >10 or CDAI >2.8, depending on originating study) following step-down, a change in analgesics/NSAIDs dosing or the addition of an analgesics/NSAIDs may be considered to manage transient flares. An unscheduled study visit may be needed to assess response to NSAIDs/analgesics and need for rescue therapy. If the patient fails to achieve low disease activity or remission, they may be returned to baricitinib 4 mg QD, and an alteration in cDMARD or corticosteroid therapy may be considered. Patients will be eligible for step-down dosing only once. If after rescue therapy and adjustment of concomitant medications, in the opinion of the investigator the patient is unable to derive adequate benefit (e.g., achieving a CDAI ≤10 (patients originating in Studies JADV, JADX, JADW, and JAGS) or CDAI ≤2.8 (patients originating in Study JADZ)) from treatment with baricitinib over an appropriate time period (e.g., 3 months), the patient should be discontinued from the study.

### *7.1.4. Rescue Therapy*

For patients originating in Studies JADA, JADV, JADW, JADX, and JAGS rescue therapy may be provided to any patient who has a CDAI score >10 at or after 3 months following enrollment into Study JADY. Patients receiving baricitinib 2 mg QD and who have normal renal function (defined as estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 $m^2$) will be rescued to baricitinib 4 mg QD. Patients receiving baricitinib 4 mg QD and patients receiving a baricitinib 2-mg QD dose due to renal impairment will continue to receive these doses.

Furthermore, addition or increase in dose of cDMARDs may occur only after rescue.

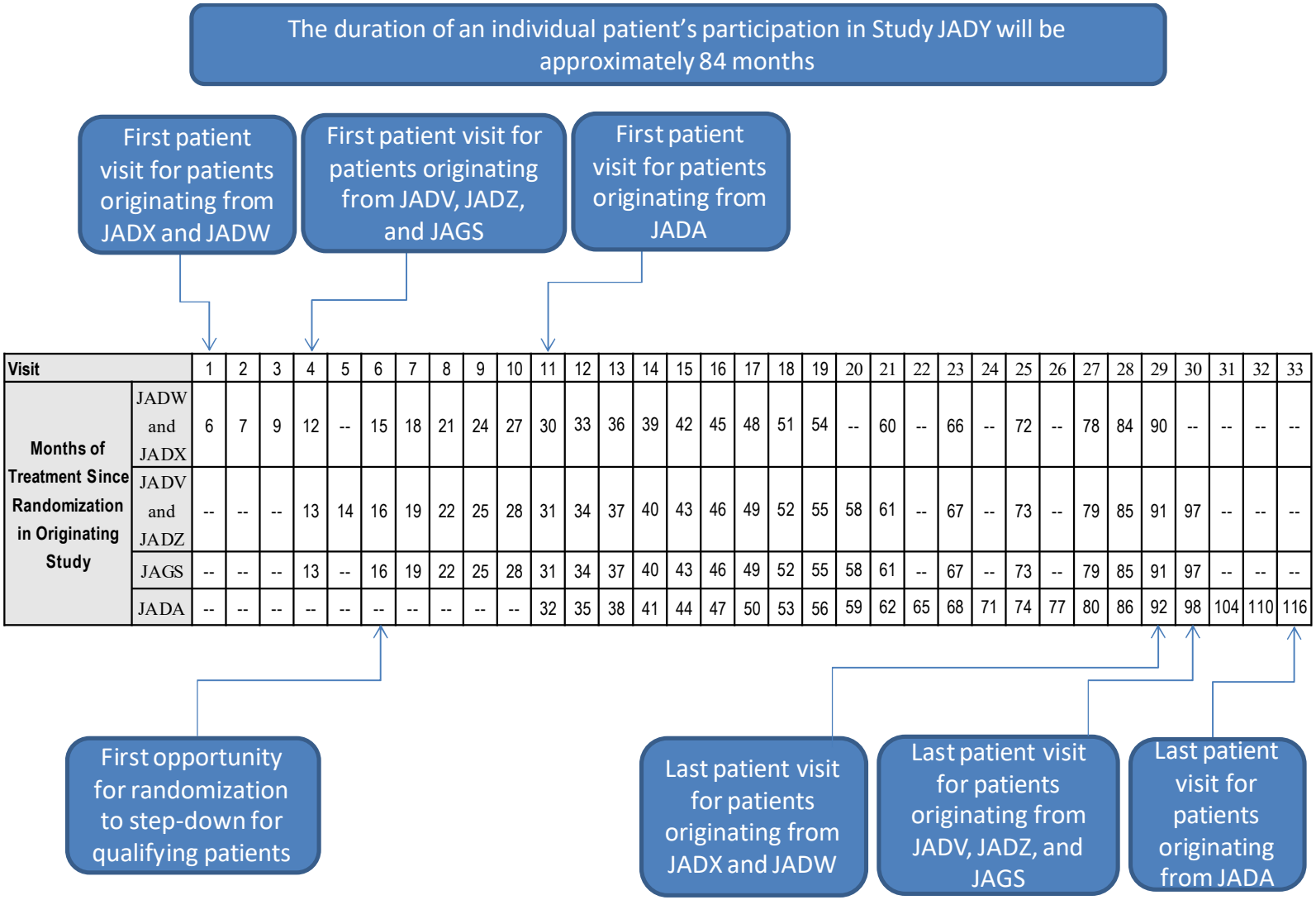
For patients originating in Study JADZ, MTX or other cDMARDs may be prescribed at the discretion of the investigator and according to local clinical practice, at any time point during Study JADY (including prior to 3 months since enrollment).

Patients originating from any study who initiate/increase MTX or other cDMARDs above the maintenance dose in the originating study during Study JADY will be considered as having received rescue therapy.

Patients who experience worsening symptoms between scheduled visits should contact the investigator to arrange an unscheduled study visit and should be assessed for rescue therapy, as appropriate. If after 3 months of rescue therapy and adjustment of concomitant medications (e.g., cDMARDs), patients are considered nonresponders (defined as failure to reach CDAI ≤22 for patients originating in Studies JADV, JADX, JADW, or JAGS and as failure to reach CDAI ≤10 for patients originating in Study JADZ), it is recommended that they should be discontinued from the study. If after 6 months of rescue therapy and adjustment of concomitant medications (e.g., cDMARDs), patients have responded but have not reached low disease activity (defined as CDAI ≤10 for patients originating in any study), it is recommended that they should be discontinued from the study.

Section 12.2.12 outlines information regarding the data monitoring committee (DMC) and interim analyses.

Figure JADY.1 illustrates the study design.




| Visit | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | 6 | 7 | 9 | 12 | -- | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 | -- | 60 | -- | 66 | -- | 72 | -- | 78 | 84 | 90 | -- | -- | -- | -- |
| | JADV and JADZ | -- | -- | -- | 13 | 14 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- |
| | JAGS | -- | -- | -- | 13 | -- | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- |
| | JADA | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 32 | 35 | 38 | 41 | 44 | 47 | 50 | 53 | 56 | 59 | 62 | 65 | 68 | 71 | 74 | 77 | 80 | 86 | 92 | 98 | 104 | 110 | 116 |

**Figure JADY.1. Illustration of study design for Clinical Protocol I4V-MC-JADY – patients enrolled after completing Study JADA, JADV, JADZ, JADX, JADW, or JAGS.**

## 7.2. Discussion of Design and Control

Baricitinib doses of 4 mg QD or 2 mg QD will be provided in this extension study. Patients receiving baricitinib during the originating study will continue on the baricitinib dose administered at the end of that study. Patients enrolling in Study JADY from Studies JADW and JADX will receive blinded investigational product (either baricitinib 4 mg QD or 2 mg QD) in order to preserve the blind of the originating study. Patients previously receiving placebo will receive the baricitinib 4-mg dose. For patients enrolling in JADY from Studies JADV and JADZ, the adalimumab investigational product (Study JADV) and MTX investigational product (Study JADZ) will be discontinued in order to preserve the blind of the originating study and to avoid the long-term administration of placebo injections. Patients previously receiving a comparator investigational product will receive the baricitinib 4-mg dose (see Section 9.4 for rationale) in Study JADY. Patients with renal impairment at baseline of the originating study will not receive doses higher than 2 mg baricitinib QD.

Background cDMARDs, NSAIDs, and low-dose oral corticosteroids are permitted during the study (see Section 9.8 for concomitant medications). For patients originating in Studies JADA, JADV, JADW, JADX, and JAGS rescue therapy may be provided after 3 months following enrollment into Study JADY. For patients originating in Study JADZ, MTX or other cDMARDs may be prescribed at the discretion of the investigator and according to local clinical practice, at any time point during Study JADY (including prior to 3 months since enrollment) to ensure adequate control of disease activity in these patients with early RA.

Safety assessment of baricitinib will be based on the total duration of baricitinib exposure including exposure during the originating study. Efficacy assessments will also be based on the total duration of baricitinib exposure using disease severity measures obtained at the time of initial randomization in the originating study as baseline values. The outcomes for patients switching from adalimumab plus MTX to baricitinib plus MTX (originating Study JADV), from MTX monotherapy to baricitinib monotherapy (originating Study JADZ), from MTX plus baricitinib to baricitinib monotherapy (originating Study JADZ) and from placebo plus MTX/cDMARD to baricitinib plus MTX/cDMARD (Studies JADW and JADX) will be described.

The effectiveness of a reduced dose of baricitinib (step-down from baricitinib 4 mg QD to baricitinib 2 mg QD) in patients who achieve a sustained low disease activity level (CDAI score ≤10) (or a sustained remission [CDAI score ≤2.8] for patients from Study JADZ) will be assessed. For patients with early RA originating in Study JADZ, more stringent eligibility criteria for step-down dosing are applied as the goal of therapy in these patients is to achieve remission. For patients originating in Studies JADV, JADW, and JADX, less stringent criteria are applied as a more reasonable goal of treatment would be attainment of low disease activity. Fifteen months of treatment with baricitinib prior to step-down was selected to allow adequate study duration (>1 year) on stable doses of baricitinib 4 mg QD to thoroughly assess the benefit/risk profile of the dose regimen, including assessment of key endpoints such as radiographic progression at 12 months. Allowing step-down after a minimum of 15 months treatment with baricitinib also ensures that patients have been on stable doses of baricitinib for at

least 3 months in the context of the JADY study prior to step-down. Both the investigator and patient will be blinded to if or when randomization to step-down dosing occurs.

# 8. Study Population

The study population will be comprised of patients diagnosed with RA who have completed any of the ongoing baricitinib studies listed in the inclusion criteria. Study investigator(s) will review patient records and screening test results to determine that the patient meets all inclusion and exclusion criteria to qualify for participation in the study.

## 8.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet the following criterion:

[1] Have completed the final active treatment study visit in Study JADV, JADZ, JADX, JADW, JADA, or JAGS

## 8.2. Exclusion Criteria

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

[2] have significant uncontrolled cerebro-cardiovascular (e.g., myocardial infarction [MI], unstable angina, unstable arterial hypertension, severe heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values that developed during a previous baricitinib study that, in the opinion of the investigator, pose an unacceptable risk to the patient if investigational product continues to be administered

[3] have a known hypersensitivity to baricitinib or any component of this investigational product

[4] had investigational product permanently discontinued at any time during a previous baricitinib study

[5] had temporary investigational product interruption at the final study visit of a previous baricitinib study **and**, in the opinion of the investigator, this poses an unacceptable risk for the patient's participation in the study

[6] have any other condition that, in the opinion of the investigator, renders the patient unable to understand the nature, scope, and possible consequences of the study or precludes the patient from following and completing the protocol

[7] are females of childbearing potential who do not agree to use 2 forms of highly effective birth control when engaging in sexual intercourse while enrolled in the study and for at least 28 days following the last dose of investigational product

a. Females of nonchildbearing potential are defined as women ≥60 years of age, women ≥40 and <60 years of age who have had a cessation of menses for at least 12 months, or women who are congenitally or surgically sterile (i.e, have had a hysterectomy or bilateral oophorectomy or tubal ligation).

b. The following birth control methods are considered highly effective (the patient should choose 2 methods to be used with their partner):

- oral, injectable, implanted, or other hormonal contraceptives (including contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release)
- condom with a spermicidal foam, gel, film, cream, or suppository
- occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository
- intrauterine device
- intrauterine system (e.g., progestin-releasing coil)
- vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate)

[8] are males who do not agree to use 2 forms of highly effective birth control (see above) while engaging in sexual intercourse with female partners of childbearing potential while enrolled in the study and for at least 28 days following the last dose of investigational product

### *8.2.1. Rationale for Exclusion of Certain Study Candidates*

The rationale for the exclusion criteria is as follows: Exclusion Criteria [2] through [6] exclude individuals with previous or concomitant medical conditions that increase the risk for their participation in the study. Exclusion Criteria [7] and [8] exclude individuals who are pregnant, breastfeeding, at risk for becoming pregnant, or at risk for impregnating their partner during the study.

## 8.3. Discontinuations

### *8.3.1. Discontinuation of Patients*

#### 8.3.1.1. Interruption of Investigational Product

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values as described in Table JADY.1 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.

The investigator must obtain approval from Lilly (or its designee) before restarting investigational product that was temporarily discontinued because of an AE or abnormal laboratory value. Investigational product must be held in the following situations involving laboratory abnormalities and may be resumed as noted in Table JADY.1.

**Table JADY.1. Criteria for Temporary Discontinuation of Investigational Product**

| Hold Investigational Product if the Following Laboratory Test Results Occur: | Investigational Product May Be Resumed after Approval from Lilly (or its Designee) and When: |
|---|---|
| WBC count <2000 cells/µL | WBC count ≥2500 cells/µL |
| ANC <1000 cells/µL | ANC >2000 cells/µL |
| Lymphocyte count <500 cells/µL | Lymphocyte count ≥750 cells/µL |
| Platelet count <75,000/µL | Platelet count ≥100,000/µL |
| eGFR <40 mL/min/1.73 $m^2$ (from serum creatinine) for patients without documented renal impairment at baseline of originating study | eGFR ≥50 mL/min/1.73 $m^2$ |
| eGFR <30 mL/min/1.73 $m^2$ (from serum creatinine) for patients with documented renal impairment at baseline of originating study | eGFR ≥40 mL/min/1.73 $m^2$ |
| ALT or AST >5 times the ULN | ALT and AST return to <2 times the ULN, and investigational product is not considered to be the cause of enzyme elevation |
| Hemoglobin <8 g/dL | Hemoglobin ≥10 g/dL |
| Symptomatic herpes zoster | All skin lesions have crusted and are resolving |
| Severe infection that, in the opinion of the investigator, merits the investigational product being discontinued | Resolution of infection |
| Clinical features of VTE (deep vein thrombosis or pulmonary embolism [DVT/PE]) are present | After confirmation that DVT/PE is not present |

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DVT/PE = deep vein thrombosis or pulmonary embolism; eGFR = estimated glomerular filtration rate; min = minute; ULN = upper limit of normal; VTE = venous thromboembolic event; WBC = white blood cell.

Although temporary interruption of investigational product is not a requirement at times of increased potential risk of VTE (e.g., surgery, significant air travel, or other situations involving prolonged immobilization), following appropriate VTE prophylaxis guidelines is recommended to help manage the VTE risk under these circumstances.

#### 8.3.1.2. Discontinuation of Investigational Product

Any patient who is permanently discontinued from investigational product for an AE or abnormal laboratory result should have the reason for investigational product discontinuation reported as the AE or abnormal laboratory value. If any of the criteria listed in Section 8.3.1.1 above recur after investigational product is restarted, the investigator must obtain approval from Lilly (or its designee) before restarting investigational product. In addition, patients will be permanently discontinued from investigational product if they experience any of the criteria listed in Table JADY.2.

**Table JADY.2. Criteria for Permanent Discontinuation of Investigational Product**

| Permanently Discontinue Investigational Product if Any of the Following Is Observed: |
|---|
| ALT or AST >8 times the ULN |
| ALT or AST >5 times the ULN persisting for more than 2 weeks after temporary interruption of investigational product |
| ALT or AST >3 times the ULN and total bilirubin level >2 times the ULN |
| ALT or AST >3 times the ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) |
| WBC count <1000 cells/μL |
| ANC <500 cells/μL |
| Lymphocyte count <200 cells/μL |
| Hemoglobin <6.5 g/dL |
| Pregnancy |
| Malignancy (except for successfully treated basal cell or squamous epithelial skin cancers) |
| HBV DNA ≥29 IU/mL[a] |
| Develop a VTE (DVT/PE) since first receiving baricitinib (including originating study)[b] with exception[c] |

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; HBV DNA = hepatitis B virus deoxyribonucleic acid; ULN = upper limit of normal; VTE = venous thromboembolic event; WBC = white blood cell.

[a] If a HBV DNA result of "target detected" 29 IU/mL or greater, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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. Refer to Section 10.3.2 for additional instruction on HBV DNA monitoring.

[b] Patients who develop a VTE may have additional follow-up and testing recommended (see Section 10.3.3 and Attachment 4).

[c] Patients who had a single occurrence of VTE (occurrence includes a DVT, PE, or DVT and PE combination at roughly the same time) prior to the protocol amendment (i) effective date may continue receiving baricitinib in Study JADY at the investigtor's discretion.

#### 8.3.1.3. Discontinuation from the Study

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, the investigator should contact Lilly or its designee to discuss whether the patient should be discontinued from investigational product. If the patient is discontinued from investigational product, the patient should remain in the study to complete study procedures listed in the Early Termination Visit and enter the posttreatment follow-up period.

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

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

- Patient classified as non-responder after 3 months of rescue therapy (as described in Section 7.1.4).
- Patient failed to reach low disease activity within 6 months after response to rescue therapy (as described in Section 7.1.4).

- Patient enrolls in any other clinical trial involving an investigational product or enrolls in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator decides that the patient should be withdrawn. If this decision is made because of an intolerable AE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. Lilly (or designee) is to be notified immediately.
- Lilly (or designee) decides that the patient should be withdrawn.
- Patient is noncompliant with protocol procedures to the extent that the noncompliance interferes with the patient's safety monitoring or hinders interpretation of study data.
- Patient requests to be withdrawn from the study.
- Investigator or Lilly (or designee), for any reason, stops the study.

Patients who discontinue the study early will have early termination procedures and follow-up performed as shown in the study schedule (Attachment 1). Infrequently, patient and investigator availability may be such that the Early Termination Visit and the Follow-up Visit may occur on or about the same date. In this instance, the visits may be combined and should occur approximately 28 days after the last dose of study drug.

### *8.3.2. Discontinuation of Study Sites*

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

### *8.3.3. Discontinuation of the Study*

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

# 9. Treatment

## 9.1. Treatments Administered

Patients in this long-term extension study will receive baricitinib doses of 2 mg or 4 mg administered orally QD according to the study they completed before entering Study JADY and as shown in Table JADY.3. Patients with renal impairment who received a baricitinib dose of 2 mg QD in the originating study will continue to receive a 2 mg QD dose of baricitinib in Study JADY. For details regarding step-down and rescue dosing, see Section 7.1.3 and Section 7.1.4.

**Table JADY.3. Treatment Regimens**

| Originating Study | Treatment at End of Originating Study | Treatment at Start of JADY |
|---|---|---|
| JADV | Baricitinib 4 mg QD | Baricitinib 4 mg QD |
| | Adalimumab 40 mg SC biweekly | |
| JADZ | Baricitinib 4 mg QD + MTX weekly | Baricitinib 4 mg QD |
| | Baricitinib 4 mg QD monotherapy | |
| | MTX monotherapy weekly | |
| JADX | Baricitinib 4 mg QD | Baricitinib 4 mg QD |
| | Baricitinib 2 mg QD | Baricitinib 2 mg QD |
| | Placebo QD | Baricitinib 4 mg QD |
| JADW | Baricitinib 4 mg QD | Baricitinib 4 mg QD |
| | Baricitinib 2 mg QD | Baricitinib 2 mg QD |
| | Placebo QD | Baricitinib 4 mg QD |
| JADA | Baricitinib 4 mg QD | Baricitinib 4 mg QD |
| JAGS | Baricitinib 4 mg QD | Baricitinib 4 mg QD |

Abbreviations: MTX = methotrexate; QD = once daily.

The investigator or his/her designee will be responsible for explaining the correct use of the investigational agent to the patient, verifying that instructions are followed properly, maintaining accurate records of investigational product dispensing and collection, and returning all unused medication to Lilly or its designee at the end of the study.

In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Patients 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.

## 9.2. Materials and Supplies

Lilly (or designee) will provide the following primary study materials:

- tablets containing 2 mg of baricitinib

- tablets containing placebo to match 2 mg baricitinib tablets
- tablets containing 4 mg of baricitinib
- tablets containing placebo to match 4 mg baricitinib tablets

Investigational product will be dispensed to the patient at the principal investigator's study site. Investigational product packaging will contain enough tablets for the longest possible interval between visits.

Investigational product will be labeled according to the country's regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Investigational products will be supplied by Lilly or its representative in accordance with current Good Manufacturing Practices, and will be supplied with lot numbers, expiry dates, and certificates of analysis (as applicable).

## 9.3. Method of Assignment to Treatment

At the start of Study JADY, patients who meet all criteria for enrollment and who have completed Study JADV, JADZ, JADX, JADW, or JAGS will be assigned to baricitinib treatment (2 mg QD or 4 mg QD) according to the study they have just completed, as outlined in Table JADY.3. Patients who meet all criteria for enrollment and who have completed Study JADA will be assigned to receive open label baricitinib 4 mg QD for the duration of Study JADY. Patients with renal impairment will receive baricitinib 2 mg QD.

Patients eligible for step-down will be assigned to step-down treatment by a computer-generated random sequence using an interactive voice-response system (IVRS) or interactive web-response system (IWRS). Randomization to baricitinib 2 mg QD or 4 mg QD will follow a 1:1 ratio allocation and will be stratified by region and originating study. The IVRS or IWRS will be used to assign packages containing double-blind investigational product to each patient. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the packages into the IVRS or IWRS before dispensing to the patient.

## 9.4. Rationale for Selection of Doses in the Study

Based on efficacy, safety, and pharmacokinetics data from the Phase 2 studies (JADC and JADA), Lilly has selected doses of 4 mg QD and 2 mg QD baricitinib for evaluation in Phase 3 studies and will continue those doses in this study.

## 9.5. Selection and Timing of Doses

Investigational product should be dispensed to the patient at the first visit of Study JADY. Baricitinib dosing will continue daily for 84 months. Oral investigational product should be taken at home at approximately the same time each day.

### *9.5.1. Special Treatment Considerations*

Step-down dosing and rescue therapy will be available (see Section 7.1.3 and Section 7.1.4).

## 9.6. Continued Access to Investigational Product

Baricitinib will not be made available at the conclusion of the study.

## 9.7. Blinding

For patients who enroll into this study after completing Study JADV, JADZ, JADA, or JAGS, the known treatment assignment at the start of JADY will be baricitinib 4 mg QD. For patients who enroll into this study after completing Study JADX or JADW and who received rescue therapy during the originating study, the known treatment assignment at the start of JADY will be baricitinib 4 mg QD. For patients who enroll from Study JADX or JADW and who did not receive rescue therapy during the originating study, baricitinib 2 mg QD or baricitinib 4 mg QD will continue to be assigned in a blinded manner at entry into JADY. Patients with renal impairment at baseline of the originating studies (defined as eGFR <60 mL/min/1.73 $m^2$) will not receive doses higher than 2 mg baricitinib QD.

Patients who qualify for the randomized step-down evaluation will receive blinded therapy upon randomization so that they are no longer aware of the baricitinib dose they are receiving. To preserve the blinding of the randomized step-down, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the primary analysis of this study phase is conducted.

The investigator should make every effort to contact the Lilly clinical research physician prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

Processes to maintain blinding during the interim analysis conducted by the DMC are described in Section 12.2.12.

## 9.8. Concomitant Therapy

Patients may continue to receive concomitant treatments for RA used during the study in which they were previously enrolled. 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.

**Concomitant DMARDs for patients who completed Study JADZ:**

During Study JADZ, concomitant MTX treatment was blinded. Therefore, MTX or other cDMARDs may be prescribed at the discretion of the investigator and according to local clinical practice, at any time point during Study JADY.

**Concomitant cDMARDs for patients who completed Study JADW, JADX, JADV, JADA, or JAGS:**

MTX or other cDMARDs may be prescribed for patients having a CDAI score >10 at or after 3 months following enrollment into Study JADY.

Patients who initiate MTX or other cDMARDs during Study JADY will be considered as having received rescue therapy.

**For all patients in Study JADY:**

- All biologic DMARD therapies are prohibited.
- cDMARDs may be added or the dose increased only after rescue. Maximum doses for the following cDMARDs are specified: hydroxychloroquine up to 400 mg/day; sulfasalazine up to 3000 mg/day; leflunomide (Arava®, Sanofi-Aventis) up to 20 mg/day; and azathioprine up to 150 mg/day or 2 mg/kg/day.
    - For patients who achieve sustained remission or low disease activity, it is recommended to consider tapering ± withdrawal of background cDMARDs in accordance with professional treatment guidelines (Singh et. al. 2016; Smolen et al. 2017)

**Analgesics and NSAID** use, including cyclooxygenase-2 (COX-2) inhibitors, is permitted up to the maximum recommended dose according to local clinical practice. Addition of analgesics or NSAIDs, or change of dose of ongoing analgesics and NSAIDs may occur at any time point during Study JADY. The choice and dose of analgesics and NSAID are at the discretion of the investigator. Dose adjustments are permitted for safety reasons and, if required, to treat worsening of symptoms. Aspirin (acetylsalicylic acid, maximum 350 mg/day) use is allowed to reduce cardiovascular risk.

**Oral corticosteroid** use is permitted as follows:

- Oral corticosteroids for treatment of RA may be initiated, and the dose may be increased to an average daily dose equivalent to 10 mg/day of prednisone for patients not previously on corticosteroid therapy at the discretion of the investigator.
- Increasing/decreasing the oral corticosteroid dose will be allowed at the investigator's discretion up to an average daily dose equivalent to 10 mg of prednisone per day for the management of RA.
- In addition, burst and taper of corticosteroids will be allowed at the discretion of the investigator so that an average daily dose equivalent to 10 mg prednisone is not exceeded over a 30-day period for management of conditions other than RA.
- To treat non-RA conditions, increased doses of oral corticosteroids may be considered on a case-by-case basis with the provision that the corticosteroid dose be reduced to previous levels when possible. For example, a non-RA condition, such as asthma, requiring an increase in oral corticosteroid dose of up to 40 mg of prednisone per day for 2 weeks or less is permitted.

**Intra-articular joint injections and bursal injections** may be given at doses and intervals at the investigator's discretion.

**Proton pump inhibitors and H2 receptor blockers** or equivalent local standard of care may be given at the recommended dose as prophylactic treatment to patients receiving NSAIDs or corticosteroids.

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

Live vaccines, including herpes zoster vaccination, are prohibited during the study. Nonlive seasonal vaccinations and/or emergency vaccination, such as rabies or tetanus vaccinations, are allowed.

All concomitant medications taken during the study must be recorded in the Concomitant Medication sections of the case report form (CRF).

## 9.9. Treatment Compliance

Patient compliance with study medication will be assessed at Visits 2 through 33 when specified in the study schedule (Attachment 1) (and, if necessary, at Early Termination) during the treatment period by counting returned tablets. Deviations from the prescribed dosage regimen should be recorded in the CRF.

A patient will be considered significantly noncompliant if he or she misses >20% of the prescribed doses during the study unless the patient's investigational product was withheld by the investigator for safety reasons.

Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of 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.

# 10. Efficacy, Health Outcome Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the study schedule (Attachment 1).

## 10.1. Efficacy Measures

The efficacy measures described below will be collected at the times shown in the study schedule (Attachment 1).

### *10.1.1. ACR20, ACR50, and ACR70 Indices*

ACR20 is defined as at least 20% improvement from baseline of originating study in the following ACR Core Set values:

- TJC (68 joint count)
- SJC (66 joint count)
- An improvement of at least 20% in at least 3 of the following 5 assessments:
  1. Patient Assessment of Pain (visual analog scale [VAS])
  2. Patient Global Assessment of Disease Activity (VAS)
  3. Physician Global Assessment of Disease Activity (VAS)
  4. Patient Assessment of Physical Function as measured by the HAQ-DI
  5. acute phase reactant as measured by hsCRP

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

#### 10.1.1.1. Hybrid American College of Rheumatology Response Measure

The hybrid ACR (bounded) response measure will be obtained as described by the ACR Committee to Reevaluate Improvement Criteria (2007); see Table JADY.4.

**Table JADY.4. Scoring Method for the Hybrid American College of Rheumatology Response Measure**

| | Mean % Change in Core Set Measures[a] | | | |
|---|---|---|---|---|
| **ACR Status** | **<20** | **≥20, <50** | **≥50, <70** | **≥70** |
| Not ACR20 | Mean % change | 19.99 | 19.99 | 19.99 |
| ACR20 but not ACR50 | 20 | Mean % change | 49.99 | 49.99 |
| ACR50 but not ACR70 | 50 | 50 | Mean % change | 69.99 |
| ACR70 | 70 | 70 | 70 | Mean % change |

Abbreviations: ACR = American College of Rheumatology; ACR20 = 20% improvement in ACR criteria; ACR50 = 50% improvement in ACR criteria; ACR70 = 70% improvement in ACR criteria.

[a] 1) Calculate the average percentage change in core set measures. For each core set measure, subtract score after treatment from baseline score (baseline of originating study) and determine percentage improvement in each measure. Next, if a core set measure worsened by >100%, limit that percentage change to 100% (set equal to -100% bound). Then, average the percentage changes for all core set measures. 2) Determine whether the patient has achieved ACR20, ACR50, or ACR70. 3) Using the table above, obtain the hybrid ACR (bounded) response measure. To use the table, take the ACR20, ACR50, or ACR70 status of the patient (left column) and the mean percentage improvement in core set items; the hybrid ACR score is where they intersect in the table.

#### 10.1.1.2. Disease Activity Score-Erythrocyte Sedimentation Rate and Disease Activity Score–High-Sensitivity C-Reactive Protein

The DAS28 is a measure of disease activity in 28 joints that consists of a composite numeric score of the following variables: TJC, SJC, hsCRP, *or* ESR, and Patient Global Assessment of Disease Activity (Vander Cruyssen et al. 2005). The 28 joints to be examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC include 14 joints on each side of the patient's body: the 2 shoulders, the 2 elbows, the 2 wrists, the 10 metacarpophalangeal joints, the 2 interphalangeal joints of the thumbs, the 8 proximal interphalangeal joints, and the 2 knees (Smolen et al. 1995).

#### 10.1.1.3. European League Against Rheumatism Responder Index

Assessments of patients with RA by European League Against Rheumatism Responder Index based on the 28-joint count (EULAR28) will be used to categorize patients as nonresponders, moderate responders, good responders, or responders (moderate + good responders) according to Table JADY.5 (van Gestel et al. 1998).

**Table JADY.5. Categorization of Patients as Nonresponders, Moderate Responders, or Good Responders**

| Postbaseline Level of DAS28 | Improvement since Baseline of Originating Study in DAS28 | | |
|---|---|---|---|
| | >1.2 | ≤1.2 and >0.6 | ≤0.6 |
| DAS28 ≤3.2 | Good response | | |
| 3.2 < DAS28 ≤5.1 | | Moderate response | |
| DAS28 >5.1 | | | No response |

Abbreviation: DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count.

#### 10.1.1.4. van der Heijde Modified Total Sharp Score

For patients who had radiographs of left and right hands/wrists and left and right feet taken during their originating study, structural progression will be measured using the mTSS. The baseline initial radiographs taken in the originating study will serve as the baseline radiographs for comparison throughout Study JADY.

For patients who completed enrollment in a previous study (JADV, JADZ, JADA, JADX, or JAGS), additional radiographs (i.e, a single posteroanterior view of each hand and a single dorsoplantar view of each foot) will be obtained as shown in the study schedule (Attachment 1).

X-rays of the hands/wrists and feet will be scored using the structural progression as measured using a modification of the mTSS (van der Heijde 2000). This methodology quantifies the extent of bone erosions and joint space narrowing for 44 and 42 joints, respectively, with higher scores representing greater damage. X-rays will also be assessed for joint space narrowing and bone erosions.

Quality control will be performed for proper imaging examination technique prior to allocation of the images to the central readers. The independent read of x-ray images will be performed by 2 primary readers and 1 adjudicator, when necessary, based on predefined criteria. The 2 primary readers will each read 100% of the study patients. All time points will be displayed in random order for a given patient. The reader will have no knowledge of the true chronologic order, patient identity, or treatment group. To ensure a consistent read by the independent readers, an inter-/intrareader variability assessment will be included in the central imaging core laboratory independent read. Repeat x-rays will be requested for all images obtained that are of poor quality as defined in the Image Acquisition Guidelines.

#### 10.1.1.5. Simplified Disease Activity Index

The SDAI is a tool for measurement of disease activity in RA that integrates measures of physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI is calculated by adding together scores from the following assessments:

- number of swollen joints (0 to 28)
- number of tender joints (0 to 28)

- hsCRP in mg/dL (0.1 to 10.0)
- patient global DAS on VAS (0 to 10.0 cm), and
- evaluator global health score on VAS (0 to 10.0 cm) (Aletaha and Smolen 2005)

Disease remission is defined as an SDAI score of ≤3.3 (Felson et al. 2011).

Low disease activity is defined as a SDAI score ≤11 (Aletaha and Smolen 2005).

#### 10.1.1.6. Clinical Disease Activity Index

The CDAI is similar to the SDAI, but it allows for immediate scoring because it does not use a laboratory result. The CDAI is calculated by adding together scores from the following assessments:

- number of swollen joints (0 to 28)
- number of tender joints (0 to 28)
- patient global DAS on VAS (0 to 10.0 cm), and
- evaluator global health score on VAS (0 to 10.0 cm) (Aletaha and Smolen 2005)

Remission is defined as a CDAI score of ≤2.8 (Felson et al. 2011).

Low disease activity is defined as a CDAI score ≤10 (Aletaha and Smolen 2005).

#### 10.1.1.7. ACR/EULAR Rheumatoid Arthritis Remission

Two new ACR/EULAR definitions of RA remission will be evaluated, a "Boolean-based definition" and an "index-based definition" (Felson et al. 2011). The "index-based definition" was discussed in Section 10.1.1.5.

For the ACR/EULAR, according to the "Boolean-based definition" of remission, all 4 criteria below must be met at the same visit:

- Tender joint counts (0 to 28) ≤1
- Swollen joint counts (0 to 28) ≤1
- hsCRP ≤1 mg/dL (10 mg/L)
- Patient global DAS on VAS (using 0 to 10.0 cm) ≤1

## 10.2. Health Outcome Measures

The health outcome measures listed below will be administered. Country-specific translations of each measure will be available in this study.

- Duration of morning joint stiffness: The duration of morning joint stiffness is a patient-administered item that allows for the patients to enter the length of time in minutes that their morning joint stiffness lasted the day prior to the visit (using an electronic patient-reported outcomes [ePRO] tablet).
- HAQ-DI: A patient-reported questionnaire that is commonly used in RA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking,

hygiene, reach, grip, and activities (Fries et al. 1980, 1982; Ramey et al. 1996). The disability section of the questionnaire scores the patient's self-perception on the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do) when dressing and grooming, arising, eating, walking, performing hygiene, reaching, gripping, and performing other daily activities. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index.

- EQ-5D-5L: The EQ-5D-5L is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his or her current health state using a 0- to 100-mm VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. It should be noted that the numerals 1 to 5 have no arithmetic properties and should not be used as a cardinal score. The VAS records the respondent's self-rated health on a vertical VAS in which the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches a value (also called weights) to each of the levels in each dimension (Brooks 1996; Herdman et al. 2011; The EuroQol Group 2013 [WWW]).
- Quick Inventory of Depressive Symptomatology Self-Rated–16 (QIDS-$SR_{16}$): The QIDS-$SR_{16}$ is a 16-item, self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the *American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (APA 1994). Patients are asked to consider each statement as it relates to the way they have felt for the past 7 days. There is a 4-point scale for each item ranging from 0 to 3. The 16 items corresponding to 9 depression domains are summed to give a single score ranging from 0 to 27. Additional information and the QIDS-$SR_{16}$ questions may be found on the University of Pittsburgh Epidemiology Data Center's web site (University of Pittsburgh IDS/QIDS page [WWW]; Rush et al. 2003; Trivedi et al. 2004).
- Healthcare resource utilization: The healthcare resource utilization data will be collected by site staff regarding the number of visits to medical care providers such as general practitioners, specialists, physical or occupational therapists, and other nonphysical care providers for services outside of the clinical study; emergency room admissions; hospital

admissions; and concomitant medications related to the treatment of RA. These data will be collected to support economic evaluations of treatment.

## 10.3. Safety Evaluations

Investigators will be responsible for monitoring the safety of patients who enter 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 will record all relevant AE/SAE information in the CRF.

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that cause the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation will be left to the discretion of the investigator.

### *10.3.1. Adverse Events*

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

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

Cases of pregnancy that occur during maternal or paternal exposures to investigational product or drug delivery system should be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures will be reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of investigational product must be reported to Lilly or its designee via electronic data entry.

Any clinically significant findings from electrocardiogram, laboratory tests, vital sign measurements, or other procedures that result in a diagnosis should be reported to Lilly or its designee.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, and/or investigational product via electronic data entry.

Study site personnel must alert Lilly or its designee within 24 hours of the investigator **unblinding** a patient's treatment group assignment for any reason.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via electronic data entry the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

#### 10.3.1.1. Adverse Events of Special Interest

Adverse events of special interest or laboratory results of special interest will include:

- severe or opportunistic infections
- venous thromboembolism (DVT/PE)
- myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia
- thrombocytosis
- elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>3 times the upper limit of normal [ULN]) and total bilirubin (>2 times the ULN)

Patients with these laboratory-value-specified events will be identified using the same criteria for the interruption of investigational product with the exception of anemia, which will be identified using the same criteria for the discontinuation of investigational product, and thrombocytosis, which will be defined as a platelet count >600,000/μL.

#### 10.3.1.2. Serious Adverse Events

SAE collection in Study JADY will begin after the patient has signed informed consent. SAEs reported prior to signing of informed consent should be reported to the study in which the patient was previously enrolled.

Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

SAEs occurring after a patient has taken the last dose of investigational product will be collected in the pharmacovigilance system and the clinical data collection database for 28 days after the last dose of investigational product, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either investigational product, drug delivery system, or protocol procedure.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB. In the RA population, the occurrence of malignancies, major cerebrocardiovascular events (including death, MI, hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock due to MI, coronary revascularization procedure, neurologic stroke, and peripheral vascular events), and serious infections is reasonably anticipated because of the age of the population, comorbid conditions, disease state, and concomitant medications.

#### *10.3.1.2.1. 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. Lilly has procedures, which are consistent with global regulations and the associated detailed guidances that will be followed for the recording and expedited reporting of SUSARs.

### *10.3.2. Other Safety Measures*

**Physical examination:** A focused physical examination will be performed prior to study enrollment to assure that the patient has not developed any condition that would meet the exclusion criteria. The focused physical examination may be repeated at the investigator's discretion any time a patient presents with physical complaints (Attachment 1).

**Tuberculosis testing:** Investigators should follow local guidelines for monitoring patients for tuberculosis (TB) if a patient is at high risk for acquiring TB or reactivation of latent TB.

**Vital signs and physical characteristics:** Vital signs (sitting blood pressure and pulse) will be measured at times indicated in the study schedule (Attachment 1). Patients should be seated and relaxed with both feet on the floor for at least 5 minutes prior to taking measurements. Simultaneous blood pressure and pulse measurements should be made using either automated or manual equipment. Three replicate blood pressure readings should be made at each time point at approximately 30- to 60-second intervals. A single pulse measurement should be taken simultaneously with at least 1 of the blood pressure readings. If measurements are machine averaged, the average reading should be recorded on the CRF. If measurements are manual or the machine does not provide an average reading, then each individual reading should be recorded on the CRF. Measurements should be made before any scheduled blood draws. Any clinically significant findings that result in a diagnosis should be captured on the CRF and reported as an AE. Additional measurements of vital signs may be performed at the discretion of the investigator. Physical characteristics including weight and waist circumference will be measured at times indicated in the study schedule (Attachment 1).

**Standard laboratory tests:** Hematology, clinical chemistry, urinalysis, lipid profile, eGFR, iron studies, hsCRP, and ESR will be measured at times indicated in the study schedule (Attachment 1).

**Pregnancy tests**: Patients should be counseled not to become pregnant during the study and to contact the investigator immediately if pregnancy is suspected. Urine pregnancy tests should be performed as needed at the discretion of the investigator.

**Hepatitis B virus (HBV) DNA monitoring:** Patients who were hepatitis B core antibody (HBcAb) positive at screening for the originator study will require HBV DNA monitoring approximately every 3 to 6 months, regardless of their hepatitis B surface antibody (HBsAb) status.

If HBV DNA result of "target detected" ≥29 IU/mL, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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.

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

- If a result of "target detected" is obtained at any time during the study with a value of ≥29 IU/mL, refer to Table JADY.2.
- If a single result of "target detected" is obtained with a value of <29 IU/mL, the test should be repeated within approximately 2 weeks.
    - If the repeat test result is "target not detected", monitoring may resume according to the study schedule.
- If the patient has two or more test results of "target detected" with a value of <29 IU/mL during Study JADY and the preceding originator baricitinib study, HBV testing should be conducted approximately once per month for the remainder of the study and referral to a hepatologist is recommended.
- Patients who met criteria for monthly HBV DNA testing in the preceding originator baricitinib study should continue with monthly testing in Study JADY.

### *10.3.3. Venous Thromboembolism Assessment*

If a patient develops the signs and symptoms of a DVT or PE, appropriate local laboratory tests and imaging should be performed, as necessary, for diagnosis of the event. For confirmed cases, additional laboratory testing may be performed, as outlined in Attachment 4. 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.

### *10.3.4. Safety Monitoring*

The Lilly clinical research physician 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 trial. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to Lilly during the clinical trial. If a death or 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 trial and minimize any potential for bias while providing for appropriate safety monitoring.

Liver function monitoring will occur frequently throughout the study. If a study patient experiences elevated ALT or AST ≥3 times the ULN or elevated total bilirubin ≥2 times the ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend on the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

Investigators will monitor vital signs and carefully review findings that may be associated with cardiovascular events. AE reports and vital signs will be collected at each study visit. The cardiovascular monitoring plan includes, in addition, the following:

- regular monitoring of lipid levels
- adjudication of major adverse cardiovascular events (all deaths and nonfatal MIs, hospitalization for unstable angina, hospitalization for heart failure, coronary interventions [such as coronary artery bypass graft or percutaneous coronary intervention], stroke, and transient ischemic attack) by a Cardiovascular Safety Committee at regular intervals to detect any clinically significant imbalance in the occurrence of these events between treatment groups
- estimation of relative rates of occurrence of select AEs using observations obtained from a matched, observational, comparator cohort of RA patients using existing RA registry/registries

A DMC (an advisory group for this study formed to protect the patients; refer to Interim Analyses, Section 12.2.12) oversaw the conduct of all of the baricitinib Phase 3 clinical trials. In the event that safety monitoring was to uncover an issue that needed to be addressed by unblinding at the group level, only members of the DMC were to be able to conduct additional analyses of the safety data.

### *10.3.5. Complaint Handling*

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

Complaints related to unblinded concomitant drugs will be reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or its delegate will be reported.

The investigator or his/her designee will be responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

## 10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study, and Attachment 2 lists the specific tests that will be performed for this study.

### *10.4.1. Samples for Standard Laboratory Testing*

Standard laboratory tests, including chemistry, hematology, and urinalysis panels will be performed. Urine pregnancy tests will be performed as needed at the discretion of the investigator. Blood and urine samples will be collected at the times specified in the study schedule (Attachment 1). Blood will be collected by venipuncture. Attachment 2 lists the specific tests that will be performed for this study.

Routine clinical laboratory tests will be analyzed by a central laboratory selected by Lilly.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests will be run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it will be acceptable to retain samples to batch the tests run or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

### *10.4.2. Exploratory Work*

#### 10.4.2.1. Nonpharmacogenetic/Biomarker Stored Samples

Collection of samples for nonpharmacogenetic biomarker research is a required part of this study. Where local regulations allow, serum, plasma, and urine samples will be collected at the times specified in the study schedule (Attachment 1).

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

Samples will be identified by the patient number (coded) and stored for a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor.

## 10.5. Appropriateness of Measurements

All of the clinical and safety assessments made in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

# 11. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- sponsor a start-up training session to instruct the investigators and study coordinators. This session 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 email, mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection

In addition, Lilly or its representatives may 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.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

## 11.1. Data Capture System

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

Electronic patient-reported outcome measures or other data reported directly by the subject will be entered into an ePRO instrument at the time that the information is obtained. Electronic physician-reported outcome measures will be directly entered by the physician or designee (Physician Global Assessment of Disease Activity) or by the joint assessor (TJC/SJC) into the electronic site tablet. In these instances for which there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

Assessments/procedures conducted during the final visit of the patient's originating study will be replicated from the originating study datasets to the JADY study datasets. For example, Study JADX Week 24/V11 data will be replicated as Month 6/V1 data. The originating study data will be the source data. Assessments with ongoing data in the originating study will be re-entered in the electronic data capture system such as continuing AEs and concomitant medications.

The ePRO records will be stored by a third party, and investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

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

CRF data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or x-ray data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic laboratories system.

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

# 12. Sample Size and Statistical Methods

## 12.1. Determination of Sample Size

It is expected that 80% of patients will complete Study JADV, JADZ, JADX, JADW, JADA, or JAGS; therefore, planned enrollment into JADY will be approximately 2400 to 3500 patients.

## 12.2. Statistical and Analytical Plans

### *12.2.1. General Considerations*

Statistical analysis of this study will be the responsibility of Eli Lilly and Company, although implementation of the SAP and IEAP may be delegated to a third party. A detailed SAP and IEAP describing the statistical methodologies will be developed or amended by Lilly or its designee.

Collected data will be presented using summary tables by treatment cohort and by treatment group for step-down. Continuous data will be summarized using the mean, median, standard deviation (SD), and range (minimum and maximum). Categorical data will be summarized in terms of frequency counts and percentages. Graphical presentations will be used to support the presentation of selected data using, but not limited to, Kaplan Meier time to event analyses (e.g., time to relapse). All statistical tests will be performed at a 2-sided significance level of 0.05, unless otherwise stated. Interaction effects, where applicable, will be performed at a 2-sided significance level of 0.1. Statistical comparisons will be made using Fisher exact test where applicable, and t-test or ANCOVA for continuous data, whichever is appropriate, unless otherwise stated. If a restricted maximum likelihood-based mixed model for repeated measures (MMRM) is used (e.g., structural progression data and other continuous endpoints), the model will include treatment, visit, and treatment-by-visit-interaction as fixed categorical effects and baseline score and baseline score-by-visit-interaction as fixed continuous effects. An unstructured (co)variance structure will be used to model the between- and within-patient errors. If this analysis fails to converge, other structures will be tested. The Kenward-Roger method will be used to estimate the degrees of freedom. Type III sums of squares for the least squares (LS) means will be used; p-values and 95% confidence interval (CI) will also be reported for each treatment group. Further details on the use of MMRM will be described in the SAP and IEAP.

Baseline collected at the originating studies will be used as baseline for all ACR categorical and HAQ-DI improvement from baseline analyses in this study unless otherwise specified. For patients who switch after randomization (step-down) to a different dose, analyses will be based on their random assignment to treatment unless otherwise specified. Details will be provided in the SAP and IEAP.

**Analysis Populations:**

The efficacy and health outcome analyses will be conducted on an intention-to-treat (ITT) basis unless otherwise specified. The ITT analysis set will include all data from all enrolled patients treated with at least 1 dose of the investigational product in Study JADY. The ITT population

will be subcategorized based on baricitinib exposure in the originating study and whether the patient required rescue therapy. Analysis of structural progression (van der Heijde mTSS) will be conducted on the ITT population using patients with available baseline (from the originating study) and at least 1 postbaseline x-ray assessment (collected in JADY). Safety analyses will be performed on the safety population, which is defined as all enrolled patients who received at least 1 dose of the investigational product in Study JADY. Patients will be analyzed for efficacy, health outcomes, and safety according to the treatment to which they were assigned. Further details will be described in the SAP and IEAP.

**Missing Data Imputation:**

In accordance with precedent set with other Phase 3 RA trials (Keystone et al. 2004, 2008, 2009; Cohen et al. 2006; Smolen et al. 2008, 2009), the following methods for imputation of missing data will be used:

1. Nonresponder imputation (NRI): All patients who discontinue the study or the study treatment at any time for any reason will be defined as nonresponders for the NRI analysis for categorical variables such as ACR20/50/70 from the time of discontinuation and onward. Patients who are eligible for rescue therapy starting at 3 months (all studies except JADZ) or at any time point (JADZ) will be analyzed as nonresponders after rescue therapy and onward. Enrolled patients without available data at a postbaseline visit will be defined as nonresponders for the NRI analysis at that visit. The time period used for the NRI analysis will be defined in the SAP and IEAP.
2. Linear extrapolation method: The linear extrapolation method will be used for analysis of the structural progression endpoint (van der Heijde mTSS) to impute missing data. The time period used for the linear extrapolation method will be defined in the SAP.
3. Multiple imputation: Methods other than linear extrapolation that include multiple imputation will be employed for analysis of the structural progression endpoint (van der Heijde mTSS) to impute missing data. Details will be provided in the SAP and IEAP.
4. Modified last observation carried forward (mLOCF): For all continuous measures including safety endpoints, the mLOCF will be a general approach to impute missing data unless otherwise specified. For patients who are eligible for rescue therapy starting at 3 months (all studies except JADZ) or at any time point (JADZ), the last nonmissing observation at or before rescue will be carried forward to subsequent time points for evaluation. For all other patients discontinuing from the study or the study treatment for any reason, the last nonmissing postbaseline observation before discontinuation will be carried forward to subsequent time points for evaluation. If the postbaseline observation is missing, then it will not be included in the analysis even if the baseline observation is not missing. The time period used for the mLOCF method will be defined in the SAP and IEAP.
5. Supportive methods to the NRI and mLOCF will be used.

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 SAP and IEAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

### *12.2.2. Patient Disposition*

The number of enrolled patients along with ITT population will be summarized by treatment cohort and randomized patients by treatment group for the step-down. Frequency counts and percentages will be presented for each treatment cohort and treatment group (step-down). All patients who discontinue from the study or the study treatment 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 by treatment cohort and treatment group (step-down).

### *12.2.3. Patient Characteristics*

Baseline characteristics will be summarized descriptively by treatment cohort and treatment group (step-down). Descriptive statistics including the number of patients, mean, SD, median, minimum, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures. No formal statistical comparisons will be made among the different cohorts or treatment groups unless otherwise stated.

### *12.2.4. Concomitant Therapy*

Concomitant medications will be descriptively summarized in terms of frequency counts and percentages using the safety population prior to and after step-down. The medications will be coded accordingly.

### *12.2.5. Treatment Compliance*

Compliance to investigational product treatment for baricitinib will be assessed through counts of returned investigational product tablets. A patient will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses during the study, unless the patient's investigational product is withheld by the investigator for safety reasons. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of investigational product. Patient compliance will be further defined in the SAP and IEAP.

### *12.2.6. Primary Outcome and Methodology*

Refer to Section 12.2.9.

### *12.2.7. Efficacy Analyses*

Change from baseline of originating studies to postbaseline visits in JADY in structural joint damage as measured by mTSS will be summarized by treatment and analyzed using a t-test. Within-treatment changes from baseline along with 95% CI will be assessed using the t-test. The

linear extrapolation method as described above will be used to impute missing mTSS. MMRM (defined in Section 12.2.1) will be used to analyze structural progression data and other continuous endpoints. Joint space narrowing and bone erosion score analysis will follow the same model specification described for mTSS.

Categorical efficacy variables including the proportion of patients with mTSS change ≤0 from baseline of originating studies to postbaseline visits in JADY; the proportion of patients maintaining a CDAI score ≤10, CDAI ≤2.8, DAS28-hsCRP ≤3.2, DAS28-ESR ≤3.2, DAS28-hsCRP <2.6, DAS28-ESR <2.6, SDAI ≤11, SDAI ≤3.3; HAQ-DI improvement from baseline (of originating studies) of ≥0.22 and ≥0.3; ACR20/50/70 response; and ACR/EULAR remission (according to the Boolean-based definition) at applicable visits in JADY will be summarized by treatment and study cohort. The 95% CI for single proportion will be provided using the Wilson Score method (Wilson 1927; Newcombe 1998). Categorical repeated measure analyses such as pseudo-likelihood-based mixed effects model for repeated measures (categorical MMRM) will be explored. The Kaplan Meier method will be used to assess durability of effect using time to relapse by treatment group. Cox regression model might be explored for time to relapse. Graphical presentations of median time to relapse will be provided.

Mean change from baseline (last assessment in originating studies) to postbaseline visits in continuous efficacy variables (including DAS28-hsCRP and DAS28-ESR) will be summarized. The t-test will be used to summarize within-group changes from baseline. Within treatment changes from baseline will be assessed by the t-test along with 95% CI. More details will be provided in the SAP and IEAP.

### *12.2.8. Health Outcome Analyses*

The health outcome measures will be analyzed using methods described for the continuous or categorical data as described for the efficacy measures in Section 12.2.7. More details are provided in the IEAP.

### *12.2.9. Safety Analyses*

Safety data including TEAEs, adverse events of special interest, SAEs, laboratory analytes (chemistry, hematology, etc.), and vital signs will be descriptively summarized by cohort and by treatment group (step-down) and analyzed using the safety population.

TEAEs are defined as AEs that first occurred or worsened in severity on or after the first dose of study treatment in JADY. The number of TEAEs as well as the number and percentage of patients who experience at least 1 TEAE will be summarized using MedDRA (*Medical Dictionary for Regulatory Activities*) for each system organ class (or a body system) and each preferred term by cohort and treatment group (step-down). Exposure-adjusted incidence rates will be provided. TEAEs will also be summarized by relationship to treatment and by severity within each cohort and treatment group (step-down). SAEs and AEs that lead to investigational product discontinuation will also be summarized by cohort and treatment group (step-down). Fisher exact test will be used for the statistical comparisons.

All clinical laboratory results will be descriptively summarized by cohort and treatment group (step-down). Individual results that are outside of normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables obtained at baseline to postbaseline visits will be summarized as changes from baseline by cohort and treatment group (step-down) and evaluated using an ANCOVA with treatment (or cohort) and baseline value in the model or the t-test where applicable. Within group changes from baseline will be assessed by the t-test. Categorical variables, including the incidence of abnormal values and incidence of adverse events of special interest, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures and analyzed by treatment (or cohort).

Observed values and changes from baseline (predose or screening if missing) for vital signs and physical characteristics will be descriptively summarized by cohort and treatment group (step-down) and time point. Change from baseline to postbaseline in vital signs, QIDS-$SR_{16}$, and body weight will be analyzed using ANCOVA with treatment (or cohort) and baseline value in the model or the t-test where applicable. Within-group changes from baseline will be assessed by the t-test.

The incidence and average duration of investigational product interruptions will be descriptively summarized by treatment (or cohort). Various techniques may be used to estimate the effects of investigational product interruptions on safety measures. Further analyses may be performed and will be planned in the program safety analysis plan (PSAP) and the SAP.

Data collected after initiation of rescue therapy will be summarized as appropriate.

### *12.2.10. Subgroup Analyses*

Subgroup analysis will be conducted for selected safety, efficacy, and health outcome measures by gender, age, race, country, region, originating study (JADV, JADX, etc.), and so on.

Definitions for the levels of the subgroup variables, the analysis methodology, and any subgroup analyses will be defined in details in the SAP, IEAP, and the PSAP. Because this study is not powered for subgroup analyses, all subgroup analyses will be treated as exploratory.

### *12.2.11. Planned Analyses*

Several analyses for regulatory purposes, such as safety updates (including the 120-day safety update), regulatory responses, yearly analyses for disclosure purposes, and a 2-year and a 5-year analysis of x-ray (radiographic progression of structural joint damage) data for publication purposes and/or to provide to regulatory agencies are planned for this study. The first analysis is planned after all of the Phase 3 original studies (JADV, JADZ, JADX, or JADW) are analyzed and a final analysis after all patients complete the study.

Unblinding details will be specified in the unblinding plan section of the SAP.

### *12.2.12. Interim Analyses*

A DMC oversaw the conduct of all the Phase 3 clinical trials evaluating baricitinib in patients with RA. The DMC consisted of members external to Lilly. This DMC followed the rules defined in the DMC charter, focusing on potential and identified risks for this molecule and for this class of compounds. DMC membership included, at a minimum, specialists with expertise in rheumatology, statistics, and other appropriate specialties. This DMC for studies of patients with RA was coordinated with the DMC(s) for other ongoing studies of baricitinib in other indications, and this coordination did not alter the number and timing of the interim analyses.

Access to the unblinded interim data was limited to the statisticians who conducted the interim analyses and the DMC. The statisticians conducting the interim analyses were independent from the study team. The study team did not have access to the unblinded data. Study sites received information about interim results ONLY if they needed to know for the safety of their patients.

The DMC reviewed study discontinuation data, AEs including SAEs, clinical laboratory data, vital sign data, and so on. The DMC recommended continuation of the study, as designed. The DMC reviewed efficacy data to investigate the benefit/risk relationship in the context of safety observations for ongoing patients in the study. The study was not stopped for positive efficacy results, and there was no planned futility assessment. Hence, there was no alpha adjustment for these interim analyses. Details of the DMC and interim safety analyses were documented in a DMC charter and DMC analysis plan, and all documentation is archived in the sponsor trial master file.

Besides DMC members, a limited number of preidentified individuals may gain access to the safety data, as specified in the unblinding plan, prior to the final database lock, to initiate the exploration for safety data (e.g., neutropenia, anemia). 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.

The DMC fulfilled the responsibilities of the Charter and have been disbanded. Ongoing safety monitoring is being conducted by the Global Patient Safety and RA-BEYOND Study team according to company policy.

# 13. Informed Consent, Ethical Review, and Regulatory Considerations

## 13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

## 13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are submitted to the ERB and are used at investigative sites(s). All ICFs must be compliant with the International Council for Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

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

- the current IB or package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

## 13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
2) the ICH GCP Guideline [E6]
3) applicable laws and regulations

The investigator or designee will promptly submit the protocol to the applicable ERB(s).

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

### *13.3.1. Protocol Signatures*

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study. After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

### *13.3.2. Final Report Signature*

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

Lilly will select a qualified investigator from among investigators participating in the design, conduct, and/or analysis of the study to serve as the clinical study report coordinating investigator.

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

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# Attachment 1. Protocol JADY Study Schedule

Study Schedule, Protocol I4V-MC-JADY

| | | Long-term Treatment Extension Part A, Visits 1 to 19[l,m] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1[a] | 2 | 3 | 4[a] | 5[b] | 6 | 7 | 8 | 9 | 10 | 11[a] | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | 6 | 7 | 9 | 12 | -- | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 |
| | JADV and JADZ | -- | -- | -- | 13 | 14 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JAGS | -- | -- | -- | 13 | -- | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JADA | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 32 | 35 | 38 | 41 | 44 | 47 | 50 | 53 | 56 |
| Visit window (days) | | ---[c] | ± 5 | ± 5 | ± 9[c] | ± 5 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9[c] | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 |
| Informed consent | | Informed consent must be obtained before any JADY study procedures | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion review | | Inclusion/exclusion must be reviewed before JADY study procedures | | | | | | | | | | | | | | | | | | |
| Clinical assessments | | | | | | | | | | | | | | | | | | | | |
| Patient demographics | | X[k] | | | X[k] | | | | | | | X[k] | | | | | | | | |
| Symptom-directed physical examination[d] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | | X[k] | | | X[k] | | | | | | | X[k] | | | | | | | | |
| Weight | | X | | | X | | | X | | X | | X | | X | | X | | X | | X |
| Waist circumference | | X | | | X | | | X | | X | | X | | X | | X | | X | | X |
| Vital signs (BP and pulse)[e] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | Long-term Treatment Extension Part A, Visits 1 to 19[l,m] | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1[a] | 2 | 3 | 4[a] | 5[b] | 6 | 7 | 8 | 9 | 10 | 11[a] | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | 6 | 7 | 9 | 12 | -- | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 |
| | JADV and JADZ | -- | -- | -- | 13 | 14 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JAGS | -- | -- | -- | 13 | -- | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JADA | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 32 | 35 | 38 | 41 | 44 | 47 | 50 | 53 | 56 |
| Visit window (days) | | ---[c] | ± 5 | ± 5 | ± 9[c] | ± 5 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9[c] | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 |
| Concomitant medications | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Randomization[f] | | | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Call IVRS or use IWRS | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Investigational product dispensed | | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X[n] |
| Investigational products returned and assess compliance | | | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tender/swollen joint count (68/66 joints) | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient Assessment of Pain VAS | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | Long-term Treatment Extension Part A, Visits 1 to 19[l,m] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1[a] | 2 | 3 | 4[a] | 5[b] | 6 | 7 | 8 | 9 | 10 | 11[a] | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | 6 | 7 | 9 | 12 | -- | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 |
| | JADV and JADZ | -- | -- | -- | 13 | 14 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JAGS | -- | -- | -- | 13 | -- | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JADA | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 32 | 35 | 38 | 41 | 44 | 47 | 50 | 53 | 56 |
| Visit window (days) | | ---[c] | ± 5 | ± 5 | ± 9[c] | ± 5 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9[c] | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 |
| Patient Global Assessment of Disease Activity | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physician Global Assessment of Disease Activity | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hand and foot x-rays[g] | | X | | | X | | | | | X | | | | X | | | | X | | |
| HAQ-DI | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Morning joint stiffness duration | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| EQ-5D-5L | | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| QIDS-SR16 | | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Healthcare resource use | | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | Long-term Treatment Extension Part A, Visits 1 to 19[l,m] | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1[a] | 2 | 3 | 4[a] | 5[b] | 6 | 7 | 8 | 9 | 10 | 11[a] | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | 6 | 7 | 9 | 12 | -- | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 |
| | JADV and JADZ | -- | -- | -- | 13 | 14 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JAGS | -- | -- | -- | 13 | -- | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JADA | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 32 | 35 | 38 | 41 | 44 | 47 | 50 | 53 | 56 |
| Visit window (days) | | ---[c] | ± 5 | ± 5 | ± 9[c] | ± 5 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9[c] | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 |
| Laboratory tests | | | | | | | | | | | | | | | | | | | | |
| Clinical chemistry[h] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Lipid panel[i] | | X | | | X | | | X | | X | | X | | X | | X | | X | | X |
| Hematology | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HBV DNA[o] | | X | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Iron studies (iron, TIBC, and ferritin) | | X | | | X | | | | | X | | | | X | | | | X | | |
| Urinalysis | | X | | | X | | | | | X | | | | X | | | | X | | |
| hsCRP | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Erythrocyte sedimentation rate[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Immunoglobulin levels (IgG, IgA, IgM) | | X | | | X | | | | | X | | | | X | | | | X | | |

| | | Long-term Treatment Extension Part A, Visits 1 to 19[l,m] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 1[a] | 2 | 3 | 4[a] | 5[b] | 6 | 7 | 8 | 9 | 10 | 11[a] | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | 6 | 7 | 9 | 12 | -- | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 | 51 | 54 |
| | JADV and JADZ | -- | -- | -- | 13 | 14 | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JAGS | -- | -- | -- | 13 | -- | 16 | 19 | 22 | 25 | 28 | 31 | 34 | 37 | 40 | 43 | 46 | 49 | 52 | 55 |
| | JADA | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 32 | 35 | 38 | 41 | 44 | 47 | 50 | 53 | 56 |
| Visit window (days) | | ---[c] | ± 5 | ± 5 | ± 9[c] | ± 5 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9[c] | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 |
| Lymphocyte subsets (T, B, NK, and T-cell subsets) | | X | | | X | | | | | X | | | | X | | | | X | | |
| Exploratory storage samples (serum and plasma) | | X | | | X | | | | | X | | | | X | | | | X | | |
| Exploratory storage samples (urine) | | X | | | X | | | | | X | | | | X | | | | X | | |

| | | | | Long-term Treatment Extension Part A, Visits 20 to 33 | | | | | | | | | | | | | Follow-up Part B |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | ET[l] | 801[m] |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | -- | 60 | -- | 66 | -- | 72 | -- | 78 | 84 | 90 | -- | -- | -- | -- | -- | -- |
| | JADV and JADZ | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JAGS | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JADA | 59 | 62 | 65 | 68 | 71 | 74 | 77 | 80 | 86 | 92 | 98 | 104 | 110 | 116 | -- | -- |
| Visit window (days) | | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | Any day | 28 ± 9 after last dose |
| Clinical assessments | | | | | | | | | | | | | | | | | |
| Symptom-directed physical examination[d] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Weight | | | X | | X | | X | | X | X | X | X | X | X | X | X | X |
| Waist circumference | | | X | | X | | X | | X | X | X | X | X | X | X | X | X |
| Vital signs (BP and pulse)[e] | | 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 |
| Concomitant medications | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Randomization[f] | | X | X | X | X | X | X | X | X | X | | | | | | | |
| Call IVRS or use IWRS | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | | | Long-term Treatment Extension Part A, Visits 20 to 33 | | | | | | | | | | | | | Follow-up Part B |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | ET[l] | 801[m] |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | -- | 60 | -- | 66 | -- | 72 | -- | 78 | 84 | 90 | -- | -- | -- | -- | -- | -- |
| | JADV and JADZ | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JAGS | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JADA | 59 | 62 | 65 | 68 | 71 | 74 | 77 | 80 | 86 | 92 | 98 | 104 | 110 | 116 | -- | -- |
| Visit window (days) | | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | Any day | 28 ± 9 after last dose |
| Investigational product dispensed | | X | X | X | X | X | X | X | X | X | X[n] | X[n] | X | X | | | |
| Investigational products returned and assess compliance | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Tender/swollen joint count (68/66 joints) | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient Assessment of Pain VAS | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient Global Assessment of Disease Activity | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | | | Long-term Treatment Extension Part A, Visits 20 to 33 | | | | | | | | | | | | | Follow-up Part B |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | ET[l] | 801[m] |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | -- | 60 | -- | 66 | -- | 72 | -- | 78 | 84 | 90 | -- | -- | -- | -- | -- | -- |
| | JADV and JADZ | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JAGS | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JADA | 59 | 62 | 65 | 68 | 71 | 74 | 77 | 80 | 86 | 92 | 98 | 104 | 110 | 116 | -- | -- |
| Visit window (days) | | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | Any day | 28 ± 9 after last dose |
| Physician Global Assessment of Disease Activity | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hand and foot x-rays[g] | | | X | | | | | | | | | | | | | X | |
| HAQ-DI | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Morning joint stiffness duration | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| EQ-5D-5L | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| QIDS-SR16 | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Healthcare resource use | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | Long-term Treatment Extension Part A, Visits 20 to 33 | | | | | | | | | | | | | | | Follow-up Part B |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | ET[l] | 801[m] |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | -- | 60 | -- | 66 | -- | 72 | -- | 78 | 84 | 90 | -- | -- | -- | -- | -- | -- |
| | JADV and JADZ | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JAGS | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JADA | 59 | 62 | 65 | 68 | 71 | 74 | 77 | 80 | 86 | 92 | 98 | 104 | 110 | 116 | -- | -- |
| Visit window (days) | | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | Any day | 28 ± 9 after last dose |
| Laboratory tests | | | | | | | | | | | | | | | | | |
| Clinical chemistry[h] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Lipid panel[i] | | | 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 |
| HBV DNA[o] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[p] | X |
| Iron studies (iron, TIBC, and ferritin) | | | X | | | | X | | | X | | X | | X | | | |
| Urinalysis | | | X | | | | X | | | X | | X | | X | | | |
| hsCRP | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Erythrocyte sedimentation rate[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | Long-term Treatment Extension Part A, Visits 20 to 33 | | | | | | | | | | | | | | | Follow-up Part B |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | ET[l] | 801[m] |
| Months of Treatment Since Randomization in Originating Study | JADW and JADX | -- | 60 | -- | 66 | -- | 72 | -- | 78 | 84 | 90 | -- | -- | -- | -- | -- | -- |
| | JADV and JADZ | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JAGS | 58 | 61 | -- | 67 | -- | 73 | -- | 79 | 85 | 91 | 97 | -- | -- | -- | -- | -- |
| | JADA | 59 | 62 | 65 | 68 | 71 | 74 | 77 | 80 | 86 | 92 | 98 | 104 | 110 | 116 | -- | -- |
| Visit window (days) | | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | ± 9 | Any day | 28 ± 9 after last dose |
| Immunoglobulin levels (IgG, IgA, IgM) | | | X | | | | X | | | X | | X | | X | | | |
| Lymphocyte subsets (T, B, NK, and T-cell subsets) | | | X | | | | X | | | X | | X | | X | | | |
| Exploratory storage samples (serum and plasma) | | | X | | | | X | | | X | | X | | X | | | |
| Exploratory storage samples (urine) | | | X | | | | X | | | X | | X | | X | | | |

Abbreviations: BP = blood pressure; CDAI = Clinical Disease Activity Index; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life-5 Dimensions-5 Level; ET = Early Termination; HAQ-DI = Health Assessment Questionnaire-Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV DNA = hepatitis B virus deoxyribonucleic acid; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; IVRS = interactive voice-response system; IWRS = interactive web-response system; NK = natural killer; QIDS-SR16 = Quick Inventory of

Depressive Symptomatology-Self-Rated (16 items); TIBC = total iron binding capacity; VAS = visual analog scale.

[a] Any assessments/procedures conducted during the final visit of the patient's originating study should not be repeated during their first visit for Study JADY.

[b] Visit 5 only applies to patients originating in Studies JADV and JADZ.

[c] The 1-day screening period should occur during the last visit of the originating study. However, in particular circumstances, this duration may be extended after consultation with the sponsor. Therefore, there is no specified visit window for patients enrolled at Visits 1, 4, and 11 entering Study JADY from the originating studies.

[d] A focused physical examination will be performed prior to study entry to assure that the patient has not developed any condition that would meet the exclusion criteria. The focused physical examination may be repeated at the investigators discretion any time a patient presents with physical complaints.

[e] At each time point, 3 replicate readings should be made at approximately 30- to 60-second intervals. Blood pressure is recorded as the average of these 3 readings. A single pulse measurement should be taken simultaneously with at least 1 of the readings at each time point.

[f] From this visit forward, patients from Study JADV, JADZ, JADW, JAGS, or JADX who never received rescue therapy, and who have received baricitinib 4 mg QD on a stable background for at least 15 months, will be eligible for step-down dosing if they achieve a CDAI score ≤10 (≤2.8 for JADZ) for a minimum of 3 months. Randomization is not performed at the final scheduled visit for each originating study.

[g] Hand and foot x-rays are not required for patients originating in Study JADW. Patients originating in studies other than JADW will have x-rays performed in Study JADY if they have an evaluable baseline x-ray from the originating study. X-rays will be taken at the following visits depending on the originating study: Study JADX Visits 1, 4, 9, 13, 17, 21, ET; Studies JADV, JADZ, and JAGS Visits 4, 9, 13, 17, 21, ET; Study JADA Visits 13, 17, 21, ET. X-rays will only be taken at the first patient visit if the most recent x-ray was at least 8 weeks earlier. X-rays will only be taken at ET if the most recent x-ray was more than 12 weeks earlier. X-ray will only be taken at ET if termination occurs prior to Visit 21.

[h] Clinical chemistry will include the following values calculated from serum creatinine: calculated creatinine clearance (Cockcroft-Gault equation) (this calculation will be performed at the visits where both weight and serum creatinine are collected, according to the Protocol JADY Study Schedule [Attachment 1]) and eGFR (calculated using the Modification of Diet in Renal Disease isotope dilution mass spectrometry traceable method).

[i] Fasting lipid profile: Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

[j] Erythrocyte sedimentation rate to be performed locally using a kit provided by the sponsor.

[k] Only required if this is a patient's entry visit.

[l] Patients who discontinue from the study prior to final scheduled visit for any reason will have an ET Visit performed. All procedures required for the ET Visit should be completed according to the study schedule. The ET visit will be done only once during the trial. If the patient completes the study through final scheduled visit, the patient will continue to Part B (Visit 801) without an ET.

[m] A Follow-up Visit (Visit 801) will be performed approximately 28 days after the last dose of investigational product is administered.

[n] Investigational product is not dispensed to patients originating from Studies JADW and JADX at Visit 29. Investigational product is not dispensed to patients originating from Studies JADV, JADZ, and JAGS at Visit 30.

[o] HBV DNA will be performed in patients who tested positive for HBcAb at screening in the originating study. HBV DNA monitoring approximately every 3 to 6 months, at an ET Visit, and at Visit 801, will be required, regardless of the patient's HBsAb status.

[p] To be performed only if previous test was more than 3 months earlier.

# Attachment 2. Protocol JADY Clinical Laboratory Tests

Clinical Laboratory Tests

| | |
|---|---|
| Hematology[a,b] | Clinical Chemistry[a,b] |
| Hemoglobin | Serum concentrations of |
| Hematocrit | Sodium |
| Erythrocyte count (RBCs) | Potassium |
| Absolute reticulocyte count | Total bilirubin |
| Mean cell volume | Direct bilirubin |
| Mean cell hemoglobin | Alkaline phosphatase |
| Mean cell hemoglobin concentration | Alanine aminotransaminase/serum glutamic pyruvic transaminase |
| Leukocytes (WBCs) | |
| Absolute count of | Aspartate aminotransferase/serum glutamic oxaloacetic transaminase |
| Neutrophils, segmented | |
| Neutrophils, juvenile (bands) | Blood urea nitrogen |
| Lymphocytes | Creatinine |
| | Estimated glomerular filtration rate[d] |
| Monocytes | Calculated creatinine clearance[e] |
| | Uric acid |
| Eosinophils | Calcium |
| Basophils | Glucose |
| Platelets | Albumin |
| Cell morphology | Creatine kinase |
| CBC, including differential and blood smear | Total protein |
| | |
| Urinalysis[a,b] | |
| Color | Lipid profile including[f] total cholesterol, HDL-C, |
| Specific gravity | LDL-C, and triglycerides, ApoA1, ApoB |
| pH | |
| Protein | Urine Pregnancy Test (females only)[g] |
| Glucose | |
| Ketones | Other Tests |
| Blood | Iron studies (iron, TIBC, and ferritin) |
| Bilirubin | High-sensitivity C-reactive protein |
| Urobilinogen | Erythrocyte sedimentation rate[h] |
| Leukocyte esterase | Immunoglobulins (IgG, IgA, IgM) |
| Nitrite | HBV DNA |
| Microscopic examination of sediment[c] | |
| | |
| Lymphocyte subsets (T, B, NK, and T-cell subsets) | |
| | |
| Stored serum, plasma, urine samples for possible exploratory biomarker analyses | |

*(Abbreviations and footnotes follow on the next page.)*

Abbreviations: ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; CBC = complete blood count; HBV DNA = hepatitis B virus deoxyribonucleic acid; HDL-C = high density lipoprotein cholesterol; Ig = immunoglobulin; LDL-C = low-density lipoprotein cholesterol; NK = natural killer; RBC = red blood cell; TIBC = total iron binding capacity; WBC = white blood cell.

[a] Assayed/calculated by a sponsor-designated laboratory.

[b] Unscheduled blood chemistry (including CPK), hematology, and urinalysis panels may be performed at the discretion of the investigator. If done to evaluate laboratory results to resume investigational product, samples must be assayed centrally.

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

[d] Estimated glomerular filtration rate for serum creatinine will be calculated by the central laboratory using the Modification of Diet in Renal Disease isotope dilution mass spectrometry traceable method.

[e] The calculated creatinine clearance will be determined by the central laboratory using the Cockcroft-Gault equation: Men: ([140 – age] x [weight in kg]) / (72 x [serum creatinine in mg/dL]) or ([140 – age] x [weight in kg]) / (0.814 x [serum creatinine in μmol/L]). Women: (above formula) x 0.85. This calculation will be performed at the visits where both weight and serum creatinine are collected, according to the Protocol JADY Study Schedule (Attachment 1).

[f] Fasting lipid profile. Patients should not eat or drink anything except water for 12 hours prior to sample collection. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.

[g] For all women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at the discretion of the investigator.

[h] Erythrocyte sedimentation rate analysis will be performed by the local laboratory.

# Attachment 3. Protocol JADY Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly designated medical monitor.

| 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[a] |
| CPK | |

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

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

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

# Attachment 4. Monitoring Tests for Confirmed VTE

Selected tests may be obtained in the event of a confirmed VTE and may be required in follow-up with patients in consultation with Eli Lilly and Company, its designee, or the clinical research physician.

| |
|---|
| 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; fXa = clotting factor Xa; MTHFR = methylene tetrahydrofolate reductase; PT = prothrombin time; PTT = partial thromboplastin time; VTE = venous thromboembolic event.

# Attachment 5. Protocol Amendment I4V-MC-JADY(i) Summary

## Overview

Protocol I4V-MC-JADY has been amended. The new protocol is indicated by amendment (i) 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 as follows:

### Amendment Summary for Protocol I4V-MC-JADY Amendment (i)

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2. Benefit/Risk | • Added text to address potential risk of VTE for baricitinib.<br>• Deleted VTE incidence imbalance | Updating text based on 2019 safety review, to include information that JAK inhibitors as a class have DVT and PE as known ADRs and warning label text. |
| 8.3.1.1. Interruption of Investigational Product | Updated text in Table JADY.1. | Includes text stating that patients may resume study after confirmation that DVT/PE is not present. |
| 8.3.1.2. Discontinuation of Investigational Product | Updated text in Table JADY.2. | Based on the 2019 updated review of reported events from clinical trials and spontaneous postmarketing cases, as well as the evolving external landscape acknowledging an association between JAK inhibitors as a class and DVT/PE as uncommon ADRs. |
| 10.3. Safety Evaluations | Updated to include text stating that investigators must record AE/SAEs in the CRF | Investigators must record AE/SAEs in the CRF. |
| Attachment 1. Protocol JADY Study Schedule | Updated footnote g | Early termination participants will only receive an X-ray if termination occurs before Visit 21. |

# Revised Protocol Sections

| | |
|---|---|
| **Note:** | Deletions have been identified by ~~strikethroughs~~.<br>Additions have been identified by the use of underscore. |

# 1. Protocol I4V-MC-JADY (i~~h~~)
# A Phase 3, Multicenter Study to Evaluate the Long-Term Safety and Efficacy of Baricitinib in Patients with Rheumatoid Arthritis

## 5.2. Benefit/Risk

The safety profile for baricitinib has been informed by results from nonclinical and clinical studies evaluating a wide range of doses (up to 40 mg once daily [QD]). There are potential risks recognized for baricitinib that will be followed carefully in the Phase 3 development program. The potential risks for baricitinib include increased AEs due to increased exposures in patients with renal impairment, myelosuppression, increased infections (including opportunistic infections and herpes zoster), increased cardiovascular events due to changes in lipids, fetal malformations, emergence of malignancies previously contained by the immune system, and pharmacologic interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and baricitinib to decrease the capacity of the kidneys to respond to hemodynamic changes.

~~Venous thromboembolic events (VTEs) 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 trials of 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 (ie, patients with RA). 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 a VTE (eg, history of VTE, increased body mass index, older age). Venous thromboembolic event risk can be managed through risk mitigation strategies. Presymptomatic screening for hypercoagulable conditions is not currently recommended, even in the prescribing information for medications with known increased risk for VTEs.~~

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), had been determined to be an important potential risk for baricitinib. Based on the 2019 updated review of reported events from clinical trials and spontaneous postmarketing cases as well as the evolving external landscape acknowledging an association with JAK inhibitors as a class, DVT and PE are proposed to be considered as adverse drug reactions (ADRs) in baricitinib labeling for United States, Europe, Canada, and Japan. Globally, labels for baricitinib carry the following warning and precaution: “Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib. Baricitinib should be used with caution in patients with risk factors for DVT/PE. If clinical

features of DVT/PE occur, interrupt baricitinib, evaluate promptly, and institute appropriate treatment."

### 8.3.1. Discontinuation of Patients

**Table JADY.1. Criteria for Temporary Discontinuation of Investigational Product**

| Hold Investigational Product if the Following Laboratory Test Results Occur: | Investigational Product May Be Resumed after Approval from Lilly (or its Designee) and When: |
|---|---|
| WBC count <2000 cells/μL | WBC count ≥2500 cells/μL |
| ANC <1000 cells/μL | ANC >2000 cells/μL |
| Lymphocyte count <500 cells/μL | Lymphocyte count ≥750 cells/μL |
| Platelet count <75,000/μL | Platelet count ≥100,000/μL |
| eGFR <40 mL/min/1.73 $m^2$ (from serum creatinine) for patients without documented renal impairment at baseline of originating study | eGFR ≥50 mL/min/1.73 $m^2$ |
| eGFR <30 mL/min/1.73 $m^2$ (from serum creatinine) for patients with documented renal impairment at baseline of originating study | eGFR ≥40 mL/min/1.73 $m^2$ |
| ALT or AST >5 times the ULN | ALT and AST return to <2 times the ULN, and investigational product is not considered to be the cause of enzyme elevation |
| Hemoglobin <8 g/dL | Hemoglobin ≥10 g/dL |
| Symptomatic herpes zoster | All skin lesions have crusted and are resolving |
| Severe infection that, in the opinion of the investigator, merits the investigational product being discontinued | Resolution of infection |
| Clinical features of VTE (deep vein thrombosis or pulmonary embolism [DVT/PE]) are present | After confirmation that DVT/PE is not present ~~evaluation and institution of appropriate treatment~~ |

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DVT/PE = deep vein thrombosis or pulmonary embolism; eGFR = estimated glomerular filtration rate; min = minute; ULN = upper limit of normal; VTE = venous thromboembolic event; WBC = white blood cell.

**Table JADY.2. Criteria for Permanent Discontinuation of Investigational Product**

| Permanently Discontinue Investigational Product if Any of the Following Is Observed: |
|---|
| ALT or AST >8 times the ULN |
| ALT or AST >5 times the ULN persisting for more than 2 weeks after temporary interruption of investigational product |
| ALT or AST >3 times the ULN and total bilirubin level >2 times the ULN |
| ALT or AST >3 times the ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) |
| WBC count <1000 cells/µL |
| ANC <500 cells/µL |
| Lymphocyte count <200 cells/µL |
| Hemoglobin <6.5 g/dL |
| Pregnancy |
| Malignancy (except for successfully treated basal cell or squamous epithelial skin cancers) |
| HBV DNA ≥29 IU/mL[a] |
| Develop a ~~second~~ VTE (DVT/PE) since first receiving baricitinib (including originating study)[b] with exception[c] |

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; HBV DNA = hepatitis B virus deoxyribonucleic acid; ULN = upper limit of normal; VTE = venous thromboembolic event; WBC = white blood cell.

a If a HBV DNA result of "target detected" 29 IU/mL or greater, then the patient should be referred to a hepatology specialist immediately. In selected cases, investigators may temporarily continue study drug 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. Refer to Section 10.3.2 for additional instruction on HBV DNA monitoring.

b Patients who develop a VTE may have additional follow-up and testing recommended (see Section 10.3.3 and Attachment 4).

c Patients who had a single occurrence of VTE (occurrence includes a DVT, PE, or DVT and PE combination at roughly the same time) prior to the protocol amendment (i) effective date may continue receiving baricitinib in Study JADY at the investigator's discretion.

## 10.3. Safety Evaluations

Investigators will be responsible for monitoring the safety of patients who enter 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 will record all relevant AE/SAE information in the CRF.

### Attachment 1. Study Schedule, Protocol I4V-MC-JADY

g Hand and foot x-rays are not required for patients originating in Study JADW. Patients originating in studies other than JADW will have x-rays performed in Study JADY if they have an evaluable baseline x-ray from the originating study. X-rays will be taken at the following visits depending on the originating study: Study JADX Visits 1, 4, 9, 13, 17, 21, ET; Studies JADV, JADZ, and JAGS Visits 4, 9, 13, 17, 21, ET; Study JADA Visits 13, 17, 21, ET. X-rays will only be taken at the first patient visit if the most recent x-ray was at least 8 weeks earlier. X-rays will only be taken at ET if the most recent x-ray was more than 12 weeks earlier. X-ray will only be taken at ET if termination occurs prior to Visit 21.

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