

Protocol I4V-MC-JAJA (f)

A Randomized, Active-Controlled, Parallel-Group, Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis

NCT03915964

Approval date: 16-Oct-2024

**Protocol I4V-MC-JAJA(f) (RA-BRIDGE)
A Randomized, Active-Controlled, Parallel-Group,
Phase 3b/4 Study of Baricitinib in Patients with
Rheumatoid Arthritis**

Confidential Information

The information contained in this document is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of baricitinib (LY3009104), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

Note to Regulatory Authorities: This document may contain protected personal data and/or commercially confidential information exempt from public disclosure. Eli Lilly and Company requests consultation regarding release/redaction prior to any public release. In the United States, this document is subject to Freedom of Information Act (FOIA) Exemption 4 and may not be reproduced or otherwise disseminated without the written approval of Eli Lilly and Company or its subsidiaries.

Baricitinib (LY3009104)

Eli Lilly and Company
Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

EudraCT Number: 2018-003351-37

EU CT Number: 2023-508022-10-00

Protocol Amendment (f) Electronically Signed and Approved by Lilly on approval date
provided below.

Document ID: VV-CLIN-067243

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
<i>Amendment e</i>	<i>22-Mar-2024</i>
<i>Amendment d</i>	<i>22-Jul-2022</i>
<i>Amendment c</i>	<i>28-Apr-2022</i>
<i>Amendment b</i>	<i>17-Mar-2021</i>
<i>Amendment a</i>	<i>19-Apr-2019</i>
<i>Original Protocol</i>	<i>13-Dec-2018</i>

Amendment [f]

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment

The main rationale for this amendment is to address the regulatory feedback received as part of the transition to the EU Clinical Trials Regulation (CTR).

Minor editorial and formatting changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
9.2.1. Serious Adverse Events	Subsection, SAE regulatory reporting Revised the wording to include applicable country-specific regulatory requirements for safety reporting	To clarify wording on SAE reporting requirements to be compliant with CTR requirement
9.2.2. Suspected Unexpected Serious Adverse Reactions	- Replaced “Directive 2001/20/EC” with “Regulation 536/2014 [submission of SUSARs to the EudraVigilance database]” - Revised the wording on processing of safety reports	To clarify wording on reporting and processing of SUSARs to be compliant with CTR requirement
Appendix 6.1. For countries within the European Union	Added “The study will be conducted in accordance with the Regulation (EU) No 536/2014.”	To add compliance statement for conformity with CTR requirement
Appendix 7. Provisions for Changes in Study Conduct During Exceptional Circumstances	Subsection, Remote visits, Revised the wording on study procedures during the mobile healthcare visits	To clarify the wording for the study procedures during mobile healthcare visits
Appendix 8. Protocol Amendment History	Added amendment (e) summary of changes table	To update amendment history

Table of Contents

Section	Page
Protocol I4V-MC-JAJA(f) (RA-BRIDGE) A Randomized, Active-Controlled, Parallel-Group, Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis	1
Protocol Amendment Summary of Changes Table.....	2
Table of Contents	3
1. Synopsis.....	9
2. Schedule of Activities.....	13
3. Introduction	20
3.1. Background.....	20
3.2. Study Rationale	21
3.3. Benefit/Risk Assessment.....	22
4. Objectives and Endpoints	23
5. Study Design	25
5.1. Overall Design.....	25
5.2. Number of Participants.....	26
5.3. End of Study Definition.....	26
5.4. Scientific Rationale for Study Design	27
5.5. Justification for Dose.....	29
6. Study Population	30
6.1. Inclusion Criteria	30
6.2. Exclusion Criteria.....	31
6.3. Screen Failures	35
7. Treatments	36
7.1. Treatments Administered	36
7.1.1. Packaging and Labeling.....	36
7.2. Method of Treatment Assignment.....	37
7.2.1. Selection and Timing of Doses	37
7.2.2. Dose Adjustment for Renal Impairment	37
7.3. Blinding.....	38
7.4. Dosage Modification (Including Rescue Therapy)	38
7.5. Preparation/Handling/Storage/Accountability	39
7.6. Treatment Compliance	39
7.7. Concomitant Therapy	39
7.8. Treatment after the End of the Study	40

8.	Discontinuation Criteria	41
8.1.	Discontinuation from Study Treatment	41
8.2.	Discontinuation from the Study	42
8.3.	Lost to Follow-Up	43
9.	Study Assessments and Procedures	44
9.1.	Efficacy Assessments	44
9.1.1.	ACR20, ACR50, and ACR70 Indices	44
9.1.2.	Disease Activity Score	44
9.1.3.	Simplified Disease Activity Index	44
9.1.4.	Clinical Disease Activity Index	45
9.1.5.	Health Outcomes and Quality-of-Life Measures	45
9.1.6.	Appropriateness of Assessments	46
9.2.	Adverse Events	47
9.2.1.	Serious Adverse Events	48
9.2.2.	Suspected Unexpected Serious Adverse Reactions	49
9.2.3.	Adverse Events of Special Interest	49
9.2.4.	Complaint Handling	49
9.3.	Treatment of Overdose	49
9.4.	Safety	49
9.4.1.	Primary and Secondary Endpoints	49
9.4.2.	Vital Signs	50
9.4.3.	Physical Examination	50
9.4.4.	Laboratory Tests	50
9.4.5.	Chest x-Ray and Tuberculosis Testing	50
9.4.6.	Hepatitis B Virus DNA Monitoring	51
9.4.7.	Safety Monitoring	51
9.4.7.1.	Venous Thromboembolic Event Assessment	51
9.4.7.2.	Hepatic Safety Monitoring	52
9.5.	Pharmacokinetics	52
9.6.	Pharmacodynamics	52
9.7.	Pharmacogenomics	52
9.8.	Biomarkers	52
9.9.	Medical Resource Utilization and Health Economics	53
10.	Statistical Considerations	54
10.1.	Sample Size Determination	54
10.2.	Populations for Analyses	54
10.3.	Statistical Analyses	55
10.3.1.	General Statistical Considerations	55

10.3.1.1.	Analysis Methods	55
10.3.1.2.	Censoring Rules	57
10.3.1.3.	Handling of Dropouts or Missing Data	57
10.3.1.4.	Multiple Comparisons/Multiplicity	57
10.3.2.	Treatment Group Comparability	58
10.3.2.1.	Patient Disposition and Duration of Exposure and Follow-Up	58
10.3.2.2.	Patient Characteristics	58
10.3.2.3.	Concomitant Therapy	58
10.3.2.4.	Treatment Compliance	58
10.3.3.	Safety Analyses	59
10.3.3.1.	Primary Analyses	59
10.3.3.2.	Secondary Analyses	59
10.3.3.3.	Other Safety Analyses	59
10.3.3.3.1.	Adverse Events	60
10.3.3.3.2.	Clinical Laboratory Tests	60
10.3.4.	Efficacy Analyses	60
10.3.4.1.	Analyses of Categorical Measures	60
10.3.4.2.	Analyses of Continuous Measures	61
10.3.5.	Interim Analyses	61
11.	References	63
12.	Appendices	68

List of Tables

Table		Page
Table JAJA.1.	Schedule of Activities	14
Table JAJA.2.	Objectives and Endpoints	23
Table JAJA.3.	Treatment Regimens.....	36
Table JAJA.4.	Analysis Populations	55
Table JAJA.5.	Criteria for Temporary Interruption of Investigational Product for Hepatic Laboratory Abnormalities	88
Table JAJA.6.	Criteria for Permanent Discontinuation of Investigational Product for Hepatic Laboratory Abnormalities	89

List of Figures

Figure

Page

Figure JAJA.1. Study I4V-MC-JAJA design.	25
---	----

List of Appendices

Appendix		Page
Appendix 1.	Abbreviations and Definitions.....	69
Appendix 2.	Clinical Laboratory Tests	74
Appendix 3.	Study Governance Considerations	76
Appendix 4.	Hepatic Monitoring Tests for Treatment-Emergent Abnormality	81
Appendix 5.	Monitoring Tests for Confirmed Venous Thromboembolism	82
Appendix 6.	Country-Specific Requirements	83
Appendix 7.	Provisions for Changes in Study Conduct During Exceptional Circumstances	94
Appendix 8.	Protocol Amendment History.....	99

1. Synopsis

Title of Study:

A Randomized, Active-Controlled, Parallel-Group, Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis.

Regulatory Agency Identifier Numbers:

EudraCT Number: 2018-003351-37

EU CT Number: 2023-508022-10-00

Rationale:

Rheumatoid arthritis (RA) is a common, systemic autoimmune inflammatory disease, characterized by synovial inflammation leading to pain, swelling, stiffness, and progressive destruction and deformity of small and large joints. Patients with RA experience impaired physical function, social participation, and health-related quality of life. These patients also have increased risk for significant non-musculoskeletal comorbidities that include the following:

- malignancy (Simon et al. 2015)
- infection (Doran et al. 2002)
- venous thromboembolism (VTE; Kim et al. 2013; Lee and Pope 2014; Ogdie et al. 2017)
 - deep vein thrombosis (DVT) and pulmonary embolism (PE) (Choi et al. 2013)
- cardiovascular (CV) disease (Picerno et al. 2015)
 - major adverse cardiovascular events (MACE) of myocardial infarction, stroke, and CV death (Aviña-Zubieta et al. 2008, 2012)
- overall early mortality (Mutru et al. 1985; Sihvonon et al. 2004).

Baricitinib is an oral, reversible, selective inhibitor of Janus kinase (JAK)1 and JAK2 (Fridman et al. 2010). In Phase 3 studies involving patients with moderately to severely active RA, baricitinib 2-mg and 4-mg once daily showed significant improvements versus placebo across relevant domains of efficacy including signs and symptoms, low disease activity and remission, physical function, other patient-reported outcomes, and radiographic progression of structural joint damage. The 4-mg dose also showed significant improvements in relevant disease measures versus oral and injectable standard of care comparators (methotrexate [MTX] and adalimumab used with background MTX, respectively). Based on the assessment of benefit/risk, baricitinib has received approval for the treatment of RA from regulatory authorities in countries including the member states of the European Union (EU), Japan, and the United States of America (USA).

In addition to the information collected in the pre-approval clinical development program, several post-approval studies are being conducted to further characterize the safety profile of baricitinib in patients with RA. These include prospective and retrospective observational studies, some involving well-established RA registries, and studies using administrative claims databases. As part of these dedicated pharmacovigilance activities, the present study is being conducted using a randomized, active comparator-controlled design to evaluate the safety of baricitinib in patients with RA.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To compare baricitinib (combined dose groups) to TNF inhibitors with respect to VTE.	Time from first dose of study treatment to first event of VTE.
Secondary (Not Multiplicity Controlled) - To compare baricitinib (combined dose groups) to TNF inhibitors with respect to key safety outcomes. - To compare each baricitinib dose to TNF inhibitors with respect to key safety outcomes.	- Time from first dose of study treatment to first event of: - ATE - MACE - Malignancy (excluding NMSC) - Opportunistic infection - Serious infection - Time from first dose of study treatment to first event of: - VTE - ATE - MACE - Malignancy (excluding NMSC) - Opportunistic infection - Serious infection

Abbreviations: ATE = arterial thromboembolic event; MACE = major adverse cardiovascular events; NMSC = nonmelanoma skin cancer; TNF = tumor necrosis factor; VTE = venous thromboembolism.

Summary of Study Design

Study I4V-MC-JAJA (JAJA) is a Phase 3b/4, multicenter, randomized, parallel-group, active-controlled, outpatient, event-driven study to evaluate the effects of baricitinib (2-mg and 4-mg daily) compared with tumor necrosis factor (TNF) inhibitors (administered according to approved local labeling) on the risk of VTE and other key safety endpoints in patients with RA. Treatment will be open label for patients and study-site personnel.

Treatment Arms and Duration

At Week 0, patients will be randomized in a 1:1:1 ratio to receive baricitinib 4-mg daily, baricitinib 2-mg daily, or a TNF inhibitor (adalimumab or etanercept). This study will continue until the planned number of primary endpoint events is achieved (VTE as adjudicated by an independent, blinded clinical endpoint committee [CEC]), unless stopped for early success under the guidance of an external data monitoring committee. The minimum and maximum individual patient treatment durations from first dose to final visit are anticipated to be approximately 2.5 and 5.5 years if the study runs to its full conclusion.

Study Population

Patients with adult-onset RA at least 18 years of age with at least 1 of the following characteristics: previous documented evidence of VTE, age ≥ 60 years, body mass index (BMI) ≥ 30 kg/m² or age 50 to <60 years and BMI 25 to <30 kg/m²; without contraindications to TNF inhibitors, or history of recent (within 12 weeks of randomization) or recurrent VTE or malignancies.

Number of Patients

Approximately 2600 patients will be randomized to ensure that the planned number of patients with primary endpoint events will be observed.

Ethical Considerations of Benefit/Risk:

Baricitinib has demonstrated significant efficacy for the treatment of moderate to severe RA in adequate and well controlled studies.

Serious infections, VTE, hepatotoxicity, and fetal malformations were identified as important potential risks with baricitinib. Inclusion and exclusion criteria in the protocol limit enrollment of patients who are at an unacceptable risk for these conditions.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of baricitinib may be found in the Investigator's Brochure (IB). Information about the known and expected benefits and risks of the TNF inhibitors may be found in the respective Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

Statistical Analysis

The results of this clinical trial will be combined analytically with another randomized trial (Study I4V-MC-JAJD [JAJD]) run concurrently and comparing the same 3 treatment groups with the objective of assessing the relative risk of VTE for baricitinib (combined doses and individual dose groups) versus TNF inhibitors. The primary, inferential statistical analyses will include data from both studies, with supportive, descriptive analyses provided from this individual study.

Unless otherwise specified, analyses of primary and secondary outcomes will be conducted on all randomized patients (combined from Studies JAJA and JAJD) who receive at least 1 dose of investigational product and who do not discontinue at the first postbaseline visit for the reason "Lost to Follow-up."

CCI

For analysis of primary and secondary endpoints other than malignancy, events will be attributed to patients according to their randomized treatment group assignment through the date of their last dose of randomized study medicine plus up to 30 days, CCI

CCI
CCI
CCI

As malignancies may result from an extended biological

process, such events will be attributed to patients through the date of their last available study visit, without regard for last dose of randomized study medicine, but censored after rescue (for analyses of individual baricitinib dose groups) or initiation of a nonpermitted RA treatment. Additional analyses conducted without censoring may also be applied.

2. Schedule of Activities

Table JAJA.1. Schedule of Activities

	Screening	Treatment						Comments
Visit (V) Number	V1	V2a	V3b	V4b	V5+c	ET	VFd	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Procedures and Assessments								
Informed consent	X							Written informed consent must be obtained before any JAJA study procedures or assessments.
Demographics	X							Collection of demographic information includes race and ethnicity.
Medical history	X							
Targeted medical history	X							Solicitation and recording of historical data on targeted events, including primary and secondary endpoint events (VTE, ATE, MACE, malignancy [excluding NMSC], opportunistic infection, and serious infection).
Physical examination	X							One complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1. All subsequent physical examinations may be symptom-directed. A complete physical examination may be repeated at the investigator's discretion any time.
Symptom-directed physical examination		X	X	X	X	X	X	
Height		X						
Weight	X	X		X	X	X	X	
Vital signs (blood pressure [BP], pulse rate, temperature)	X	X	X	X	X	X	X	
Substance use (caffeine, alcohol, tobacco)	X							

	Screening	Treatment						Comments
Visit (V) Number	V1	V2a	V3b	V4b	V5+c	ET	VFd	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Administer Tuberculosis (TB) test	X							See Exclusion Criterion [17] for details of TB testing. In countries where the QuantiFERON®-TB Gold test or T-SPOT®.TB test is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be done locally or centrally; the T-SPOT®.TB test must be performed locally.
Read Purified Protein Derivative (PPD) test	X							For those patients with a PPD placed at Visit 1, the PPD must be read 2 to 3 days (48 to 72 hours) post-Visit 1. The PPD test result does not need to be read at the site, but must be assessed by a trained healthcare professional, and documented results provided to the site as soon as possible.
Chest x-ray	X							A chest x-ray (posterior-anterior view) will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available for review by the investigator.
Previous Rheumatoid Arthritis (RA) therapy	X	X						
Review inclusion/exclusion criteria	X	X						
Preexisting conditions	X	X						
Adverse events		X	X	X	X	X	X	

	Screening	Treatment						Comments
Visit (V) Number	V1	V2a	V3b	V4b	V5+c	ET	VFd	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Targeted events			X	X	X	X	X	Solicitation and recording of data on targeted events, including new primary and secondary endpoint events (VTE, ATE, MACE, malignancy [excluding NMSC], opportunistic infection, and serious infection), will be conducted at all visits after randomization.
Concomitant medications	X	X	X	X	X	X	X	
Log in IWRS	X	X	X	X	X	X	X	The screening eGFR result must be entered into IWRS at Visit 2 for appropriate baricitinib dose adjustment to occur if necessary (Section 5.5). For those patients randomly assigned to baricitinib 4 mg with baseline eGFR ≥ 60 mL/min/1.73 m ² , the dose may subsequently be reduced to 2 mg at any time during the trial, but only for patients constrained by eGFR (< 60 mL/min/1.73 m ²) post-baseline (Section 7.4). Conversely, if a patient is assigned to baricitinib 2 mg at Visit 2 and requires rescue to baricitinib 4 mg after 1 year, the most recent eGFR will be used to determine if the patient qualifies.
Randomization		X						Patients will be randomized with stratification CCI CCI
Investigational Product (IP) dispensed		X	X	X	X			Additional dispensing visits may occur if required.
IP compliance assessed			X	X	X	X	X	

	Screening	Treatment						Comments
Visit (V) Number	V1	V2a	V3b	V4b	V5+c	ET	Vfd	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Patient RA Assessments ^{e,f}								
Patient's Global Assessment of Disease Activity (GAD)		X	X	X	X	X	X	Assessments will not be administered if investigational product was permanently discontinued and the last dose was >28 days ago.
Health Assessment Questionnaire-Disability Index (HAQ-DI)		X	X	X	X	X	X	
Rheumatoid Arthritis Impact of Disease (RAID)		X	X	X	X	X	X	
Patient-Reported Outcome Measurement Information System (PROMIS) PI		X	X	X	X	X	X	PROMIS assessments to be administered only in countries where translated versions are available.
PROMIS SSRA		X	X	X	X	X	X	
PROMIS CF		X	X	X	X	X	X	
PROMIS D		X	X	X	X	X	X	
PROMIS SD		X	X	X	X	X	X	
Health Care Professional RA Assessments ^e								
Physician's GAD		X	X	X	X	X	X	Assessments will not be administered if investigational product was permanently discontinued and the last dose was >28 days ago.
Tender joint count (TJC)/Swollen joint count (SJC) (28 joints)	X	X	X	X	X	X	X	
Laboratory Tests ^e								
hsCRP		X	X	X	X	X	X	Assessment will be recorded EXCEPT if the investigational product was permanently discontinued and the last dose was >28 days ago.

	Screening	Treatment						Comments
Visit (V) Number	V1	V2a	V3b	V4b	V5+c	ET	VFd	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Rheumatoid Factor/ACPA	X							
Thyroid-stimulating hormone (TSH)	X							
Hepatitis C Virus (HCV) antibody testing	X							For patients who are positive for HCV antibody, a follow-up test for HCV ribonucleic acid (RNA) will be performed automatically. Patients who are positive for HCV antibody and negative for HCV RNA may be enrolled.
Hepatitis B Virus (HBV) serology (HBsAg, HBcAb, HBsAb)	X							For patients who are positive for HBcAb, testing for HBV DNA will be performed. Patients who are positive for HBcAb and negative for HBV DNA may be enrolled.
HBV deoxyribonucleic acid (DNA)	X		X	X	X	X	X	HBV DNA testing post-randomization applies only to patients who are HBcAb positive at screening. In addition to scheduled assessments, these laboratory tests may also be performed as clinically indicated.
Serum pregnancy test	X							For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 (prior to randomization), and may be performed thereafter at the discretion of the investigator or according to local regulations or guidelines.
Urine pregnancy test		X						
Follicle-stimulating hormone (FSH)	X							For female patients aged 50 to ≤55 years with an intact uterus, not on hormone therapy, with 6 to ≤12 months of spontaneous amenorrhea, an FSH test will be performed to confirm nonchildbearing potential (FSH >40 mIU/mL).

	Screening	Treatment						Comments
Visit (V) Number	V1	V2 ^a	V3 ^b	V4 ^b	V5 ^c	ET	VF ^d	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Clinical chemistry	X	X	X	X	X	X	X	In addition to scheduled assessments, these laboratory tests may also be performed as clinically indicated. Patients should not eat or drink anything except water for 12 hours prior to fasting lipid/glucose sample collection.
Fasting lipid panel		X	X			X	X	
Hematology	X	X	X	X	X	X	X	In addition to scheduled assessments, these laboratory tests may also be performed as clinically indicated.
Urinalysis	X	X	X	X		X	X	
Exploratory stored samples (plasma and serum)		X						

Abbreviations: ACPA = anti-citrullinated peptide antibodies; ATE = arterial thromboembolic event; BMI = body mass index; DMC = data monitoring committee; eGFR = estimated glomerular filtration rate; ET = early termination; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; hsCRP = high-sensitivity C-reactive protein; IWRS = interactive web-response system; MACE = major adverse cardiovascular events; NMSC = nonmelanoma skin cancer; PROMIS CF = PROMIS Short Form v2.0 Cognitive Function 8a; PROMIS D = PROMIS Short Form v1.0 Depression 8b; PROMIS PI = PROMIS Short Form v1.0 Pain Interference 8a; PROMIS SD = PROMIS Short Form v1.0 Sleep Disturbance 8a; PROMIS SSRA = PROMIS Short Form v2.0 Satisfaction with Social Roles/Activities 8a; RA = rheumatoid arthritis; TNF = tumor necrosis factor; VF = final visit; VTE = venous thromboembolism.

- a At Visit 2, all baseline assessments must be performed and baseline laboratory samples must be drawn PRIOR to administration of the first dose of investigational product for randomized patients.
- b Visits 3 and 4 should be scheduled to occur as close as possible to 12 and 28 weeks, respectively, after the first dose of investigational product, remaining within permissible visit windows.
- c Visits are scheduled every 24 weeks as calculated from Visit 2 (i.e., Weeks 52, 76, 100, 124, etc.) until the study reaches the planned number of adjudicated primary endpoint events. Permitted windows are ± 14 days, except Visit 5 (Week 52), which is 0 to +14 days.
- d When the planned number of adjudicated primary endpoint events has occurred or if the DMC recommends stopping the study early, a Final Visit will be conducted for each patient. The visit window is calculated from time of Sponsor notification to the site.
- e The following order of assessments is recommended: patient RA assessments, health care professional assessments, laboratory tests.
- f Will be collected as electronic clinical outcome assessment data.

3. Introduction

3.1. Background

Rheumatoid arthritis (RA) is a common, systemic autoimmune inflammatory disease, characterized by synovial inflammation leading to pain, swelling, stiffness, and progressive destruction and deformity of small and large joints. Patients experience impaired physical function, social participation, and health-related quality of life. Patients also have increased risk of significant non-musculoskeletal comorbidities, including the following:

- malignancy (Simon et al. 2015)
- infection (Doran et al. 2002)
- venous thromboembolism (VTE; Kim et al. 2013; Lee and Pope 2014; Ogdie et al. 2017)
 - deep vein thrombosis (DVT) and pulmonary embolism (PE) (Choi et al. 2013)
- cardiovascular (CV) disease (Picerno et al. 2015)
 - major adverse cardiovascular events (MACE) of myocardial infarction, stroke, and CV death (Aviña-Zubieta et al. 2008, 2012)
- overall early mortality (Muru et al. 1985; Sihvonen et al. 2004).

Cardiovascular risk in RA features the “lipid paradox,” whereby active RA increases CV risk, but with decreased low-density lipoprotein (LDL), and effective treatment of RA disease activity appears to reduce CV risk while increasing LDL (Myasoedova et al. 2011). Among disease-modifying antirheumatic drugs (DMARDs), treatment-associated increases in LDL (predominantly larger particles) appear most pronounced for targeted interleukin (IL)-6 and Janus kinase (JAK) inhibitors (Robertson et al. 2013; Souto et al. 2015; Gabay et al. 2016; Actemra® package insert 2018; Olumiant® package insert 2018; Taylor et al. 2018; Xeljanz® package insert 2018). A recent randomized CV outcomes trial was successful in demonstrating that the risk of MACE for the IL-6 inhibitor tocilizumab was well within a prespecified noninferiority margin compared with the tumor necrosis factor (TNF) inhibitor etanercept (Giles et al. 2016).

Current treatment of RA prioritizes timely initiation and modification of DMARD therapy to bring patients to a target of sustained low disease activity or remission (Singh et al. 2016; Smolen et al. 2017). Achievement of these targets improves short- and long-term patient health outcomes, including prevention of progressive, irreversible structural joint damage (Maini et al. 2004; Smolen et al. 2017). Patients typically begin treatment with oral conventional synthetic DMARDs (csDMARDs), such as methotrexate (MTX), and modify treatment as needed and tolerated, to achieve these targets.

Treatment modification often involves use of a targeted DMARD therapy. With enhanced focus on tight disease control and increased availability of novel targeted therapies, the prognosis has greatly improved in patients with RA in recent years. Targeted DMARD options currently include injectable biologic DMARDs (bDMARDs), such as TNF inhibitors, and oral targeted synthetic DMARDs (tsDMARDs), including JAK inhibitors.

Members of the JAK family of protein tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase-2 [TYK2]) play an important role in intracellular signal transduction following extracellular cytokines and growth factors binding to their respective cell membrane receptors. Aberrant production of cytokines and growth factors has been associated with a number of chronic inflammatory conditions, including RA. Many of the proinflammatory cytokines implicated in the pathogenesis of RA, including IL-6, granulocyte-macrophage colony-stimulating factor, 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 (Kremer et al. 2009).

3.2. Study Rationale

Baricitinib is an oral, reversible, selective inhibitor of JAK1 and JAK2 (Fridman et al. 2010). It has demonstrated clinical efficacy and safety in patients with autoimmune diseases, including the following:

- rheumatoid arthritis (Genovese et al. 2016; Dougados et al. 2017; Fleischmann et al. 2017; Taylor et al. 2017),
- systemic lupus erythematosus (Wallace et al. 2018), and
- autoinflammatory diseases
 - chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) and
 - stimulator of interferon genes-associated vasculopathy with onset during infancy (SAVI) (Sanchez et al. 2018).

In Phase 3 studies involving patients with moderately to severely active RA, baricitinib 2-mg and 4-mg once daily showed significant improvements versus placebo across relevant domains of efficacy including the following:

- signs and symptoms,
- remission and low disease activity,
- patient-reported outcomes, and
- radiographically assessed progression of structural joint damage.

The 4-mg dose also showed significant improvements in relevant disease measures versus oral and injectable standard-of-care comparators (MTX, and adalimumab used with background MTX, respectively).

In the 24-week placebo-controlled period of the Phase 3 trials of patients with RA, there was a numerical imbalance in reports of VTE. As part of dedicated pharmacovigilance activities, the present study is being conducted to further evaluate the safety profile of baricitinib in patients with RA using a randomized, active comparator-controlled design, with primary outcome measure as VTE.

3.3. Benefit/Risk Assessment

As noted in Section 3.2, baricitinib has demonstrated significant efficacy for the treatment of moderate to severe RA in adequate and well-controlled studies.

Serious infections, VTE, hepatotoxicity, and fetal malformations were identified as important potential risks with baricitinib. Inclusion and exclusion criteria in the protocol limit enrollment of patients who are at an unacceptable risk for these conditions.

The incidence rate of serious infection in patients exposed to baricitinib in the RA program was 3.0 per 100 patient-years. During the controlled period (through 16 weeks), rates were similar in both baricitinib- and placebo-treated patients. The nonserious infections (upper respiratory tract infections, herpes zoster, and herpes simplex) associated with baricitinib in the RA program are readily diagnosed, manageable, and typically resolve without long-term sequelae. It is recommended that vaccination schedules (including herpes zoster where applicable) be brought up to date prior to receiving baricitinib.

Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin have been observed in patients with RA taking baricitinib. Most of these increases improved with continued use or temporary discontinuation of baricitinib with no long-term effects. No cases of severe drug-induced liver injury were observed with baricitinib treatment.

Fetal malformations were reported in nonclinical toxicology studies at higher doses than what is used in human patients. Only a small number of patients have become pregnant in baricitinib clinical trials, and there have been no reports of fetal malformations in these pregnancies.

Venous thromboembolic events have been classified as an important potential risk for baricitinib. With long-term exposures, the exposure-adjusted incidence rate of VTE for baricitinib-treated patients with RA was similar to the background rates published in the literature for the target population. There was no pattern of increased or decreased risk during long-term exposures, and cases observed with baricitinib were confounded by 1 or more recognized risk factors for VTE. Potential study participants with multiple prior VTE will not be enrolled and study participants who develop a VTE during the study will be permanently discontinued from the study.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of baricitinib may be found in the Investigator's Brochure (IB). Information about the known and expected benefits and risks of the TNF inhibitors may be found in the respective Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

4. Objectives and Endpoints

Table JAJA.2 shows the objectives and endpoints of the study.

Table JAJA.2. Objectives and Endpoints

Objectives	Endpoints
Primary To compare baricitinib (combined dose groups) to TNF inhibitors with respect to VTE.	Time from first dose of study treatment to first event of VTE.
Secondary (Not Multiplicity Controlled) - To compare baricitinib (combined dose groups) to TNF inhibitors with respect to key safety outcomes. - To compare each baricitinib dose to TNF inhibitors with respect to key safety outcomes.	- Time from first dose of study treatment to first event of - ATE - MACE - Malignancy (excluding NMSC) - Opportunistic infection - Serious infection - Time from first dose of study treatment to first event of - VTE - ATE - MACE - Malignancy (excluding NMSC) - Opportunistic infection - Serious infection
Exploratory - To describe the effects of baricitinib (individual and combined dose groups) and TNF inhibitors with respect to other safety outcomes. - To compare baricitinib (individual dose groups) to TNF inhibitors with respect to their effects on disease activity measures and patient-reported outcomes.	- Individual components of key safety outcomes, including - VTE - ATE - MACE - Malignancy - Opportunistic infection - Serious infection - SAEs (including all-cause mortality) - TEAEs - AEs leading to permanent study drug discontinuation - ACR20, ACR50, and ACR70 - DAS28-CRP - SDAI - CDAI - HAQ-DI - Tender joint counts - Swollen joint counts - Patient's Global Assessment of Disease Activity - Physician's Global Assessment of Disease Activity - RAID pain domain score - CRP - PROMIS

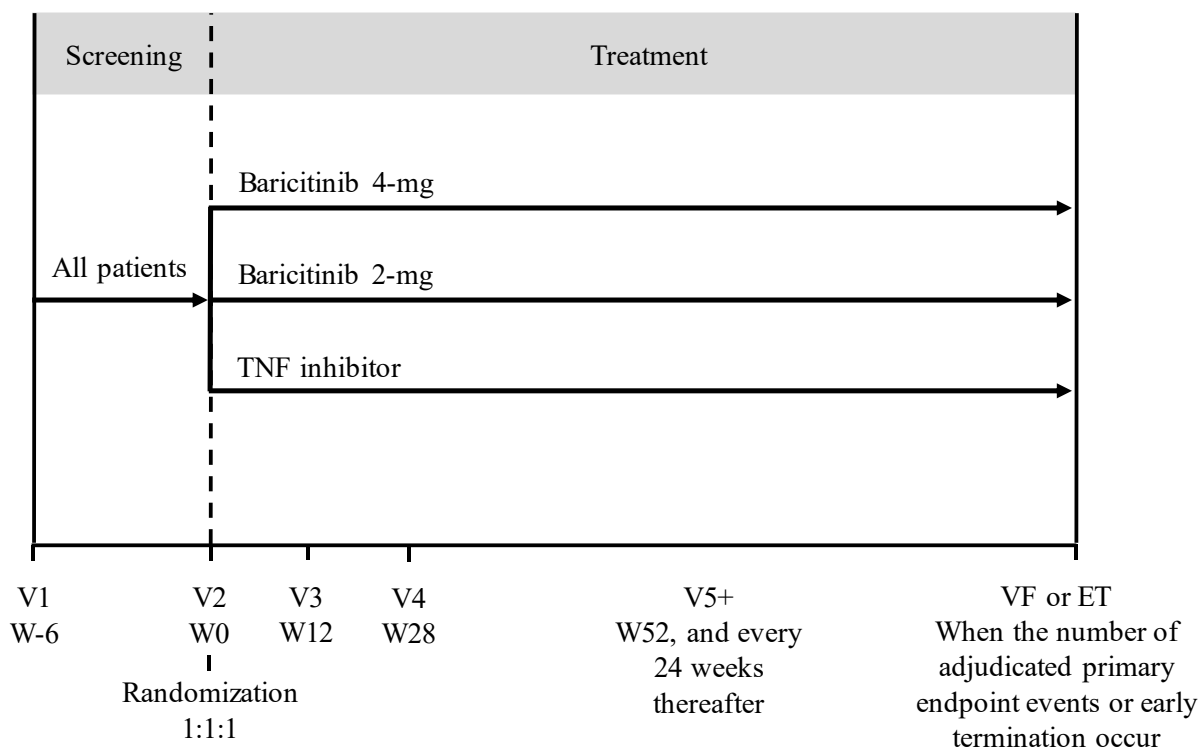
Objectives	Endpoints
	○ Pain Interference, ○ Depression, ○ Cognitive Function, ○ Satisfaction with Social Roles and Activities, and ○ Sleep Disturbance ● RAID

Abbreviations: ACR20/50/70 = American College of Rheumatology 20%/50%/70% response rate; AE = adverse event; ATE = arterial thromboembolic event; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAS28 = Disease Activity Score based on 28-joint assessment; HAQ-DI = Health Assessment Questionnaire-Disability Index; MACE = major adverse cardiovascular events; NMSC = nonmelanoma skin cancer; SAE = serious adverse event; PROMIS = Patient-Reported Outcome Measurement Information System; RAID = Rheumatoid Arthritis Impact of Disease; SDAI = Simplified Disease Activity Index; TEAE = treatment-emergent adverse event; TNF = tumor necrosis factor; VTE = venous thromboembolism.

5. Study Design

5.1. Overall Design

Study I4V-MC-JAJA (JAJA) is a Phase 3b/4, multicenter, randomized, parallel-group, active-controlled, outpatient, event-driven study to evaluate the effects of baricitinib (2-mg and 4-mg daily) compared to TNF inhibitors (administered according to approved labeling) on the risk of VTE and other key safety endpoints in patients with RA ([Figure JAJA.1](#)).



Abbreviations: ET = early termination visit; TNF = tumor necrosis factor; V = visit; VF = final visit; W = week. Recommendations and options for management of RA disease activity are outlined in [Section 7.4](#).

Figure JAJA.1. Study I4V-MC-JAJA design.

Patients may be eligible to participate if they have active RA despite having been treated with at least 1 DMARD and have selected risk factors for VTE ([Section 6.1](#)). Approximately 2600 patients will be randomized in a 1:1:1 ratio to receive baricitinib 4-mg daily, baricitinib 2-mg daily, or TNF inhibitor (adalimumab or etanercept) to ensure that the planned number of patients with events will be observed. Patients will be stratified at randomization according to a history of VTE (DVT/PE), age and body mass index (BMI) combination, prior inadequate response or intolerance to a TNF inhibitor, and geographic region (defined in the statistical analysis plan [SAP]). Treatment will be open label for patients and study site personnel ([Section 7.3](#)). [Section 7.7](#) describes permitted concomitant therapy. All procedures to be conducted during the study, including timing of procedures, are indicated in the Schedule of Activities ([Section 2, Table JAJA.1](#)). Patients will continue in the study until the number of primary endpoint events

occur or early discontinuation occurs, at which time they will have a final or early termination visit.

Study governance considerations are described in detail in [Appendix 3](#).

The study consists of 2 periods:

Screening Period: The screening period is up to 42 days and begins when the patient signs the informed consent form (ICF). In exceptional circumstances, the screening window can be extended where permitted by local laws and regulations and after consultation with the sponsor. During the screening period, the site must confirm that the patient meets all inclusion and no exclusion criteria for the study prior to randomization (Section 6). Screening procedures will be performed according to the Schedule of Activities, and eligible patients will be randomized at Week 0, Visit 2 ([Table JAJA.1](#)).

Treatment Period: Randomized patients will initiate treatment with baricitinib or TNF inhibitor as outlined in Section 7.2. Clinical and laboratory assessments will occur according to the Schedule of Activities ([Table JAJA.1](#)). As clinically indicated, unscheduled study visits/assessments may also occur. Among the assessments outlined in the Schedule of Activities, patients will be directly queried to solicit evidence of primary and secondary endpoint events (VTE [DVT/PE], arterial thromboembolic event (ATE) and MACE, malignancy [excluding nonmelanoma skin cancer (NMSC)], opportunistic infection, serious infection).

In addition to receiving randomized treatment and adhering to the study visit schedule, patients should be managed and monitored according to standard medical practice, using permitted background standard-of-care RA therapy (Section 6.2 and Section 7.7), and routine nonstudy clinic attendances as needed. Investigators should continue to assess the individual patient benefit/risk for patients to remain enrolled throughout the study and consider discontinuing patients if sufficient clinical benefit is not observed with protocol-permitted treatments.

When the planned number of adjudicated primary endpoint events has occurred, a final visit will be conducted for each patient, with procedures as outlined in the Schedule of Activities ([Table JAJA.1](#)). Based on expected event accrual, the minimum and maximum individual patient treatment durations from first dose to final visit are anticipated to be approximately 2.5 and 5.5 years. Wherever possible, patients who discontinue from the study prematurely (Section 8) will complete an early termination visit.

5.2. Number of Participants

Approximately 2600 patients will be randomized into 3 treatment groups to ensure that a sufficient number of patients with events will be observed to assess the primary and secondary study objectives related to VTE. Refer to Section 10.1.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities for the last patient.

5.4. Scientific Rationale for Study Design

This study will be active comparator-controlled and blinded to the core study team to minimize bias (Section 7.3).

The population studied will have active RA at baseline. This ensures that participants can have a reasonable expectation of benefit from the active treatment to which they will be randomized, each of which has demonstrated significant efficacy for the treatment of RA. Patients with prior TNF inhibitor use are permitted to enroll, as cycling between different members of this class is a common treatment strategy and thus such patients have a reasonable chance of benefit even if randomized to the TNF inhibitor group (Smolen et al. 2017). Patients with prior use of a JAK inhibitor are prohibited from entering the study, as there is currently insufficient evidence to support the potential clinical utility of cycling between JAK inhibitors.

The TNF inhibitor class was considered an appropriate active comparator, as this is the most well-established and commonly used class of targeted DMARDs in RA care. Patients who are randomized to the TNF inhibitor group will receive etanercept or adalimumab and, if necessary, may cycle to the other permitted TNF inhibitor during the study treatment period. This is appropriate, as different members of this class do not appear to exhibit important differences regarding the key safety measures of interest for this study (Porter et al. 2016; Smolen et al. 2017). In addition, offering patients in the TNF inhibitor group the flexibility to apply the well-established practice of TNF inhibitor cycling if needed serves to increase study power indirectly by increasing the observation time they can contribute for the primary analysis.

The primary outcome measure of this randomized postmarketing safety study is VTE, an important potential risk for baricitinib (Section 3.2 and 3.3). The sample size selected via the power calculation for this endpoint is also anticipated to provide appropriate power to assess other key topics including MACE, malignancy, and serious infections (Section 10.1).

To optimize the designation of primary endpoint events, adjudication of potential VTE will be performed by a clinical endpoint committee (CEC), which is independent of the sponsor and blinded to patient treatment assignment, as outlined in the CEC charter. The primary objective employs a between-group noninferiority comparison based on hazard ratio for time-to-event. These are well-established methods for randomized event-based trials such as postmarketing safety studies of this kind (FDA/CDER Guidance 2008). A noninferiority margin of **CC** was selected; this is also supported by precedent, including in the recent RA randomized postmarketing CV outcomes trial, ENTRACTE, comparing tocilizumab and a TNF inhibitor (Giles et al. 2016).

The population is enriched for VTE risk based on age, BMI, and history of prior VTE. The selection of these known VTE risk factors as inclusion criteria, and the associated anticipated rate of event accrual, was informed by data from the baricitinib RA clinical development program and designed to allow the study to enroll and read out in a timely manner. The numbers of adjudicated VTE selected to trigger the interim and final primary analyses provide adequate (>80%) power to test the primary noninferiority null hypothesis under an assumption of no true

difference between baricitinib and TNF inhibitor, as well as an assumption of a slight CCI imbalance in hazard ratio towards higher risk with baricitinib.

Several measures assure that study integrity is maintained during planned interim analyses. A data monitoring committee (DMC) that is independent of the sponsor will review the unblinded results of these analyses and provide relevant information to the blinded core sponsor team without prematurely compromising their blinded status, as outlined in the DMC charter. In addition, appropriate adjustments will be implemented to control the analysis of the primary study objective for type I error over multiple interim analyses and the final analysis.

The primary objective is based on a comparison between the active comparator and pooled baricitinib dose groups. This approach is appropriate for a variety of reasons. For the primary endpoint (VTE), incidence rates for baricitinib 2-mg and 4-mg in analyses including short- and long-term exposure were similar in both dose groups in the baricitinib RA development program (FDA 2018 [Lilly briefing document for baricitinib advisory committee]). In addition, the pooled dose approach provides a conservative assessment for the 2-mg dose, for which AE rates can, in principle, be anticipated as not higher than those for 4-mg. Finally, secondary objectives will include assessment of each dose separately versus TNF inhibitor. These supportive comparisons are anticipated to have adequate (>80%) power for tests based on a noninferiority margin of CCI for VTE between each dose and the active comparator.

The primary analysis for adjudicated VTE will be based on an as-randomized approach, with observation time censored at last dose of randomized study drug plus up to 30 days. This approach is considered appropriate for a VTE endpoint, where any hypothetical causal relationship between the drug and the event would be anticipated to be acute and not subject to a long latency period between exposure and outcome, such as might pertain to malignancy or to an association between drug and MACE that was mediated by drug-induced lipid changes.

In this context, crossover (from TNF inhibitor to baricitinib or from baricitinib to TNF inhibitor) is prohibited during the study. Although such an approach may increase overall time on each treatment arm, including post-crossover time, it (a) would not inform the primary analysis, (b) may encourage reduced time per patient on randomized treatment for the primary analysis, and (c) may unduly confound other study analyses based on randomized group without censoring (e.g., for malignancy), as events occurring after crossover could not be appropriately attributed to either treatment group.

Lack of permitted crossover is justified, as patients who do not achieve adequate control of RA disease activity with their randomized treatment may modify background therapy to attain control, and all randomized treatment options have been shown to be effective. Targeted or biologic therapies for the treatment of RA other than baricitinib or TNF inhibitor are prohibited prior to permanent study medication discontinuation, as combination targeted or biologic therapy is not currently recommended in RA care.

For patients who do not achieve adequate RA control in the baricitinib 2-mg group despite modification of permitted background therapy, rescue to baricitinib 4-mg is permitted after Week 52. This is appropriate, as 4-mg is an approved dose in many countries and may be of added

benefit for some patients. It is justified, as rescued patients will remain in the pooled baricitinib group used for the primary analysis. This provides a suitably conservative estimate of risk for the 2-mg dose group, and rescue does not impact the randomized assessment of the 4-mg group.

Given the flexibility with which background RA therapies can be modified, rescue rates are anticipated to be lower than those observed in the baricitinib RA development program (7% [csDMARD-IR] to 22% [bDMARD-IR]) in completed Phase 3 studies up to 24 weeks (FDA 2018 [Lilly briefing document for baricitinib advisory committee]). To assure that the assessment of secondary (2-mg) objectives is not unacceptably impacted by excessive early attrition from this group through rescue, a minimum period of stability on baricitinib 2-mg is required before rescue to 4-mg is permitted. A required minimum period of 1 year was selected as a relevant regulatory landmark for safety exposure. The collection of demographic information includes race and ethnicity. This information is needed to assess variable responses in VTE based on race or ethnic background, as incidence rates vary by race (Goldhaber 2014)

5.5. Justification for Dose

As noted above (Section 3.2), the doses of baricitinib included in this study have been evaluated in a confirmatory RA development program. Based on assessment of benefit/risk, both doses have received approval for the treatment of RA from regulatory authorities in over 50 countries including the member states of the EU and Japan. The 2-mg dose is approved in the USA. Tumor necrosis factor inhibitor will be prescribed at doses that align with the approved local product labeling. Assessment of these dose regimens is therefore considered appropriate, as all have been approved by major regulators for the treatment of patients with active RA.

Dose Adjustment for Renal Impairment

As detailed in the IB, baricitinib exposure increases with decreased renal function (Study I4V-MC-JADL). Based on pharmacokinetic (PK) simulations, dose adjustment is not required for patients with estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m². Patients with eGFR < 60 mL/min/1.73 m² at screening who are randomized to the baricitinib 4-mg dose will receive a dose of 2-mg once daily, which will ensure that exposures do not exceed those of the 4-mg once-daily dose in patients with eGFR ≥ 60 mL/min/1.73 m². For the same reason, patients who have been randomized to the baricitinib 4 mg dose and whose eGFR decreases to < 60 mL/min/1.73 m² during study treatment will be switched to a dose of 2 mg once daily. For patients randomized to the 2-mg dose, there will be no dose reduction based on renal function.

See Section 7.2.2 for the method of treatment assignment in patients with renal impairment.

6. Study Population

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

Study investigator(s) will review patient history and screening test results at Visits 1 and 2 to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for randomization in the study. All screening activities must be completed and reviewed before the patient is randomized.

6.1. Inclusion Criteria

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

Rheumatoid arthritis Characteristics

- [1] Have a diagnosis of adult-onset RA as defined by the 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative (Aletaha et al. 2010).
- [2] If RA symptom onset is <6 months, are rheumatoid factor or anticitrullinated antibody positive as assessed by the central laboratory during screening.
- [3] Have moderately to severely active RA defined as the presence of at least 3/28 tender joints and at least 3/28 swollen joints assessed at Visits 1 and 2. Joints with significant surgical treatment or injury cannot be counted towards the minimum number of tender and swollen joints for enrollment purposes.
- [4] Have had an inadequate response or intolerance to at least 1 DMARD (synthetic or biologic).

Demographic Characteristics

- [5] Are male or female patients who are at least 18 years of age.
- [6] Have at least 1 of the following 4 characteristics:
 - a. Documented evidence of a VTE prior to this study
 - b. Age ≥ 60 years
 - c. BMI ≥ 30 kg/m²
 - d. Age 50 to <60 years AND BMI 25 to <30 kg/m²

Reproductive Characteristics

- [7] Nonpregnant, nonbreastfeeding female patient of childbearing potential:
 - a. Patients who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with the opposite sex during the entirety of the study and for 1 week after the last dose of baricitinib, 3 weeks after the last dose of etanercept, and 5 months after the last dose of adalimumab.

Total abstinence is defined as refraining from intercourse during the entirety of the study and for 1 week after the last dose of baricitinib, 3 weeks after the last dose of etanercept, and 5 months after the last dose of adalimumab. Periodic abstinence such as calendar, ovulation, symptothermal, postovulation methods, and withdrawal are not acceptable methods of contraception.

- b. Otherwise, female patients must agree to use 1 highly effective method of contraception (defined as less than 1% failure rate per year when used consistently and correctly), such as combination oral contraceptives, implanted contraceptives, or intrauterine devices, for the entirety of the study and for 1 week after the last dose of baricitinib, 3 weeks after the last dose of etanercept, and 5 months after the last dose of adalimumab.

Female patients of non-childbearing potential may participate without requirements for contraception. This includes female patients who are

- a. Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
- b. Postmenopausal – defined as either
 - i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
 - 1. Cessation of menses for at least 1 year, or
 - 2. At least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
 - ii. A woman 56 years of age or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
 - iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Informed Consent

- [8] Must read and understand the informed consent approved by Eli Lilly and Company (Lilly), or its designee, and the institutional review board (IRB)/ethics review board (ERB) governing the site, and provide written informed consent.

6.2. Exclusion Criteria

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

Medical Conditions

- [9] Have any contraindications to a TNF inhibitor as addressed in local product labeling or local clinical practice that would preclude the patient from participating in this study.
- [10] Are pregnant or breastfeeding. Prior to initiation of treatment, female patients of childbearing potential must have a negative serum pregnancy test at the central laboratory during screening and a negative urine pregnancy test at Visit 2.

[11] Have a history of VTE (DVT/PE) within 12 weeks prior to randomization or have a history of recurrent (>1) VTE (DVT/PE).

- a. Prior DVT with PE where events overlapped in time (i.e., with PE considered resulting from DVT) is not considered recurrent DVT/PE for the purpose of this criterion.

[12] Have active primary or recurrent malignant disease or have been in remission from clinically significant malignancy for <5 years prior to randomization.

The following may be exempted:

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

[13] Have active herpes zoster.

[14] Have a clinically serious infection or have any other active or recent infection that in the opinion of the investigator would pose an unacceptable risk to the patient if participating in the study.

[15] Have a history or presence of any illness that in the opinion of the investigator could pose an unacceptable risk to the patient if participating in the study or interfere with the interpretation of data.

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

[17] Have evidence of active TB or untreated/inadequately/inappropriately treated for latent TB.

- a. Have evidence of active TB, defined in this study as clinical and/or chest x-ray features consistent with active TB and the following:
 - Positive purified protein derivative (PPD) test (≥ 5 -mm induration between approximately 2 and 3 days after application, regardless of vaccination history).
 - QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. Patients are excluded from the study if the test is not negative and there is clinical evidence of active TB.

Exception: Patients with a history of active TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other entry criteria are met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest

x-ray at screening (i.e., a chest x-ray performed within the past 6 months will not be accepted).

- b. Have evidence of untreated or inadequately or inappropriately treated latent TB, defined in this study as the following:
- Positive PPD test, no clinical features consistent with active TB, and a chest x-ray with no evidence of active TB at screening; or
 - If the PPD test is positive and the patient has no medical history or chest x-ray findings consistent with active TB, the patient may have a QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines). If the test results are not negative, the patient will be considered to have latent TB (for purposes of this study); or
 - QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test. If the test results are positive, the patient will be considered to have latent TB. If the test is neither negative nor positive, the test may be repeated once within approximately 2 weeks of the initial value. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).

Exception: Patients who have evidence of latent TB may be enrolled if they complete at least 4 weeks of appropriate treatment prior to randomization and agree to complete the remainder of treatment while in the trial.

Exception: Patients with a history of latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, have no clinical features of active TB, and have a screening chest x-ray with no evidence of active TB may be enrolled if other criteria met. Such patients would not be required to undergo the protocol-specific TB testing for PPD, QuantiFERON®-TB Gold test, or T-SPOT®.TB test but must have a chest x-ray at screening (i.e., a chest x-ray performed within the past 6 months will not be accepted).

Prior/Concomitant Medications

- [18] Have received more than 1 prior TNF inhibitor that was:
- a. Discontinued for inadequate response for RA (lack or loss of efficacy) or
 - b. Discontinued for intolerance (AE) when used for any indication
- [19] Have been treated with a bDMARD within 4 weeks of randomization (within 24 weeks of randomization for rituximab).
- [20] Are being treated with more than 2 csDMARDs.
- [21] Have been treated with a JAK inhibitor.

- [22] Have received a live vaccine within 4 weeks of randomization or are expected to need/receive a live vaccine during the course of the study. Investigators should update immunizations (including, where applicable, herpes zoster) in agreement with current immunization guidelines prior to randomization.
- [23] Are being treated with a strong organic anion transporter 3 (OAT3) inhibitor, such as probenecid, that cannot be discontinued for the duration of the study.
- [24] Are being treated with an anticoagulant (e.g., direct and indirect factor Xa inhibitors [including fondaparinux], direct thrombin inhibitors, heparins, enoxaparin, vitamin K antagonists). Antiplatelet agents such as aspirin, clopidogrel, and prasugrel are not considered anticoagulants for the purpose of this study.
- [25] Have been previously enrolled (i.e., randomized or received IP) in any baricitinib study (including this JAJA study).

Central Laboratory Screening Assessments

- [26] Have any of the following:
 - a. ALT or AST >2 x the upper limit of normal (ULN)
 - b. alkaline phosphatase (ALP) ≥ 2 x ULN
 - c. total bilirubin level (TBL) ≥ 1.5 x ULN
 - d. hemoglobin <8 g/dL (80.0 g/L)
 - e. neutropenia (absolute neutrophil count <1000 cells/ μ L) ($<1.00 \times 10^3/\mu$ L or <1.00 GI/L)
 - f. lymphopenia (lymphocyte count <500 cells/ μ L) ($<0.50 \times 10^3/\mu$ L or <0.50 GI/L)
 - g. eGFR (Modification of Diet in Renal Disease [MDRD]) <30 mL/min/ 1.73 m².
- [27] Have any screening laboratory test values outside the reference range for the population that in the opinion of the investigator pose an unacceptable risk for the patient's participation in the study.

In the case of any of the aforementioned central laboratory abnormalities (Criteria [26] and [27]), the tests may be repeated once during screening, and resulting values may be accepted for enrollment eligibility if they meet the eligibility criterion.

- [28] Have hepatitis B virus (HBV) infection defined as:
 - a. positive for hepatitis B surface antigen (HBsAg), or
 - b. positive for HBV DNA

Patients who are positive for hepatitis B core antibody (HBcAb) will require HBV DNA monitoring during the study (refer to Schedule of Activities Section 2).

- [29] Have hepatitis C virus (HCV) infection defined as:
 - a. positive for hepatitis C antibody, and
 - b. positive for HCV ribonucleic acid [RNA]

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

Other Exclusion Criteria

- [30] Are currently enrolled in or have discontinued within 4 weeks of screening from any other clinical trial involving an investigational product or nonapproved use of a drug or device or any other type of medical research judged not to be scientifically or medically compatible with this study.
- [31] Are largely or wholly incapacitated, permitting little or no self-care, such as being bedridden.
- [32] Have a history of intravenous drug abuse, other illicit drug abuse, or chronic alcohol abuse within approximately 1 year prior to screening or are concurrently using or expected to use illicit drugs during the study.
- [33] Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.
- [34] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [35] Are Lilly or Incyte employees or their designee.
- [36] In the opinion of the investigator, are at an unacceptable risk for participating in the study for any reason.

Patients with laboratory test results that did not meet the inclusion or exclusion criteria may have the relevant test(s) repeated once during the screening period if thought to represent a laboratory error; a reversible, clinically insignificant, and/or intermittent condition; or inconsistent with the patient's historical values. If inclusion or exclusion criteria were not met after repeat testing, the patient should not be enrolled in the study.

6.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. The interval between initial screen failure and rescreening Visit 1 should be at least 4 weeks. When rescreening is performed, the individual must sign a new ICF, repeat all screening procedures as described in the Schedule of Activities, and will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

Study treatment is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

This study involves a comparison of baricitinib 4 mg or 2 mg administered orally once daily with TNF inhibitors administered according to the local product label. [Table JAJA.3](#) shows the treatment regimens.

Table JAJA.3. Treatment Regimens

Treatment Group	Treatments Administered	Authorized as defined by EU Clinical Trial Regulation
Baricitinib 4 mg QD ^a	1 baricitinib 4 mg tablet	Authorized and used according to EU marketing authorization
Baricitinib 2 mg QD	1 baricitinib 2 mg tablet	
TNF inhibitor ^b	adalimumab or etanercept administered according to the local product label	Authorized and used according to EU marketing authorization

Abbreviations: QD = once daily; mg = milligram; TNF = tumor necrosis factor.

^a Patients with eGFR <60 mL/min/1.73 m² at screening who are randomized to the 4-mg dose will receive a dose of 2-mg QD until and unless the patient later qualifies for rescue to baricitinib 4 mg (see Section 7.4).

^b Patients that are TNF inadequate responders (TNF-IR) are prohibited from receiving a TNF inhibitor that they have previously discontinued due to inadequate response or intolerance.

The investigator or their designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the patient
- verifying that instructions are followed properly
- maintaining accurate records of baricitinib dispensing and collection
- at the end of the study returning all unused baricitinib to Lilly or its designee, unless the sponsor and sites have agreed that all unused baricitinib is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

Study drug will be supplied by the sponsor in accordance with current Good Manufacturing Practice. Study treatments will be labeled as appropriate for country requirements.

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

- tablets containing 4 mg of baricitinib
- tablets containing 2 mg of baricitinib

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

Baricitinib will be labeled according to the country's regulatory requirements. Patients assigned to baricitinib will be instructed to take 1 tablet each day.

Baricitinib will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Baricitinib will be supplied by Lilly or its representative in accordance with current Good Manufacturing Practices.

TNF inhibitor: TNF inhibitor will be dispensed according to approved labeling. Patients assigned to TNF inhibitor will be instructed on its correct use, including administration, storage, and disposal, according to approved local medical practice.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized in a 1:1:1 ratio (baricitinib 4 mg; baricitinib 2-mg; TNF inhibitor) to open-label treatment at Visit 2. Randomization will be stratified by a history of a VTE, age/BMI combination, prior inadequate response or intolerance to a TNF inhibitor, and geographic region, as defined in the SAP.

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

7.2.1. Selection and Timing of Doses

Following randomization at Visit 2:

Baricitinib: Investigational product will be provided to applicable patients at Visit 2 (Week 0). The first dose should be taken on the same day as Visit 2, after all applicable visit procedures have been completed. One tablet should be taken orally each day, without regard to food, and if possible at approximately the same time every day.

TNF inhibitor: TNF inhibitor will be provided for applicable patients. Where investigational product is provided through the investigative site at Visit 2 (Week 0), the first dose should be taken that day, after all applicable visit procedures have been completed. Where investigational product is provided at a later date (either through the investigative site or another [e.g., pharmacy] channel), this should be as soon as possible after Visit 2, and the first dose should be taken that day. Dosing will be according to approved labeling.

7.2.2. Dose Adjustment for Renal Impairment

The eGFR value from screening will be entered into IWRS at Visit 2, and IWRS will assign the treatment doses at randomization accordingly for patients assigned to baricitinib.

- Patients with documented renal impairment (defined as screening eGFR ≥ 30 to <60 mL/min/1.73 m²) who are randomized to baricitinib (either the 4-mg arm or the 2-mg arm) will receive a baricitinib 2-mg once-daily dose by the IWRS.

- No baricitinib dose adjustment will be made for patients with screening eGFR ≥ 60 mL/min/1.73 m².

For calculation of eGFR the MDRD formula will be used in central laboratory. On occasions where local laboratories are required for testing, the MDRD formula should also be used if possible.

The rationale for dose adjustment in patients with documented renal impairment and receiving baricitinib is detailed in Section 5.5. For details on dose modifications during the treatment period (after randomization), refer to Section 7.4.

7.3. Blinding

This is an open-label study. Each patient will be aware of his or her own assigned treatment group. At each investigative site, all staff involved in treating and caring for study patients will have full knowledge of treatment assignments for the patients under their care.

To minimize bias, aggregate review of summary data by the blinded core study team (i.e., clinical research physician/clinical research scientist accountable for the strategy, analysis and interpretation of the study, statisticians, and statistical analysts, who will not have direct site contact for the purposes of this study) will remain blinded until after the final database is locked.

The CEC/ Infection Adjudication Committee (IAC) involved in adjudication of key safety events will remain blinded to individual treatment assignments throughout the study.

Processes to maintain blinding during interim analyses conducted by the independent DMC are described in Section 10.3.5.

7.4. Dosage Modification (Including Rescue Therapy)

Initial treatment assignment will occur as described in Sections 7.1 and 7.2.

Rheumatoid arthritis disease activity that is inadequately controlled by randomized treatment (i.e., baricitinib 2-mg, baricitinib 4-mg, TNF inhibitor) should be managed in the first instance by modification of permitted concomitant RA therapy (Section 7.7).

Otherwise, patients with inadequate control of disease activity despite modification of permitted concomitant RA therapy may be managed as follows:

1. Baricitinib 2-mg:
 - a. may rescue to baricitinib 4 mg after 1 year (Visit 5 or after). The patient's most recent central laboratory results preceding rescue to baricitinib 4 mg must reflect an eGFR ≥ 60 mL/min/1.73 m². Once a patient is rescued to baricitinib 4 mg, they cannot transition back to baricitinib 2 mg.
 - b. may not crossover to TNF inhibitor
2. Baricitinib 4-mg:
 - a. may not crossover to TNF inhibitor
3. TNF inhibitor:

- a. may cycle at any time between permitted TNF inhibitors.
Use of the specific TNF inhibitor that patients had prior inadequate response (IR) or intolerance prior to the study is not permitted (Section 7.1, Table JAJA.3)
- b. may not crossover to baricitinib.

Patients receiving baricitinib 4 mg (as randomized) may transition to baricitinib 2 mg only if constrained by renal function (i.e., eGFR <60 mL/min/1.73 m²) at any time during the trial. Once patients have transitioned to baricitinib 2 mg, they cannot transition back to baricitinib 4 mg.

7.5. Preparation/Handling/Storage/Accountability

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

Storage and handling instructions are provided on the baricitinib product packaging and should be followed.

TNF inhibitor: TNF inhibitor will be handled, stored, and disposed of by the patient or site according to approved practice.

7.6. Treatment Compliance

Patient compliance with investigational product will be assessed during the treatment period by counting returned tablets (baricitinib) or by patient reporting (TNF inhibitor). Deviations from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

Patients will be considered significantly noncompliant if they miss >20% of the prescribed doses during the treatment period, unless withheld by the investigator for safety reasons.

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

7.7. Concomitant Therapy

All medications, whether prescription or over-the-counter, used at baseline and/or during the course of the study must be documented in the eCRF with start and stop dates.

Use of the following is prohibited during the study treatment period:

- JAK inhibitors or other tsDMARDs (other than baricitinib)
- bDMARDs other than TNF inhibitor investigational product (etanercept/adalimumab)
- More than 2 background csDMARDs (at any time prior to permanent discontinuation of investigational product; a maximum of 3 simultaneous csDMARDs may be used thereafter)

- Live vaccines (at any time prior to permanent discontinuation of investigational product)
- OAT3 inhibitors (at any time prior to permanent discontinuation of investigational product)
- Anticoagulants (e.g., direct and indirect factor Xa inhibitors [including fondaparinux], direct thrombin inhibitors, heparins, enoxaparin, vitamin K antagonists), except if clinically required according to standard practice for the management of study-emergent events, such as treatment of acute thrombotic events and perioperative prophylaxis. Use of anticoagulants for study-emergent events is limited to ≤ 30 days. Antiplatelet agents such as aspirin, clopidogrel, prasugrel are not considered anticoagulants for the purpose of this study.

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

7.8. Treatment after the End of the Study

Neither baricitinib nor TNF inhibitor will be made available by the sponsor after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

It may be necessary to temporarily interrupt or permanently discontinue investigational product during the study. Except where specific direction is provided in this protocol, please refer to the investigational products' local product label for warnings and precautions related to laboratory abnormalities and AEs that may lead to temporary interruption or permanent discontinuation of study treatment. Further guidance is provided below:

Temporary interruption

It is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting treatment for reasons other than those described in the protocol or local product label. Treatment that was temporarily interrupted because of an AE or abnormal laboratory value may be restarted at the discretion of the investigator according to the local product label recommendations. Retest timing and frequency is at the investigator's discretion. Baricitinib is not recommended for use in patients with estimated GFR of <30 mL/min/1.73 m².

Permanent discontinuation

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

- Subject decision
 - the patient requests to discontinue investigational product.
- Investigator decision
 - the investigator decides that the patient should be discontinued from investigational product.
- Serious or opportunistic infection that in the opinion of the investigator merits the investigational product being discontinued.

Permanent discontinuation of study medication must occur:

- If the patient becomes pregnant
- If the patient presents with active primary or recurrent malignant disease (except for successfully treated basal cell or squamous epithelial skin cancers)
- If the patient experiences a VTE (DVT/PE), ATE or MACE, including myocardial infarction or stroke (cerebrovascular accident) during the study
- If eGFR <30 mL/min/1.73 m² for a patient taking baricitinib 2 mg or if eGFR <60 mL/min/1.73 m² for a patient taking baricitinib 4 mg and eGFR does not sufficiently improve within 30 days of temporary discontinuation of study medication. For patients taking baricitinib 4 mg, this applies only if dose reduction is not an option due to having already undergone 1 dose adjustment (see Section 7.4)
- If any of the following are observed:

- ALT or AST $>8 \times$ ULN
- ALT or AST $>5 \times$ ULN persisting for more than 2 weeks after temporary interruption of investigational product
- ALT or AST $>3 \times$ ULN and total bilirubin level $>2 \times$ ULN
- ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).

The date of study drug discontinuation must be documented.

Throughout the trial, investigators should continue to assess benefit/risk for patients to remain in the trial and should consider discontinuing patients if sufficient clinical benefit is not observed with protocol-allowed concomitant therapy.

8.2. Discontinuation from the Study

Patients may be discontinued from the study in the following circumstances:

- Patient decision (the patient requests to be withdrawn from the study).
- At the discretion of the investigator or sponsor for safety, behavioral, compliance, or administrative reasons.

Patients must be discontinued from the study in the following circumstances:

- If enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).
- The patient experiences any conditions that require permanent discontinuation from study medication (Section 8.1). Patients who experience a VTE (DVT/PE) during the study will be requested to undergo additional laboratory monitoring tests (Appendix 5) prior to permanent discontinuation from the study.
- The patient requires chronic (>30 days) treatment with an anticoagulant (Section 7.7).

If a patient prematurely permanently discontinues investigational product for any reason, except reasons outlined above requiring study medication discontinuation, the patient should be encouraged to remain in the study and adhere to the visit schedule until the final visit. If the patient is unwilling or unable to return for applicable follow-up visits, the site should attempt to collect as much follow-up information as possible. Patients discontinuing from the study prematurely for any reason should complete AE and other safety -follow-up procedures per the Schedule of Activities (Table JAJA.1, early termination visit) and Section 9.4 (Safety) of the protocol.

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

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

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

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

9.1. Efficacy Assessments

9.1.1. ACR20, ACR50, and ACR70 Indices

American College of Rheumatology (ACR)20 will be defined as at least 20% improvement in the following ACR Core Set values:

- Tender joint count (TJC) (28 joint count)
- Swollen joint count (SJC) (28 joint count)
- An improvement of at least 20% in at least 3 of the following 5 assessments:
 1. Rheumatoid Arthritis Impact of Disease (RAID) pain domain (Numeric Rating Scale [NRS])
 2. Patient's Global Assessment of Disease Activity (0 to 100 mm Visual Analog Scale [VAS])
 3. Physician's Global Assessment of Disease Activity (0 to 100 mm VAS)
 4. Patient's assessment of physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI)
 5. Acute phase reactant as measured by high-sensitivity C-reactive protein (hsCRP).

ACR50 and ACR70 responses will be calculated as improvements of at least 50% and of at least 70%, respectively, in the ACR Core Set values.

9.1.2. Disease Activity Score

The Disease Activity Score (DAS)28 is a measure of disease activity in 28 joints that consists of a composite numeric score of the following variables: TJC, SJC, hsCRP, and Patient's 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 thumb, the 8 proximal interphalangeal joints, and the 2 knees (Smolen et al. 1995).

9.1.3. Simplified Disease Activity Index

The Simplified Disease Activity Index (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 (Aletaha and Smolen 2005):

- number of swollen joints (0 to 28)
- number of tender joints (0 to 28)
- C-reactive protein in mg/dL (0.1 to 10.0)
- patient global DAS on VAS (0 to 10.0 cm)
- evaluator global health score on VAS (0 to 10.0 cm)

9.1.4. Clinical Disease Activity Index

The Clinical Disease Activity Index (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 (Aletaha and Smolen 2005):

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

9.1.5. Health Outcomes and Quality-of-Life Measures

The self-reported questionnaires will be administered via an electronic tablet as specified in the Schedule of Activities ([Table JAJA.1](#)), provided that an appropriately translated version is available from the time of the patient's baseline visit.

Health Assessment Questionnaire–Disability Index

Health Assessment Questionnaire–Disability Index is 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 and 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, hygiene, reach, grip, 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.

Rheumatoid Arthritis Impact of Disease

The RAID is a composite instrument that is used to assess the impact of RA on 7 domains of importance to patients – fatigue, sleep disturbance, pain, physical well-being, function, psychological well-being, and coping (Gossec et al. 2011). It consists of 7 questions, and the responses use a 0 to 10 NRS (0 = none/no difficulty, 10 = extreme). Each domain can be reported individually, and there is also a total score that can be calculated. The final RAID value is 0 to 10, where higher scores indicate worse status.

PROMIS Short Form v1.0 Pain Interference 8a

The Patient-Reported Outcome Measurement Information System (PROMIS) is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children (HealthMeasures, 2018). It can be used with the general population and with individuals living with chronic conditions. The Pain Interference questionnaire assesses consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The questionnaire consists of 8 questions and uses a 5-point Likert scale (1 = not at all; 5 = very much). Scores are totaled and higher scores indicate more interference.

PROMIS Short Form v2.0 Satisfaction with Social Roles/Activities 8a

The PROMIS Satisfaction with Social Roles and Activities questionnaire assesses satisfaction with performing one's usual social roles and activities. The questionnaire consists of 8 questions and uses a 5-point Likert scale (1 = not at all; 5 = very much). Scores are totaled and higher scores indicate more satisfaction.

PROMIS Short Form v2.0 Cognitive Function 8a

The PROMIS Cognitive Function questionnaire assesses mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and perceived changes in these cognitive functions. The extent to which cognitive impairments interfere with daily functioning, whether other people observe cognitive impairments, and the impact of cognitive dysfunction on quality of life are also assessed. The questionnaire consists of 8 questions and uses a 5-point Likert scale (5 = never; 1 = very often). Scores are totaled and higher scores indicate better cognitive ability.

PROMIS Short Form v1.0 Depression 8b

The PROMIS Depression questionnaire assesses negative mood (sadness and guilt), views of self (self-criticism and worthlessness), and social cognition (loneliness and interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The questionnaire consists of 8 questions and uses a 5-point Likert scale (1 = never; 5 = always). Scores are totaled and higher scores indicate more depressive symptoms.

PROMIS Short Form v1.0 Sleep Disturbance 8a

The PROMIS Sleep Disturbance questionnaire assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep. The questionnaire consists of 8 questions and uses a 5-point Likert scale (5 = very poor/not at all; 1 = very good/very much). Scores are totaled and higher scores indicate worse sleep.

9.1.6. Appropriateness of Assessments

A patients' disease severity and extent of activity may be a driver and predictor of the CV, infection, and malignancy event outcomes. Concurrent collection of these data will support the

benefit/risk assessment in the study population. All assessments and/or concepts included in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. Events meeting the AE definition are medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

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

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves or until the event stabilizes with appropriate diagnostic evaluation. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of preexisting conditions of each patient, including clinically significant signs and symptoms of the disease under treatment in the study.

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

Site personnel will record any change in the condition(s) and any new conditions as AEs.

The investigator will record all relevant AE and SAE information in the eCRF. Investigators should record the following for each AE:

- time of onset,
- time of termination,
- severity, and
- their assessment of the potential relatedness of each AE to protocol procedure or investigational product.

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

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

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

Lack of drug effect is not considered to be an AE in this clinical study, as efficacy is evaluated among the exploratory study objectives. Rheumatoid arthritis flares must be reported as an AE only if they fulfill 1 of the criteria for an SAE or if, in the opinion of the investigator, the event represents a clinically significant worsening.

9.2.1. *Serious Adverse Events*

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines if it is considered reasonably possibly related to study procedure.

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

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

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

SAE regulatory reporting:

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to regulatory requirements in the participating regions and countries. The sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority (United States 21 CFR 312.32, European Union Clinical Trial Regulation 536/2014 [submission of SUSARs to the EudraVigilance database], and national regulatory requirements in other participating countries), IRB/IEC, and investigators in the participating regions and countries.

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the baricitinib IB or the investigational products' local product label and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations (CFR) 312.32, European Union Clinical Trial Regulation 536/2014 [submission of SUSARs to the EudraVigilance database], and the associated detailed guidance or national regulatory requirements in participating regions and countries require the reporting of SUSARs. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to regulatory requirements in the participating regions and countries.

9.2.3. Adverse Events of Special Interest

Adverse events of special interest for this study are the primary and secondary endpoint events.

9.2.4. Complaint Handling

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

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the baricitinib IB or investigational products' local product label.

9.4. Safety**9.4.1. Primary and Secondary Endpoints**

The primary endpoint is the time to first occurrence (after first dose of study treatment) of VTE (DVT/PE). The secondary endpoints are the time to first occurrence (after first dose of study treatment) of MACE, ATE, malignancy (excluding NMSC), opportunistic infection, and serious infection.

An independent CEC/IAC will adjudicate primary endpoint events, and selected secondary events including ATE, MACE (myocardial infarction, stroke and cardiovascular death) and opportunistic infections. The CEC/IAC charter will contain the final detailed event definitions used for adjudication. All potential or suspected primary endpoint and other events requiring adjudication must be reported as soon as the site staff learns of the clinical event. Study sites should send the requested source documentation to the CEC/IAC in a timely fashion for adjudication of the event.

Serious infection is defined as all infections that meet SAE criteria (Section 9.2.1).

9.4.2. Vital Signs

For each patient, vital signs (sitting blood pressure, heart rate, and temperature) should be measured according to the Schedule of Activities (Table JAJA.1). Subjects should be seated and relaxed with both feet on the floor for at least 5 minutes before measurements are taken. Blood pressure and pulse should be measured using either automated or manual equipment. If measurements are machine averaged, the average blood pressure 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 taken before any scheduled blood draws. Vital signs should be measured at the discretion of the investigator.

9.4.3. Physical Examination

For each patient, physical examinations will be conducted according to the Schedule of Activities (Table JAJA.1). One complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1 (Screening). All remaining physical examinations throughout the study should include a symptom-directed physical examination. A complete physical examination may be repeated at the investigator's discretion at any time a patient presents with physical complaints.

9.4.4. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Table JAJA.1).

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

9.4.5. Chest x-Ray and Tuberculosis Testing

A posterior–anterior view chest x-ray will be obtained locally at screening (Visit 1), unless results from a chest x-ray obtained within 6 months prior to the study are available. The chest x-ray will be reviewed by the investigator or his or her designee to exclude patients with active TB infection. In addition, patients will be tested at screening (Visit 1) for evidence of active or latent TB as described in the exclusion criteria (Section 6.2).

Investigators should follow local guidelines for monitoring patients for TB.

9.4.6. Hepatitis B Virus DNA Monitoring

Enrolled patients with positive HBcAb results at screening will be monitored during the study for HBV DNA as outlined in the Schedule of Activities ([Table JAJA.1](#)). If HBV DNA is detected, then consultation with a hepatologist is recommended.

9.4.7. Safety Monitoring

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

The Lilly-designated medical monitor will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures. The Lilly-designated medical monitor will, as is appropriate, consult with the functionally independent Global Patient Safety (GPS) 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 its designee may require further evaluation.

All deaths and SAE reports will be reviewed by Lilly during the clinical trial. These reports will be reviewed to ensure completeness and accuracy but will not be unblinded to the core Lilly study team during the clinical trial. If a death or clinical AE is deemed serious, unexpected, and possibly related to study treatment, Lilly GPS 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.

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

- Monitoring of lipid levels in a manner consistent with baricitinib labeling
- Potential VTE (DVT/PE), ATE, MACE, and other CV events, such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, and coronary interventions, will be identified by the investigative site or through medical review and will be sent to a blinded CEC for adjudication at regular intervals.

Data will also be collected for non-CV deaths, malignancy (excluding nonmelanoma skin cancer), opportunistic infection, and serious infection.

9.4.7.1. Venous Thromboembolic Event Assessment

If a patient develops clinical features of a DVT or PE, appropriate local laboratory tests and imaging should be performed, as necessary, for the diagnosis of the event. For confirmed cases, additional laboratory testing is recommended as outlined in [Appendix 5](#).

9.4.7.2. Hepatic Safety Monitoring

If a study patient experiences elevated ALT $\geq 3 \times$ ULN, ALP $\geq 2 \times$ ULN, or elevated TBL $\geq 2 \times$ ULN, liver testing ([Appendix 4](#)) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

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

- Elevation of serum ALT to $\geq 5 \times$ ULN on 2 or more consecutive blood tests
- Elevated serum TBL to $\geq 2 \times$ ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to $\geq 2 \times$ ULN on 2 or more consecutive blood tests
- Patient discontinued from study treatment because of a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE.

9.5. Pharmacokinetics

This study is not planned to include PK assessments.

9.6. Pharmacodynamics

This study is not planned to include pharmacodynamic (PD) assessments.

9.7. Pharmacogenomics

This study is not planned to include pharmacogenomic assessments.

9.8. Biomarkers

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

In this study, serum and plasma for biomarker research will be collected at the times specified in the Schedule of Activities ([Table JAJA.1](#)) where local regulations allow.

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

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

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

9.9. Medical Resource Utilization and Health Economics

This study is not planned to include health economics or medical resource utilization assessments.

10. Statistical Considerations

10.1. Sample Size Determination

The results of this clinical trial (JAJA) will be combined analytically with another randomized trial (Study JAJD) run concurrently and comparing the same 3 treatment groups with the objective of assessing the relative risk of VTE for baricitinib (combined doses and individual dose groups) versus TNF inhibitors. The primary, inferential statistical analyses will include data from both studies, with supportive, descriptive analyses provided from this individual study.

At least **CCl** patients with events from the combined studies' planned final analysis ensures >80% power to demonstrate that the hazard ratio for the risk of VTE events in the combined baricitinib group (i.e., across dose groups) relative to the TNF inhibitor group is less than **CCl** based on the upper limit of the **CCl** confidence interval (CI) of the hazard ratio, assuming a true hazard ratio of **CCl**. Following this assumption and prorating to approximately **CCl** events across 2 treatment groups (one baricitinib group and the TNF inhibitor group), this also ensures >80% power to demonstrate that the hazard ratio for the risk of VTE in each baricitinib dose group relative to the TNF inhibitor group is **CCl** based on a similar approach.

Studies JAJA and JAJD together aim to enroll approximately 3900 patients (2600 in JAJA, 1300 or more in JAJD) in a 1:1:1 ratio among baricitinib 4-mg, baricitinib 2-mg, and TNF inhibitor groups in order to observe the planned number of events. These sample size estimates are based on assumed incidence rates of **CCl** per 100 patient-years in each of the baricitinib dose groups and **CCl** per 100 patient-years in the TNF inhibitor group in these studies' enrolled patient populations, an 18-month enrollment period, and an annual dropout rate from assigned treatment of **CCl**. The **CCl** incidence rate was estimated from the baricitinib RA clinical program using all patients treated with baricitinib through **CCl** and subsetting for patients who would meet entry criteria for this study **CCl**.

The total number of enrolled patients in this study may be increased up to 3900 without protocol amendment in cases of reduced enrollment in Study JAJD, delayed enrollment in either study, lower than expected event rates, or higher than expected dropout rate in either study in order to preserve adequate statistical power for the assessment of the primary objective within the planned time frame. At a minimum, if studies JAJA and JAJD are not stopped early, **CCl** of the **CCl** planned patients with events between these 2 studies will come from Study JAJA. Study JAJA will continue until that number is achieved. However, as an exception, Study JAJA may stop early based on the number of events estimated for the planned interim analyses (see Section 10.3.5).

Sample size and power estimates were obtained from EAST® software Version 6.4 (Cytel, Cambridge, Massachusetts) using a 2-sample log-rank test for noninferiority.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined as outlined in [Table JAJA.4](#).

Table JAJA.4. Analysis Populations

Population	Description
Intent-to-Treat (ITT) Population	All patients who are randomized will be included in the ITT population. Patients will be analyzed according to the investigational product to which they were randomized. Unless otherwise specified, efficacy and health outcomes analyses will be conducted on the ITT population.
Safety Population	The safety population is defined as all randomized patients who receive at least 1 dose of investigational product and who did not discontinue from the study for the reason “Lost to Follow-up” at the first postbaseline visit. Patients will be analyzed according to the investigational product to which they were randomized. The safety population will be the primary analysis population for the primary and secondary analyses, as well as for other safety analyses.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Detailed SAP(s) describing the statistical methodologies for the combined analyses of Studies JAJA and JAJD and for the specific analyses of this study will be developed by Lilly or its designee.

Efficacy and health outcomes analyses will be conducted on the intent-to-treat (ITT) population, whereas the primary, secondary, and exploratory safety analyses will be conducted on the safety population, as described in [Table JAJA.4](#).

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

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

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

10.3.1.1. Analysis Methods

Time from first dose to first event for the primary and secondary analyses will be analyzed using a Cox proportional hazards regression model stratified by study with treatment group and randomization stratification factors (VTE history, age/BMI combination, prior inadequate response or intolerance to a TNF inhibitor, and geographic region) as explanatory variables. Hazard ratios, their 95% CIs, and associated p-values will be presented for treatment comparisons and assessments of superiority/inferiority and noninferiority, where applicable.

Poisson regression will be used to evaluate incidence rates of AEs, SAEs, discontinuations, and other categorical safety data for between-treatment group comparisons. Continuous safety data including laboratory results will be analyzed by analysis of covariance based on observed data with treatment group, study (where applicable), and baseline value in the model. Shift tables for select categorical safety outcomes (e.g., “high” or “low” laboratory results) will also be produced.

Analyses of dichotomous efficacy and health outcomes data from Study JAJA will use a logistic regression model with geographic region, prior inadequate response or intolerance to a TNF inhibitor, BMI, and treatment group as explanatory factors, providing the p-value and 95% CI for the odds ratio for treatment group differences. The difference in unadjusted percentages and 95% CI of the difference using the Newcombe–Wilson method without continuity correction are used for descriptive purposes, unless otherwise specified. When there are quasi-complete or complete separation warnings from the logistic regression analyses, Firth’s penalized likelihood approach may be used. Missing data will be imputed using nonresponder imputation (NRI), as described in Section [10.3.1.3](#).

Analyses of continuous efficacy and health outcome data from Study JAJA will use a restricted maximum likelihood-based mixed model for repeated measures (MMRM). The model will include geographic region, prior inadequate response or intolerance to a TNF inhibitor, BMI, treatment, visit, and treatment-by-visit interaction as fixed categorical effects, and baseline value and baseline value-by-visit interaction as fixed continuous effects to estimate change from baseline across postbaseline visits. An unstructured covariance matrix will be used to model the between- and within-patient errors. If the unstructured covariance configuration results in a lack of convergence, then the following variance-covariance matrix will be used (in order) until one converges: Heterogeneous Toeplitz, Heterogeneous First Order Autoregressive, Heterogeneous Compound Symmetry, Toeplitz; First Order Autoregressive, and Compound Symmetry. If all the selected variance-covariance matrices fail to converge, Variance Components will be used as the next attempt at convergence. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the least-squares (LS) means will be used for the statistical comparisons. The LS mean difference, standard error, p-value, and CIs will also be reported. Treatment group comparisons at specific study visits will be tested using the t-test obtained from the MMRM results. If the MMRM fails to converge, a multiple imputation approach will be used for imputation of missing data, followed by analysis of covariance for each by-visit analysis.

10.3.1.2. Censoring Rules

For analysis of primary and secondary endpoints other than malignancy, events will be attributed to patients according to their randomized treatment group assignment through the date of their last dose of randomized study medicine plus up to 30 days, censored after rescue or initiation of a nonpermitted RA treatment. For analyses of combined baricitinib dose groups, censoring will not occur upon rescue from 2-mg to 4-mg, and all events occurring on either dose will be attributed to the combined dose group. The window of 30 days allows for the accumulation of events that take time to accrue, while censoring is applied to avoid the attribution of effects of subsequent therapies.

Because malignancies may result from an extended biological process, such events will be attributed to patients through the date of their last available study visit, without regard for last dose of randomized study medicine, but censored after rescue (for analyses of individual baricitinib dose groups) or initiation of a nonpermitted RA treatment.

Supportive analyses will be conducted in which all events during the study are attributed to the patient's randomized treatment group regardless of any subsequent rescue or initiation of a nonpermitted RA treatment.

10.3.1.3. Handling of Dropouts or Missing Data

As with any clinical study, patient dropouts and, consequently, missing data are expected. Patients who discontinue assigned treatment, unless they withdraw consent, will be encouraged to remain in the study and follow the scheduled visits to provide additional safety data. Although every effort will be made to reduce missing data, the methods described below will be used to provide a conservative approach for assessing efficacy and health outcomes endpoints when patients have missing data.

The following rules for handling of dropouts or missing data will be used:

- Nonresponder imputation: For analysis of categorical efficacy and health outcomes data, patients who discontinue study treatment early, are rescued, or initiate nonpermitted RA treatments will be defined as nonresponders after discontinuation, rescue, or new medicine initiation, respectively.
- Mixed-model repeated measures: For continuous data, MMRM analysis will be applied with a missing-at-random assumption for handling missing data. This analysis takes into account both missingness of data and the correlation of the repeated measurements. No imputation methods will be applied to the MMRM analysis. Observed data will be analyzed with the exception that any data that occur after rescue, study treatment discontinuation, or initiation of nonpermitted RA treatments will be censored in order to estimate the effects of the randomized treatment.

10.3.1.4. Multiple Comparisons/Multiplicity

No multiplicity control will be conducted for any of the analyses described in this protocol other than the evaluation of the primary objective over repeated interim and final analyses.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition and Duration of Exposure and Follow-Up

A detailed description of patient disposition by treatment group will be summarized with reasons for discontinuation. Frequency counts and percentages will be presented for each treatment group. All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported along with their reason for discontinuation. Duration of exposure to study treatment and follow-up time in the study following first dose of study treatment will be summarized by treatment group using summary statistics (e.g., mean and standard deviation) and distributional summaries, including Kaplan–Meier estimates.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Descriptive statistics including the number of patients, mean, standard deviation, median, minimum, and maximum will be provided for continuous measures, and frequency counts and percentages will be tabulated for categorical measures. No formal statistical comparisons will be made among treatment groups unless otherwise stated. A complete list of patient characteristics and baseline clinical measures will be provided in the SAP.

10.3.2.3. Concomitant Therapy

Concomitant medications will be coded and descriptively summarized by treatment group in terms of frequencies and percentages using the safety population.

10.3.2.4. Treatment Compliance

Compliance with investigational product treatment for baricitinib and TNF inhibitors will be assessed through counts of returned investigational product tablets for baricitinib or patient self-reporting of medication use for TNF inhibitors. A patient will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses during the study or during key study visit intervals, that is, compliance is <80%. 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.

10.3.3. Safety Analyses

10.3.3.1. Primary Analyses

The primary analysis is to compare the combined baricitinib dose group against the TNF inhibitor group in time from first dose to first VTE while patients are on their randomized treatment (as defined in Section 10.3.1.2). A Cox proportional hazards model stratified by study with treatment group and randomization stratification factors (VTE history, age/BMI combination, prior inadequate response or intolerance to a TNF inhibitor, and geographic region) as explanatory variables will be used to estimate the hazard ratio, its 95% CI, and associated p-value for the noninferiority assessment (hazard ratio **CCI** among the safety population across Studies JAJA and JAJD. Patients who initiate a nonpermitted treatment for RA will be censored at the time of first dose of the new treatment. Patients who discontinue the study early will be censored at the time of discontinuation or 30 days after their last dose of study medication, whichever occurs first.

An additional analysis of the time from first dose to first VTE will be conducted using all time after the first dose of randomized treatment without regard to compliance status with nonpermitted RA treatments. The same analysis model will be used. Compliance of the data to the proportional hazards assumption will be evaluated, with appropriate sensitivity analyses considered, using methods described in the SAPs.

10.3.3.2. Secondary Analyses

The primary analysis described in Section 10.3.3.1 will be repeated for comparisons between each baricitinib dose group and the TNF inhibitor group to assess for noninferiority, based on a hazard ratio **CCI**. Similar analysis methods as described above will be used, except that patients who rescue from baricitinib 2 mg to baricitinib 4 mg will be censored after rescue. Patients who were randomized to the baricitinib 4 mg dose and received a 2 mg dose at screening or during study treatment because their eGFR was <60 mL/min/1.73 m² will not be censored from the 4-mg dose group.

These (primary and secondary) analyses will be repeated for the comparison between baricitinib (combined groups and each individual dose group) and the TNF inhibitor group for:

- ATE,
- MACE,
- malignancy (excluding NMSC),
- opportunistic infection, and
- serious infection.

10.3.3.3. Other Safety Analyses

All other safety data will be summarized by treatment group and analyzed using the safety population. Safety assessments will include AEs and laboratory analytes. Analyses will focus on comparisons of each baricitinib dose group to the TNF inhibitor group using the safety analysis methods described in Section 10.3.1.1.

10.3.3.3.1. Adverse Events

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as AEs that first occurred or worsened in severity on or after the date of the first dose of assigned treatment. The incidence rate of treatment-emergent adverse events (TEAEs) will be summarized using MedDRA for each system organ class (or a body system) and each preferred term by treatment group. For events that are sex specific, the computation of the incidence rates will include only patients from the given sex.

Serious AEs (including deaths), TEAEs of special interest, and AEs that led to discontinuation from assigned treatment will also be summarized using MedDRA for each system organ class and each preferred term by treatment group. Potential AEs of special interest will be identified by a standardized MedDRA query or a Lilly-defined MedDRA query. Details of the AEs of special interest (listed in Section 9.2.3) and other events of interest and analysis methods will be documented in the SAP or the program safety analysis plan.

10.3.3.3.2. Clinical Laboratory Tests

Clinical laboratory results will be descriptively summarized by treatment group. Individual results that are outside the normal reference ranges will be flagged in data listings. Quantitative clinical hematology, chemistry, and urinalysis variables obtained at baseline and the extremes of postbaseline visits (maximum value, minimum value, and last value) will be summarized as changes from baseline. Categorical variables, including the incidence of abnormal values and incidence of AEs of special interest, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures.

10.3.4. Efficacy Analyses**10.3.4.1. Analyses of Categorical Measures**

The following outcomes will be compared between each baricitinib dose group and the TNF inhibitor group through the first 52 weeks:

Proportion of patients achieving

- ACR20
- ACR50
- ACR70
- DAS28-C-reactive protein (CRP) ≤ 3.2
- DAS28-CRP < 2.6
- SDAI ≤ 11
- SDAI ≤ 3.3
- CDAI ≤ 10
- CDAI ≤ 2.8 .

A logistic regression model with factors for treatment group, BMI, geographic region, and prior inadequate response or intolerance to a TNF inhibitor will be used to test for treatment differences. The NRI method as described above will be used to impute for missing data. The

same analysis method may be used for subsequent time points when there are a reasonable number of patients on their originally randomized treatment. Otherwise, only summary statistics based on observed data will be provided.

10.3.4.2. Analyses of Continuous Measures

The following outcomes will be compared between each baricitinib dose group and the TNF inhibitor group through the first 52 weeks:

Change from baseline in:

- DAS28-CRP
- SDAI
- CDAI
- HAQ-DI
- Patient's Global Assessment of Disease Activity
- PROMIS pain interference score
- PROMIS depression score
- PROMIS cognitive function score
- PROMIS satisfaction with social roles/activities score
- PROMIS sleep disturbance score
- RAID total score
- each of the RAID domain scores (fatigue, sleep disturbance, pain, physical well-being, function, psychological well-being, and coping)
- TJC
- SJC
- Physician's Global Assessment of Disease Activity
- RAID pain domain score (NRS)
- CRP

An MMRM analysis method described in Section 10.3.1.1 will be used to test for treatment differences. The same analysis method may be used for subsequent time points when there are a reasonable number of patients on their originally randomized treatment. Otherwise, only summary statistics based on observed data will be provided.

10.3.5. Interim Analyses

A DMC will oversee the conduct of this study in conjunction with Study JAJD. The DMC will consist of members external to Lilly who have expertise in rheumatology, statistics, or other appropriate specialties. This DMC will follow the rules defined in the DMC charter.

Access within Lilly and by its designees to the aggregated unblinded data will be limited to the DMC and statisticians providing the data. These statisticians may be internal to Lilly but external and independent to the baricitinib development team. The blinded core study team will not have access to unblinded treatment codes nor the aggregated unblinded data. Only the DMC is authorized to evaluate unblinded interim analyses. The study sites will receive information about aggregated interim results only if they need to know for the safety of their patients.

The data from Studies JAJA and JAJD will be evaluated by the DMC at interim analyses in order to determine if the combined evidence is sufficient to meet the studies' primary objective with respect to VTE. A separate SAP governing these meta-analyses for the DMC and the final analysis will describe the details of these analyses. CCI interim data analyses are planned to occur based on the cumulative number of patients with events of VTE observed in these 2 trials: CCI analyses to evaluate safety with no consideration of the studies' primary objective and CCI subsequent analyses to evaluate safety and whether the primary objective has been met. The first CCI analyses are planned to occur when approximately CCI of the planned total patients with VTE events are observed (across studies). The CCI analyses to evaluate the primary objective will occur when approximately CCI of the planned total across studies) and CCI of the planned total across studies) patients with VTE events are observed. CCI

CCI
CCI

The studies can be stopped early at the CCI interim analyses for success based on the primary safety analysis. CCI

CCI
CCI

If the accumulation of events for VTE is lagging considerably behind that anticipated when planning study enrollment (see Section 10.1), then an unblinded assessment will occur after the CCI percentile of the expected patient-years of exposure (PYE) for the combined studies' final analysis, which is expected to account for at least CCI patient-years or CCI of the anticipated total PYE and corresponding to each patient having the opportunity for CCI years of follow-up, assuming the expected enrollment timelines. CCI

CCI
CCI

CCI

If the study is not stopped by these rules or by the rules for early stopping for success, it is continued until the full planned number of patients with events is observed.

11. References

- ACTEMRA® (tocilizumab) [package insert]. South San Francisco, CA: Genentech, Inc.; 2018.
- Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-2581.
- Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol*. 2005;23(5 suppl 39):S100-S108.
- Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum*. 2008;59(12):1690-1697.
- Aviña-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis*. 2012;71(9):1524-1529.
- Choi HK, Rho YH, Zhu Y, Cea-Soriano L, Aviña-Zubieta JA, Zhang Y. The risk of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a UK population-based outpatient cohort study. *Ann Rheum Dis*. 2013;72(7):1182-1187.
- Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum*. 2002;46(9):2287-2293.
- Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, de la Torre I, Gaich C, Rooney T, Schlichting D, de Bono S, Emery P. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95.
- [FDA] Food and Drug Administration. Advisory Committee Meeting Briefing Document: NDA 207924 [Baricitinib (LY3009104); Rheumatoid Arthritis]. 23 April 2018. Eli Lilly and Company. Available at: <https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf>. Accessed November 14, 2018.
- [FDA/CDER] Food and Drug Administration/Center for Drug Evaluation and Research. Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf>. Published December 2008. Accessed July 11, 2018.
- Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, Gurbuz S, Dickson C, de Bono S, Schlichting D, Beattie S, Kuo WL, Rooney T, Macias W, Takeuchi T. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis

- and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol.* 2017;69(3):506-517.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18(6):499-502.
- Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum.* 1980;23(2):137-145.
- Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol.* 1982;9(5):789-793.
- Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, Covington MB, Thomas B, Collier P, Favata MF, Wen X, Shi J, McGee R, Haley PJ, Shepard S, Rodgers JD, Yeleswaram S, Hollis G, Newton RC, Metcalf B, Friedman SM, Vaddi K. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol.* 2010;184(9):5298-5307.
- Gabay C, McInnes IB, Kavanaugh A, Tuckwell K, Klearman M, Pulley J, Sattar N. Comparison of lipid and lipid-associated cardiovascular risk marker changes after treatment with tocilizumab or adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2016;75(10):1806-1812.
- Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, Beattie SD, Koch AE, Cardillo TE, Rooney TP, Macias WL, de Bono S, Schlichting DE, Smolen JS. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med.* 2016;374(13):1243-1252.
- Giles JT, Sattar N, Gabriel SE, Ridker PM, Gay S, Warne C, Musselman D, Brockwell L, Shittu E, Klearman M, Fleming T. Comparative cardiovascular safety of tocilizumab vs etanercept in rheumatoid arthritis: results of a randomized, parallel-group, multicenter, noninferiority, phase 4 clinical trial [abstract]. *Arthritis Rheumatol.* 2016;68(suppl 10).
- Goldhaber SZ. Race and Venous Thromboembolism Nature or Nurture [editorial]? *Circulation.* 2014;129(14):1463-1465.
- Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, de Wit M, Dijkmans BAC, Dougados M, Englbrecht M, Gogus F, Heiberg T, Hernandez C, Kirwan JR, Mola EM, Matucci Cerinic M, Otsa K, Schett G, Sholte-Voshaar M, Sokka T, von Krause G, Wells GA, Kvien TK. Finalisation and validation of the rheumatoid arthritis impact of disease score, a patient-derived composite measure of impact of rheumatoid arthritis: a EULAR initiative. *Ann Rheum Dis.* 2011;70(6):935-942.
- Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol.* 1971;44(526):793-797.
- HealthMeasures. PROMIS® website. Available at: <https://www.healthmeasures.net/explore-measurement-systems/promis>. Accessed January 25, 2024.
- Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton, FL: Chapman and Hall/CRC; 2000.

- Kim SC, Schneeweiss S, Liu J, Solomon DH. Risk of venous thromboembolism in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2013;65(10):1600-1607.
- Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, Krishnaswami S, Burgos-Vargas R, Wilkinson B, Zerbini CA, Zwillich SH. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum*. 2009;60(7):1895-1905.
- Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. *Arthritis Res Ther*. 2014;16(5):435.
- Maini RN, Breedveld FC, Kalden JR, Smolen JS, Furst D, Weisman MH, St Clair EW, Keenan GF, van der Heijde D, Marsters PA, Lipsky PE. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum*. 2004;50(4):1051-1065.
- Mutru O, Laakso M, Isomäki H, Koota K. Ten year mortality and causes of death in patients with rheumatoid arthritis. *Br J Med J (Clin Res Ed.)*. 1985;290(6484):1797-1799.
- Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, Gabriel SE. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis*. 2011;70(3):482-487.
- Ogdie A, Kay McGill N, Shin DB, Takeshita J, Jon Love T, Noe MH, Chiesa Fuxench ZC, Choi HK, Mehta NN, Gelfand JM. Risk of venous thromboembolism in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a general population-based cohort study [published online April 20, 2017]. *Eur Heart J*. doi:10.1093/eurheartj/ehx145.
- OLUMIANT® (baricitinib) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2018.
- Picerno V, Ferro F, Adinolfi A, Valentini E, Tani C, Alunno A. One year in review: the pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol*. 2015;33(4):551-558.
- Porter D, Melckebeke J, Dale J, Messow CM, McConnachie A, Walker A, Munro R, McLaren J, McRorie E, Packham J, Buckley CD, Harvie J, Taylor P, Choy E, Pitzalis C, McInnes IB. Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. *Lancet*. 2016;388(10041):239-247.
- Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995: status and review. In: Spiker B, editor. *Quality of life and pharmacoeconomics in clinical trials*. 2nd ed. Philadelphia (PA): Lippincott-Raven; 1996:p 227-237.
- Robertson J, Peters MJ, McInnes IB, Sattar N. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. *Nat Rev Rheumatol*. 2013;9(9):513-523.
- Sanchez GA, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, Schalm S, Murias Montealegre Sanchez S, Dare JA, Brown D, Stone DL, Gao L, Klausmeier T, Foell D, de Jesus AA, Chappelle DC, Kim H, Dill S, Colbert R, Failla L, Kost B, O'Brien M, Reynolds JC, Folio LR, Calvo KR, Paul KM, Weir N, Brofferio A, Soldatos A, Biancotto A, Cowen EW, Digiovanna JG, Gadina M, Lipton AJ, Hadigan C, Holland SM, Fontana J, Alawad AS, Brown

- RJ, Rother KI, Heller T, Brooks KM, Kumar P, Brooks SR, Waldman M, Singh HK, Nickeleit V, Silk M, Prakash A, Janes JM, Ozen S, Wakim PG, Brogan PA, Macias WL, Goldbach-Mansky R. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies [published online June 11, 2018]. *J Clin Invest*. doi:10.1172/JCI98814.
- Sihvonen S, Korpela M, Laippala P, Mustonen J, Pasternack A. Death rates and causes of death in patients with rheumatoid arthritis: a population-based study. *Scand J Rheumatol*. 2004;33(4):221-227.
- Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther*. 2015;17:212.
- Singh JA, Saag KG, Bridges SL Jr, Aki EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-26.
- Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, Kirkpatrick J. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum*. 1995;38(1):38-43.
- Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D, Aringer M, Boers M, Buckley CD, Buttgerit F, Bykerk V, Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg JE, Hazes JMW, Huizinga T, Jani M, Karateev D, Kouloumas M, Kvien T, Li Z, Mariette X, McInnes I, Mysler E, Nash P, Pavelka K, Poór G, Richez C, van Riel P, Rubbert-Roth A, Saag K, da Silva J, Stamm T, Takeuchi T, Westhovens R, de Wit M, van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76(6):960-977.
- Souto A, Salgado E, Maneiro JR, Mera A, Carmona L, Gómez-Reino JJ. Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis. *Arthritis Rheumatol*. 2015;67(1):117-127.
- Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, del Carmen Morales L, Gonzaga JR, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich C, Rooney T, Schlichting D, Macias W, de Bono S, Tanaka Y. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376(7):652-662.
- Taylor PC, Kremer JM, Emery P, Zuckerman SH, Ruotolo G, Zhong J, Chen L, Witt S, Saifan C, Kurzawa M, Otvos JD, Connelly MA, Macias WL, Schlichting DE, Rooney TP, de Bono S, McInnes IB. Lipid profile and effect of statin treatment in pooled phase II and phase III baricitinib studies. *Ann Rheum Dis*. 2018;77(7):988-995.
- Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, Veys EM, Mielants H, De Clerck L, Peretz A, Malaise M, Verbruggen L, Vastesaeger N, Geldhof A, Boullart L, De Keyser F. DAS28 best reflects the physician's clinical judgment of response to

infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. *Arthritis Res Ther*. 2005;7(5):R1063-1071.

Wallace DJ, Furie RA, Tanaka Y, Baricitinib in systemic lupus erythematosus (SLE): results from a phase 2, randomized, double-blind, placebo-controlled study. Presented at: European League Against Rheumatism (EULAR) Congress 2018; 13-16 June 2018; Amsterdam, The Netherlands. Abstract OP0019.

XELJANZ® (tofacitinib) [package insert]. New York, NY: Pfizer Laboratories Div Pfizer Inc.; 2018.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
ACR	American College of Rheumatology
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATE	arterial thromboembolic event
blinding/masking	A double-blind study is one in which neither the [patient/subject] nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
bDMARD	biologic disease-modifying antirheumatic drug
BMI	body mass index
CANDLE	Chronic Atypical Neutrophilic Dermatositis with Lipodystrophy and Elevated temperatures
CDAI	Clinical Disease Activity Index
CEC	clinical endpoint committee
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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.
CRP	C-reactive protein
CSR	clinical study report

csDMARD	conventional synthetic disease-modifying antirheumatic drug
CV	cardiovascular
DAS28	Disease Activity Score based on 28-joint assessment
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee
DVT	deep vein thrombosis
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eCOA	electronic clinical outcome assessment
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcome
ERB	ethics review board
EU	European Union
GCP	good clinical practice
GPS	Global Patient Safety
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hsCRP	high-sensitivity C-reactive protein
IAC	infection adjudication committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

IEC	independent ethics committee
IL	interleukin
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
JAK	Janus kinase
LDL	low-density lipoprotein
LS	least squares
MACE	major adverse cardiovascular events
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MedDRA	Medical Dictionary for Regulatory Activities
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMRM	mixed model for repeated measures

MTX	methotrexate
NRI	nonresponder imputation
NRS	Numeric Rating Scale
OAT3	organic anion transporter 3
PE	pulmonary embolism
PD	pharmacodynamic(s)
PK	pharmacokinetic
PPD	purified protein derivative
PROMIS	Patient-Reported Outcome Measurement Information System
PYE	patient years of exposure
RA	rheumatoid arthritis
RAID	Rheumatoid Arthritis Impact of Disease
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAVI	stimulator of interferon genes (STING)-associated vasculopathy with onset during infancy
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDAI	Simplified Disease Activity Index
SJC	swollen joint count
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
TB	tuberculosis
TBL	total bilirubin level

TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
TJC	tender joint count
TNF	tumor necrosis factor
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
TYK	tyrosine kinase
ULN	upper limit of normal
USA	United States of America
VAS	Visual Analog Scale
VTE	venous thromboembolism

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests^a

Hematology^b

Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Absolute reticulocyte count
Mean cell volume (MCV)
Mean platelet volume (MPV)
Mean cell hemoglobin (MCH)

Mean cell hemoglobin concentration (MCHC)
Leukocytes (WBC)
Absolute count of
 Neutrophils, segmented
 Neutrophils, juvenile (bands)
 Lymphocytes
 Monocytes
 Eosinophils
 Basophils
 Platelets
Cell morphology
Differential and blood smear^c

Urinalysis^b

Color
Specific gravity
pH
Urine Protein
Glucose
Ketones
Blood
Bilirubin
Urobilinogen
Leukocyte esterase
Nitrite
Microscopic examination of sediment^j
Urine creatinine
Urine protein
Urine protein–creatinine ratio

Autoantibodies

Rheumatoid factor
Anticitrullinated peptide antibodies

Clinical Chemistry^b

Serum Concentrations of:
Sodium
Potassium
Total bilirubin
Direct bilirubin
Alkaline phosphatase (ALP)
Alanine aminotransaminase (ALT)/serum glutamic pyruvic transaminase
Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase
Blood urea nitrogen (BUN)
Creatinine
Estimated glomerular filtration rate (eGFR)^c
Uric acid
Calcium
Glucose^d
Albumin
Creatine phosphokinase (CPK)
Total protein
Iron studies (iron, TIBC, and ferritin)

Lipid Profile^{d,f}

Total cholesterol
High-density lipoprotein cholesterol (HDL-C)
Low-density lipoprotein cholesterol (LDL-C)
Triglycerides

Other Tests

Serum pregnancy test (females only)^g
Urine pregnancy test (females only)^g
Follicle-stimulating hormone (FSH) (females only)^h
Hepatitis B surface antigen (HBsAg)
Hepatitis B surface antibody (HBsAb)
Hepatitis B core antibody (HBcAb)
Hepatitis C antibodyⁱ
HBV DNA^k
HCV RNAⁱ
PPD or QuantiFERON[®]-TB Gold, or T-SPOT[®].TB^l
Thyroid-stimulating hormone (TSH)

Stored serum, plasma samples for exploratory biomarker analyses

Abbreviations: HBV DNA = hepatitis B virus deoxyribonucleic acid; HCV RNA = hepatitis C virus ribonucleic acid; Ig = immunoglobulin; mRNA = messenger ribonucleic acid; PPD = purified protein derivative; RBC = red blood cells; TIBC = total iron binding capacity; WBC = white blood cells.

- a All laboratories will be assayed/calculated by a Lilly-designated laboratory unless otherwise noted.
- b Unscheduled blood chemistry hematology, and urinalysis panels may be performed at the discretion of the investigator.
- c eGFR for serum creatinine will be calculated by the central laboratory using the Modification of Diet in Renal Disease (MDRD) isotope dilution mass spectrometry traceable method. On occasions where local laboratories are required for testing, the MDRD formula should also be used if possible.
- d Fasting laboratory values for glucose and lipids will be required at baseline, Week 12, and early termination or final visit. Patients should not eat or drink anything except water for 12 hours prior to test. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation.
- e Differential and blood smear may be performed if necessary.
- f Lipid panel consists of direct HDL-C, triglycerides, cholesterol, and LDL-C (calculation from Friedewald et al. 1972).
- g For women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at Visit 2 (prior to randomization), and may be performed thereafter at the discretion of the investigator or according to local regulations or guidelines.
- h For female patients aged 50 to ≤ 55 years with an intact uterus, not on hormone therapy, with 6 to ≤ 12 months of spontaneous amenorrhea, an FSH test will be performed to confirm nonchildbearing potential (FSH >40 mIU/mL).
- i A confirmatory test of HCV RNA will be performed if the patient is positive for HCV antibody.
- j Microscopic examination of sediment will be performed if abnormalities are noted on the routine urinalysis.
- k HBV DNA testing will be performed in patients who tested positive for HBcAb at screening.
- l In countries where the QuantiFERON®-TB Gold test or T-SPOT®.TB test is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be performed locally or centrally; the T-SPOT®.TB test must be performed locally.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

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

Appendix 3.1.2. Recruitment

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

Appendix 3.1.3. Ethical Review

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

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

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

- the protocol and related amendments and addenda, current Investigator's Brochure (IB), and updates during the course of the study

- informed consent form
- other relevant documents (e.g., curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

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

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

The investigator is responsible for reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Appendix 3.1.5. Investigator Information

Physicians with a specialty in rheumatology will participate as investigators in this clinical trial.

Physicians with other specialties and experience in treatment of patients with RA may also participate as investigators.

Appendix 3.1.6. Protocol Signatures

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

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

Appendix 3.1.7. Final Report Signature

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

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

Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate

- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database.

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

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

Appendix 3.2.1. Data Capture System

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

Electronic patient-reported outcome (ePRO) measures (e.g., a rating scale) and electronic clinical outcome assessments (eCOAs) are entered into an ePRO/eCOA instrument at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO/eCOA instrument record will serve as the source.

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

Any data for which the ePRO/eCOA data record will serve as source data will be documented by the site in their study file.

Case report form data collected by a third party will be encoded by the third party and stored electronically in the third party's database system. Validated data will subsequently be transferred to the sponsor's data warehouse, using standard Lilly file transfer processes.

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

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

Appendix 3.2.2. Data Protection

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

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

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

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

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

Appendix 3.2.3. Reports

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

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

Appendix 3.3. Study and Site Closure**Appendix 3.3.1. Discontinuation of Study Sites**

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

Appendix 3.3.2. Discontinuation of the Study

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

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

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	Alkaline Phosphatase Isoenzymes^a
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)^a

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

^a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Monitoring Tests for Confirmed Venous Thromboembolism

Selected tests may be obtained in the event of a confirmed venous thromboembolic event and may be required in follow-up with patients in consultation with Eli Lilly and Company, its designee, or the Lilly-designated medical monitor. Testing would be performed and analyzed in an algorithmic manner such that it is possible or even likely that only a subset of the tests on the list will be performed and that they will be assessed by clinical laboratorians with expertise in hemostasis and thrombosis. The choice and optimal timing of these tests will be directed by the patient's management and may require ongoing follow-up after study medication discontinuation.

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

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

Appendix 6. Country-Specific Requirements

Appendix 6.1 For countries within the European Union

The study will be conducted in accordance with the Regulation (EU) No 536/2014.

This appendix for Study JAJA contains regulatory requirements from European regulatory authorities. This appendix applies to all sites in the following countries within the European Union: Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Hungary, Italy, Lithuania, Poland, Romania, Slovakia, and Spain.

This table describes changes to the protocol sections to be applied by the above countries.

Section	Change
2.0. Schedule of Activities	Clarifications for tuberculosis testing. Clarifications for urine pregnancy testing. Addition of text for pregnancy testing requirements.
6.2. Exclusion Criteria	Revision to Criterion 9. Addition of text to include hypersensitivity to active substances or excipients.
6.2. Exclusion Criteria	Revision to Criterion 14. Addition of text to specify patients with HIV.
7.7. Concomitant Therapy	Addition of allowed concomitant medications.
8.1. Discontinuation from Study Treatment	Clarifications for temporary and permanent discontinuation criteria for hepatic laboratory abnormalities. Addition of Table JAJA.5 and Table JAJA.6.
9.4.7.2. Hepatic Safety Monitoring	Clarifications for hepatic safety monitoring.
Appendix 1. Abbreviations and Definitions	Removed reference to legally acceptable representatives because subjects incapable of giving informed consent will not be included in the study.
Appendix 2. Clinical Laboratory Tests	Clarification of urine pregnancy testing in footnote g.
Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process	Removed reference to legally acceptable representatives because subjects incapable of giving informed consent will not be included in the study.

Protocol Additions

All deletions are identified by ~~striketrough~~ and all additions are identified by the use of underscore.

Section 2.0. Schedule of Activities

	Screening	Treatment						Comments
Visit (V) Number	V1	V2 ^a	V3 ^b	V4 ^b	V5 ^{+c}	ET	VF ^d	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Procedures and Assessments								
Administer Tuberculosis (TB) test	X				<u>X*</u>			See Exclusion Criterion [17] for details of TB testing. In countries where the QuantiFERON®-TB Gold test or T-SPOT®.TB test is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be done locally or centrally; the T-SPOT®.TB test must be performed locally. <u>^aTB testing should be repeated approximately every 52 weeks as calculated from V2 for patients with negative screening tests. If the TB test becomes positive, investigators should follow local guidelines for monitoring and treatment.</u>
Read Purified Protein Derivative (PPD) test	X				<u>X*</u>			For those patients with a PPD placed at Visit 1 and thereafter, the PPD must be read 2 to 3 days (48 to 72 hours) post-visit [†] . The PPD test result does not need to be read at the site, but must be assessed by a trained healthcare professional, and documented results provided to the site as soon as possible.

(continued)

	Screening	Treatment						Comments
Visit (V) Number	V1	V2a	V3b	V4b	V5+c	ET	VFd	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Procedures and Assessments								
Laboratory Tests ^e								
Urine pregnancy test		X [‡]						For all women of childbearing potential, a serum pregnancy test (central laboratory) will be performed at Visit 1. Urine pregnancy tests (local laboratory) will be performed at Visit 2 (prior to randomization) [‡] , and <u>will may</u> be performed <u>approximately every 4 weeks</u> thereafter <u>using self-testing, at the discretion of the investigator or according to local regulations or guidelines.</u> Patients will be directed to inform the site <u>immediately if their pregnancy test is positive.</u>

^a TB testing can be performed every 48 weeks as calculated from Visit 2 to align with scheduled visits (for example, V5, V7, V9, V11 etc)

Section 6.2. Exclusion Criteria

- [9] ~~Have any contraindications to a TNF inhibitor as addressed in local product labeling or local clinical practice that would preclude the patient from participating in this study.~~

Have any contraindications or hypersensitivity to:

- a TNF inhibitor
- baricitinib
- the active substance, or
- any of the excipients listed in the SmPC Section 6.1.

- [14] Have a clinically serious infection or have any other active or recent infection that in the opinion of the investigator would pose an unacceptable risk to the patient if participating in the study. This is also applicable to patients with evidence of HIV infection and/or who are positive for anti-HIV antibodies.

Section 7.7. Concomitant Therapy

Use of the following concomitant medications are allowed (list not exhaustive):

- Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 [COX-2] inhibitors, and corticosteroids are permitted according to local clinical practice.
- csDMARDs are permissible for use with the limitation of no more than 2 csDMARDs. Examples are:
 - methotrexate,
 - hydroxychloroquine,
 - sulfasalazine, or
 - leflunomide.

Section 8.1 Discontinuation from Study Treatment

Temporary interruption

It is recommended that the investigator consult with Lilly (or its designee) before temporarily interrupting treatment for reasons other than those described in the protocol or local product label. Treatment that was temporarily interrupted because of an AE or abnormal laboratory value may be restarted at the discretion of the investigator according to the local product label recommendations. Investigational product must be held in the following situations involving hepatic laboratory abnormalities and may be resumed as noted in [Table JAJA.5](#). Retest timing and frequency is at the investigator's discretion. Baricitinib is not recommended for use in patients with estimated GFR of <30 mL/min/1.73 m².

Table JAJA.5. Criteria for Temporary Interruption of Investigational Product for Hepatic Laboratory Abnormalities

<u>Hold Investigational Product if the Following Laboratory Test Results Occur:</u>	<u>Investigational Product May Be Resumed When:</u>
<u>ALT or AST >5 x ULN</u>	<u>ALT and AST return to <2 x ULN, and investigational product is not considered to be the cause of enzyme elevation</u>
<u>If ALT or AST are elevated and drug-induced liver injury is suspected</u>	<u>diagnosis of drug-induced liver injury is excluded</u>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Permanent discontinuation

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

- Subject decision
 - the patient requests to discontinue investigational product.
- Investigator decision
 - the investigator decides that the patient should be discontinued from investigational product.
- Serious or opportunistic infection that in the opinion of the investigator merits the investigational product being discontinued.

Permanent discontinuation of study medication must occur:

- If the patient becomes pregnant
- If the patient presents with active primary or recurrent malignant disease (except for successfully treated basal cell or squamous epithelial skin cancers)
- If the patient experiences a VTE (DVT/PE), ATE, or MACE, including myocardial infarction or stroke (cerebrovascular accident) during the study
- If eGFR <30 mL/min/1.73 m² for a patient taking baricitinib 2 mg or if eGFR <60 mL/min/1.73 m² for a patient taking baricitinib 4 mg and eGFR does not sufficiently improve within 30 days of temporary discontinuation of study medication. For patients taking baricitinib 4 mg, this applies only if dose reduction is not an option due to having already undergone one dose adjustment (see Section 7.4)
- If any of the following are observed:
 - ALT or AST >8 x ULN
 - ALT or AST >5 x ULN persisting for more than 2 weeks after temporary interruption of investigational product
 - ALT or AST >3 x ULN and total bilirubin level >2 x ULN
 - ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

The date of study drug discontinuation must be documented.

Throughout the trial, investigators should continue to assess benefit/risk for patients to remain in the trial and should consider discontinuing patients if sufficient clinical benefit is not observed with protocol-allowed concomitant therapy.

In addition, patients will be permanently discontinued from investigational product if they experience any of the hepatic laboratory abnormality criteria listed in [Table JAJA.6](#).

Table JAJA.6. Criteria for Permanent Discontinuation of Investigational Product for Hepatic Laboratory Abnormalities

<u>Permanently Discontinue Investigational Product if any of the Following Are Observed:</u>
<u>ALT or AST >8 x ULN</u>
<u>ALT or AST >5 x ULN persisting for more than 2 weeks after temporary interruption of investigational product</u>
<u>ALT or AST >3 x ULN and total bilirubin level >2 x ULN</u>
<u>ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)</u>

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Section 9.4.7.2 Hepatic Safety Monitoring

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

Investigational product must be held temporarily or permanently discontinued in situations involving laboratory abnormalities as noted in Section 8.1 ([Table JAJA.5](#) and [Table JAJA.6](#)).

Appendix 1. Abbreviations and Definitions

enter

Patients entered into a trial are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~

Appendix 2. Clinical Laboratory Tests

Footnote g: For women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at Visit 2 (prior to randomization), and ~~will may~~ be performed approximately every 4 weeks thereafter using self-testing. at the discretion of the investigator or according to local regulations or guidelines. Patients will be directed to inform the site immediately if their pregnancy test is positive.

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient ~~or legal representative~~. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the participant ~~or the participant's legal representative~~ and is kept on file.

ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

The authorized person obtaining the informed consent must also sign the ICF.

Appendix 6.2 For sites in France

This appendix for Study JAJA contains regulatory requirements from the French Agency, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM). This appendix applies to all sites in France conducting this clinical trial.

This table describes changes to the protocol sections to be applied by France.

Section	Change
1.0. Synopsis	Indicate that Study JAJA is a non-inferiority study
2.0. Schedule of Activities	Clarifications for tuberculosis testing
5.1. Overall Design	Indicate that Study JAJA is a non-inferiority study
6.2. Exclusion Criteria	Exclude patients under legal protection

Protocol Additions

All deletions are identified by ~~striketrough~~, and all additions are identified by the use of underscore.

Section 2.0. Schedule of Activities

	Screening	Treatment						Comments
Visit (V) Number	V1	V2 ^a	V3 ^b	V4 ^b	V5 ^{+c}	ET	VF ^d	
Study Week		0	12	28	Week 52, and every 24 weeks thereafter	Any	-	
Permitted Window, Days	-42 to -3	1	± 7	± 7	± 14	Any	0 to + 14	
Procedures and Assessments								
Administer Tuberculosis (TB) test	X				<u>X*</u>			See Exclusion Criterion [17] for details of TB testing. In countries where the QuantiFERON®-TB Gold test or T-SPOT®.TB test is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test may be done locally or centrally; the T-SPOT®.TB test must be performed locally. <u>^aTB testing should be repeated approximately every 52 weeks as calculated from V2 for patients with negative screening tests. If the TB test becomes positive, investigators should follow local guidelines for monitoring and treatment</u>
Read Purified Protein Derivative (PPD) test	X				<u>X*</u>			For those patients with a PPD placed at Visit 1 <u>and thereafter</u> , The PPD must be read 2 to 3 days (48 to 72 hours) after Visit ~~1~~ . The PPD test result does not need to be read at the site, but must be assessed by a trained healthcare professional, and documented results provided to the site as soon as possible.

^a TB testing can be performed every 48 weeks as calculated from Visit 2 to align with scheduled visits (for example, V5,V7,V9, V11 etc)

Section 1: Synopsis**Summary of Study Design**

Study I4V-MC-JAJA (JAJA) is a Phase 3b/4, multicenter, randomized, parallel-group, active-controlled, outpatient, event-driven, non-inferiority study to evaluate the effects of baricitinib (2-mg and 4-mg daily) compared with tumor necrosis factor (TNF) inhibitors (administered according to approved local labeling) on the risk of VTE and other key safety endpoints in patients with RA. Treatment will be open label for patients and study-site personnel.

Section 5.1: Overall Design

Study I4V-MC-JAJA (JAJA) is a Phase 3b/4, multicenter, randomized, parallel-group, active-controlled, outpatient, event-driven, non-inferiority study to evaluate the effects of baricitinib (2-mg and 4-mg daily) compared to TNF inhibitors (administered according to approved labeling) on the risk of VTE and other key safety endpoints in patients with RA (Figure JAJA.1).

Section 6.2: Exclusion Criterion**Other Exclusion Criteria**

- [33] Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures. This includes patients under legal protection.

Appendix 7. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Visit 1 and Visit 2 cannot be performed remotely, even in exceptional circumstances.

Types of remote visits

Telemedicine - Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to assessment of study medication compliance, review of concomitant medications, collection of adverse and targeted events and patient RA assessments.

Mobile healthcare - Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Mobile healthcare visits may be performed by a qualified mobile research nurse service provider or trained site personnel (investigator or other medical personnel), following sponsor written approval and if permitted by local regulations. Procedures performed at such visits include, but are not limited to, review of concomitant medication, assessment of weight and vital signs, collection of adverse and targeted events, dispensation and assessment of compliance of investigational product, collection of blood and urine samples. The investigator or other medical site personnel will be immediately available for emergencies and other questions.

The below procedures also may be performed but require additional qualifications (investigator or a designee who is a physician) and sponsor approval: assessment of adverse and targeted events, Symptom-directed physical examination; Physician's GAD and Tender joint count (TJC)/Swollen joint count (SJC) (28 joints).

Other alternative locations - In case it is required, local laboratories can be used for laboratory tests, as discussed below.

Data capture

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

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing for safety labs including: Clinical chemistry, hematology, fasting lipid panel, Tuberculosis testing, and HBV DNA. However, if possible, only central laboratory testing should be used for: hsCRP and serum creatinine (eGFR). Where local laboratories are required for testing serum creatinine (eGFR), the MDRD formula should also be used if possible. The local laboratory must be qualified in accordance with applicable local regulations.

- Investigators must document their review of each laboratory safety report and retain in the source documentation. Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to Lilly or its designee as an AE via eCRF.
- Laboratory testing may be performed centrally or locally based on logistics related sample stability and feasibility to collect at alternate location. Local laboratory collections will be used for immediate patient management and safety but will not be included in the data for analysis. See information related to local laboratory testing options below.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).

- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that Visits 3 and 4 can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study. The Table 1 describes the mitigations to allow for expanded visits windows during exceptional circumstances.

Table 1. Extended Visit Windows for Exceptional Circumstances

This table describes the allowed adjustments to visit windows.

Visit Number	Protocol Specified Week	Protocol Specified Visit Interval Tolerance	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range
V 3	12	± 7 days	± 14 days	
V4	28	± 7 days	± 14 days	
V 5+	Week 52, and every 24 weeks thereafter	± 14 days	± 28 days	
ET	Any	Any	N/A	
FV	-	0 to + 14 days	0 to +28 days	Every attempt should be made to complete the FV within the identified permitted window. To maximize the ability for FV to take place on site and to minimize missing data, the visit window may be extended up to 28 days upon specific guidance from the sponsor.

Abbreviations: ET = early termination; FV = final visit; N/A = not applicable; V = visit.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Future patient visits must be adjusted to bring the patient back into compliance with the protocol defined visit windows.

Documentation***Changes to study conduct will be documented***

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Appendix 8. Protocol Amendment History

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

Amendment [e]: (22-Mar-2024)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is

- to align with the new EU Clinical Trial Regulation requirements
- to allow the use of biosimilars within the tumor necrosis factor (TNF) inhibitor treatment arm, and
- to make provision for conducting ad hoc interim analyses to address regulatory requests.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added Regulatory Agency Identifier Number(s)	For EU-CTR compliance
1. Synopsis	Added • Regulatory Agency Identifier Numbers • Study Population • Ethical Considerations of Benefit/Risk	For EU-CTR compliance
	Removed the brand names “Humira [®] ” and “Enbrel [®] ”	To allow for biosimilars
5.1. Overall Design 5.4. Scientific Rationale for Study Design 7.1. Treatments Administered 7.4. Dosage Modification (Including Rescue Therapy)	Removed the brand names “Humira [®] ” and “Enbrel [®] ”	To allow for biosimilars
7.1. Treatments Administered	• Added the definition of study treatment • Added the last column “Authorized as defined by EU Clinical Trial Regulation”	For EU-CTR compliance
7.1.1. Packaging and Labeling	Added packaging and labeling information	For EU-CTR compliance
7.2.2. Dose Adjustment for Renal Impairment	Added the use of Modification of Diet in Renal Disease (MDRD) formula for estimated glomerular filtration rate (eGFR) calculation	To ensure consistency in renal function data

Section # and Name	Description of Change	Brief Rationale
7.3. Blinding 9.4.1. Primary and Secondary Endpoints	Added “Infection Adjudication Committee (IAC)” for adjudication of opportunistic infections.	For clarification
7.7. Concomitant Therapy	Replaced “Enbrel®” with “etanercept” and “Humira®” with “adalimumab”.	To allow for biosimilars
8.1. Discontinuation from Study Treatment	Added ATE as a permanent discontinuation of investigational product.	To clarify the secondary endpoint of ATE as a specific condition under which study medication must be permanently discontinued.
Appendix 6.1 For countries within the European Union, Section 8.1 Discontinuation from Study Treatment	Added hepatic laboratory abnormality criteria for permanent discontinuation of study medication.	For clarification
9.2. Adverse Events	Added the events meeting the AE definition	For EU-CTR compliance
9.2.1. Serious Adverse Events	Added SAE regulatory reporting paragraph	For EU-CTR compliance
9.4.1. Primary and Secondary Endpoints	Added “myocardial infarction, stroke and cardiovascular death” to MACE; removed “CV events incorporating”	To clarify cardiovascular events considered as MACE.
	Added “Serious infection is defined as all infections that meet SAE criteria (Section 9.2.1).”	To clarify definition of serious infection.
10.3.1. General Statistical Considerations	Added the paragraph regarding handling of missing, unused, and spurious data	For EU-CTR compliance
10.3.5. Interim Analyses		
Appendix 2. Clinical Laboratory Tests	Added “(MDRD)” and “On occasions where local laboratories are required for testing, the MDRD formula should also be used if possible.” to footnote “c”	For consistency in renal function data
Appendix 3.1.4. Regulatory Considerations	Added “The investigator is responsible for reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity”.	For EU-CTR compliance
Appendix 3.2.2. Data Protection	Added this new section	For EU-CTR compliance
Appendix 3.2.3. Reports	Added this new section	For EU-CTR compliance
Appendix 6.1 For countries within the European Union,	In Administer Tuberculosis (TB) test row, added specification that 52 weeks	TB testing can be performed every 48 weeks from Visit 2 to align with

Section # and Name	Description of Change	Brief Rationale
Section 2.0. Schedule of Activities	are counted from Visit 2 and also included the possibility to perform follow up tests at 48 weeks	scheduled visits (for example, V5, V7, V9, V11 etc) to reduce unscheduled visits.
Appendix 6.2 For sites in France, Section 2.0. Schedule of Activities		
Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances	Added this new appendix and the appendix number of subsequent appendix is changed	Updated as per Harmonized Clinical Protocol template
Throughout the protocol	Modified conventional DMARD (cDMARD) to conventional synthetic DMARD (csDMARD)	Correction
Throughout the protocol	Minor formatting and editorial changes.	Minor, therefore, not detailed.

Amendment [d] : (22-Jul-2022)

This amendment is considered to be non-substantial.

Overall Rationale for the Amendment:

The main rationale for the amendment is to update contraception language based on requirement from UK Medicines and Healthcare products Regulatory Agency.

Section # and Name	Description of Change	Brief Rationale
Section 4 Objectives and Endpoints	Specifically added all-cause mortality to the exploratory endpoint of SAEs	To clarify that all-cause mortality will be assessed as part of SAEs
Section 6.1 Inclusion Criteria	Updated Inclusion Criterion 7a and 7b to clarify that participants should continue to remain abstinent or use at least 1 highly effective method of contraception for 1 week after the last dose of baricitinib, 3 weeks after last dose of etanercept and 5 months after last dose of adalimumab	Regulatory requirement and to align with informed consent form
Appendix 2 Clinical Laboratory Tests	Updated Footnote d regarding collection of glucose and lipid laboratory values	Prior footnote referred to the requirement only at baseline and Week 12, despite the SOA also requiring these tests at early termination or final visit

Amendment [c]: (28-Apr-2022)

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Updated text related to randomization via IWRS	Clarification added that if a participant is randomized to baricitinib 4 mg at baseline, a subsequent reduction to baricitinib 2 mg may be implemented at any time for safety reasons if constrained by renal function
Section 5.4 Scientific Rationale for Study Design	Updated text related to targeted or biologic therapies	Clarification added that participants may not receive other bDMARDs or tsDMARDs prior to permanent discontinuation of study medication rather than discontinuation from the trial, as it is not reasonable to encourage participants to continue in the study for follow-up without permitting appropriate RA therapy
Section 5.5 Justification for Dose	Added text regarding dose reduction of patients from baricitinib 4 mg to 2 mg dose based on renal constraint post-baseline	Rather than discontinuing patients from study medication when the baricitinib 4 mg dose is not appropriate due to safety concerns (specifically, eGFR post-baseline <60 mL/min/1.73 m ²), the protocol was adjusted to allow continuation on baricitinib at the 2 mg dose
Section 6.2 Exclusion Criteria	Added text indicating relevant laboratory tests may be repeated once for patients not meeting eligibility criteria	Provides flexibility so that patients with potentially spurious laboratory findings are not screen-failed in error
Section 7.1 Treatments Administered	Updated footnote in table JAJA.3	The protocol was updated to clarify that patients who received the baricitinib 2 mg dose at baseline due to constrained renal function may subsequently be rescued to baricitinib 4 mg if eGFR ≥ 60 mL/min/1.73 m ²
Section 7.2.2 Dose Adjustment for Renal Impairment	Minor edits	To clarify that Section 7.2.2 pertains only to dose adjustments for baricitinib patients at the time of randomization and refers to Section 7.4 for dose adjustments post-randomization

Section # and Name	Description of Change	Brief Rationale
Section 7.4 Dosage Modification (Including Rescue Therapy)	Updated text regarding rescue of patients to baricitinib 4 mg (based on the most recent eGFR) and potential to dose-reduce from baricitinib 4 mg to 2 mg dose if constrained by renal function. Included text that once a patient is rescued to baricitinib 4 mg or dose-reduced to baricitinib 2 mg, subsequent dosing changes are not permitted	Regarding rescue of patients to baricitinib 4 mg after 1 year, the protocol was clarified to indicate that rescue of patients was permitted based upon most recent eGFR, not based upon baseline value. In addition, the prior version of the protocol did not permit dose-reductions to baricitinib 2 mg for any reason. Rather than discontinuing patients from study medication when the baricitinib 4 mg dose was not appropriate due to safety concerns (specifically, eGFR post-baseline <60 mL/min/1.73 m ²), the protocol was adjusted to allow continuation on baricitinib at the 2 mg dose. To avoid data analysis issues, multiple dose adjustments will not be permitted
Section 7.7 Concomitant Therapy	Updated use of prohibited concomitant therapy to indicate that use of anticoagulants for >30 days is not permitted	Chronic use of anticoagulant therapy contravenes the primary endpoint of the study. Therefore, clarification of the use of anticoagulants was provided
Section 8.1 Discontinuation from Study Treatment	Updated circumstances for permanent discontinuation of study medication Deleted sub-section on inadvertently enrolled patients	To clarify specific conditions under which study medication must be discontinued, which include VTE, MACE, and malignancy, which are all study endpoints. In addition, if renal function declines and does not improve with temporary discontinuation of study medication, this is now a reason for permanent study medication discontinuation. Deleted sub-section on inadvertently enrolled patients to align with updated procedures
Section 8.2 Discontinuation from the Study	Updated circumstances for discontinuation from the study	Any conditions requiring permanent study medication discontinuation also now require permanent study discontinuation
Section 9.2 Adverse Events	Added clarification about reporting RA flares as AEs	To clarify that although generally RA flares would represent lack of efficacy rather than an AE, there may be

Section # and Name	Description of Change	Brief Rationale
		circumstances for which it is appropriate to include as an AE
Section 10.1 Sample Size Determination	Updated text regarding total enrollment in the study	To clarify that another reason enrollment may be increased without amendment of the protocol is to accommodate a higher than anticipated dropout rate, which would adversely impact the overall exposure and therefore the accumulation of study events
Section 10.3.3.2 Secondary Analyses	Added that patients randomized to baricitinib 4 mg but receiving the 2 mg dose at any time during the study based on renal constraint will not be censored from the 4-mg dose group	Patients with reduced renal function receiving baricitinib 2 mg are expected to have the same exposure as those with normal renal function receiving baricitinib 4 mg
Appendix 6 Country-Specific Requirements	Added content from protocol addenda 1.1 and 2.1 as country-specific appendices	To comply with the European Union Clinical Trial Regulation, which aims to harmonize the protocol across member states through a single application via the Clinical Trial Information System

Amendment [b]: (17-Mar-2021)**Amendment Summary for Protocol I4V-MC-JAJA Amendment (b)**

Section # and Name	Description of Change	Brief Rationale
Section 10.3.2.4. Treatment Compliance	Updated to remove language regarding the use of diaries for recording medication compliance for TNF inhibitors.	Clarification added as patient diaries are not required to track medication compliance but are an optional tool.

Amendment [a]: (19-Apr-2019)

Section # and Name	Description of Change	Brief Rationale
Section 1 Synopsis – Statistical Analysis	Addition/deletion of text: Unless otherwise specified, analyses of primary and secondary outcomes will be conducted on all randomized patients <u>(combined from Studies JAJA and JAJD)</u> who receive at least 1 dose of investigational product and who do not discontinue at the first postbaseline visit for the reason “Lost to Follow-up.” Time from first dose to first event ~~while patients are on their randomized treatment~~ for the primary and secondary analyses will be analyzed using a Cox proportional hazards regression model stratified by study with treatment group and randomization stratification factors as explanatory variables. Additional analyses conducted without censoring ~~will~~ <u>may</u> also be applied.	Alignment with Study JAJD per FDA feedback and other clarifications.
Section 2 Schedule of Activities	Change in description for Targeted Medical History: Solicitation and recording of historical <u>data on targeted events, including</u> primary and secondary endpoint events (VTE, ~~[DVT/PE]~~, ATE, <u>MACE</u>, ~~cardiovascular events~~, malignancy <u>[excluding NMSC]</u>, opportunistic infection, <u>and</u> serious infection)	Clarification
Section 2 Schedule of Activities	Change in wording for Administer Tuberculosis (TB) test:	Added option for local QuantiFERON.

	See Exclusion Criterion [17] for details of TB testing. In countries where the QuantiFERON®-TB Gold test or T-SPOT®.TB test is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test <u>may be done locally or must be performed centrally</u> ; the T-SPOT®.TB test must be performed locally.	
Section 2 Schedule of Activities	Change in description for Targeted Events: Solicitation and recording of ~~historical~~ data on <u>targeted events</u> , <u>including</u> new primary and secondary endpoint events (VTE ~~[DVT/PE]~~ , ATE, ~~and~~ MACE, malignancy [excluding NMSC], opportunistic infection, <u>and</u> serious infection), will be conducted at all visits after randomization.	Clarification
Section 2 Schedule of Activities	Addition of footnote for demographics: † <u>Collection of demographic information includes race and ethnicity.</u>	Needed per European Union General Data Protection regulatory requirements.
Section 4 Objectives and Endpoints	Change in description for exploratory objective: - PROMIS - Pain Interference, - Depression, ~~Cognition~~ <u>Cognitive Function</u>, - Satisfaction <u>with</u> Social Roles <u>and</u> Activities, and - Sleep <u>Disturbance</u>	Corrected to list the adult domains

Section 5.4. Scientific Rationale for Study Design		Clarification
Section 5.4. Scientific Rationale for Study Design	<u>To assure that the assessment of secondary (2-mg) objectives is not unacceptably impacted by excessive early attrition from this group through rescue, Requiring a minimum period of stability on baricitinib 2-mg is required before rescue to 4-mg is permitted permissible is justified to assure that the assessment of secondary (2-mg) objectives is not unacceptably impacted by excessive early attrition from this group through rescue.</u>	Clarification
Section 5.4. Scientific Rationale for Study Design	<u>Addition of text:</u> <u>The collection of demographic information includes race and ethnicity. This information is needed to assess variable responses in VTE based on race or ethnic background, as incidence rates vary by race (Goldhaber 2014).</u>	This provides a scientific rationale for the data collection per European Union General Data Protection regulatory requirements.
Section 6 Study Population	Deletion of sentence: ~~Patient eligibility will be reviewed and must be confirmed by an eligibility review committee prior to randomization.~~	Entry error
Section 6.2 Exclusion Criteria	Addition/deletion of text:	Clarification

	[18] Have <u>received</u> ~~had an~~ <u>inadequate response or intolerance</u> ~~to~~ more than 1 prior TNF inhibitor <u>that was:</u> ~~Prior TNF inhibitors discontinued for reasons other than:~~ a. <u>Discontinued for</u> inadequate response for RA (~~that is,~~ lack or loss of efficacy) ~~for RA~~, or b. <u>Discontinued for</u> intolerance (<u>AE</u>) <u>when used</u> for any indication <u>use</u> (~~that is, AEs~~) <u>are not considered for the purpose of this criterion</u>	
Section 6.2 Exclusion Criteria	[26] Have any of the following: - ALT or AST >2 x the upper limit of normal (ULN) - alkaline phosphatase (ALP) $\geq 2 \times$ ULN - total bilirubin level (TBL) $\geq 1.5 \times$ ULN - hemoglobin $< \underline{98}$ g/dL (~~90~~80.0 g/L) - neutropenia (absolute neutrophil count $< \underline{1200}$1000 cells/μL) (< 1.2~~2000~~ $\times 10^3/\mu$L or $< \underline{1.20}$1.00 GI/L) - lymphopenia (lymphocyte count $< \underline{750}$500 cells/μL) (< 0.75~~0.50~~ $\times 10^3/\mu$L or $< \underline{0.75}$0.50 GI/L) - eGFR (Modification of Diet in Renal Disease) $< \underline{40}$30 mL/min/1.73 m²	Alignment with Study JAJD per FDA feedback.
Section 7.2.2. Dose Adjustment for Renal Impairment	Patients with documented renal impairment (defined as screening eGFR $\geq \underline{40}$30 to < 60 mL/min/1.73 m²) who are randomized to baricitinib	Updated to match new exclusion criteria
Section 8.1. Discontinuation from Study Treatment	Moved last bullet to 3rd bullet, and addition/deletion of text for possible reasons that may lead to permanent discontinuation of investigational product.	Clarification and alignment with Study JAJD

	• <u>Serious or opportunistic</u> infection that in the opinion of the investigator merits the investigational product being discontinued. <u>Permanent discontinuation of study medication should occur:</u> • <u>If the patient becomes pregnant</u> • <u>If the ~~study participant~~ patient presents with active primary or recurrent malignant disease</u> ~~Malignancy~~ (except for successfully treated basal cell or squamous epithelial skin cancers) • <u>If the patient experiences</u> ~~Occurrence~~ of a VTE (DVT/PE) during the study.	
Section 9.1.5. Health Outcomes and Quality-of-Life Measures PROMIS Short Form v1.0 Pain Interference 8a, and PROMIS Short Form v2.0 Satisfaction with Social Roles/Activities 8a	Addition/deletion of text: The questionnaire consists of 8 questions and uses a 5-point Likert scale (~~0 = not at all~~ <u>1 = not at all</u> ; 5 = very much).	Correction
Section 9.1.5. Health Outcomes and Quality-of-Life Measures PROMIS Short Form v2.0 Cognitive Function 8a	Addition/deletion of text: The questionnaire consists of 8 questions and uses a 5-point Likert scale (~~0 = not at all~~ <u>5 = never</u> ; ~~5 = very much~~ 1 = very often).	Correction
Section 9.1.5. Health Outcomes and Quality-of-Life Measures PROMIS Short Form v1.0 Depression 8b	Addition/deletion of text: The questionnaire consists of 8 questions and uses a 5-point Likert scale (~~0 = never~~ <u>1 = never</u> ; 5 = always).	Correction
Section 9.1.5. Health Outcomes and Quality-of-Life Measures PROMIS Short Form v1.0 Sleep Disturbance 8a	Addition/deletion of text: The questionnaire consists of 8 questions and uses a 5-point Likert scale (~~0 = very poor~~ <u>5 = very poor/not at all</u> ; ~~5 = very good~~ <u>1 = very good/very much</u>) Scores are totaled and higher scores indicate ~~better~~ <u>worse</u> sleep.	Correction
Section 9.2. Adverse Events	Addition of text: <u>The investigator will record all relevant AE and SAE information in the eCRF.</u>	New Lilly required text. Existing text was also moved within this section so related topics were together.

Section 9.4.6. Hepatitis B Virus DNA Monitoring	Addition of text: <u>If HBV DNA is detected, then consultation with a hepatologist is recommended.</u>	Clarification
Section 10.1. Sample Size Determination	Addition/deletion of text: The total number of enrolled patients in this study may be increased up to 3900 without protocol amendment in cases of reduced enrollment in Study JAJD, delayed enrollment in either study, or lower than expected event rates, in order to preserve adequate statistical power for the assessment of the primary objective within the planned time frame. <u>At a minimum, if studies JAJA and JAJD are not stopped early, ^{CC} of the ^{CC} planned patients with events between these 2 studies will come from Study JAJA. Study JAJA will continue until that number is achieved. However, as an exception, ~~Also~~, Study JAJA may stop early based on the number of events estimated for the planned interim analyses (see Section 10.3.5).</u>	Requirement agreed with FDA.
Section 10.3.1.1. Analysis Methods	Addition/deletion of text: Time ~~from first dose~~ to first event for the primary and secondary analyses will be analyzed using a Cox proportional hazards regression model stratified by study with treatment group and randomization stratification factors (VTE history, age/BMI combination, prior inadequate response or intolerance to a TNF inhibitor, and geographic region) as explanatory variables. Hazard ratios, their 95% CIs, and associated p-values will be presented for treatment comparisons and assessments of superiority/inferiority and noninferiority, where applicable. ~~If the proportional hazards assumption is violated, other~~	Clarifications

	~~models that relax the proportional hazards assumption will be considered.~~ Analyses of dichotomous efficacy and health outcomes data from Study JAJA will use a logistic regression model with geographic region, prior inadequate response or intolerance to a TNF inhibitor, <u>BMI</u>, and treatment group as explanatory factors, providing the p-value and 95% CI for the odds ratio for treatment group differences. Missing data will be imputed using nonresponder imputation (NRI) ~~up to Week 28~~, as described in Section 10.3.1.3.	
--	---	--

Section 10.3.1.1. Analysis Methods	The model will include geographic region, prior inadequate response or intolerance to a TNF inhibitor, <u>BMI</u>, treatment, visit, and treatment-by-visit interaction as fixed categorical effects, and baseline value and baseline value-by-visit interaction as fixed continuous effects to estimate change from baseline across postbaseline visits. <u>An unstructured covariance matrix will be used to model the between- and within-patient errors. If the unstructured covariance configuration results in a lack of convergence, then the following variance-covariance matrix will be used (in order) until one converges: Heterogeneous Toeplitz, Heterogeneous First Order Autoregressive, Heterogeneous Compound Symmetry, Toeplitz, First Order Autoregressive, and Compound Symmetry. If all the selected variance-covariance matrices fail to converge, Variance Components will be used as the next attempt at convergence. An unstructured covariance structure will be used to model the between- and within-patient errors for analyses over the first 28 weeks; for models of longer term data, heterogeneous Toeplitz will be used.</u>	Expanded explanation for model.
Section 10.3.1.2. Censoring Rules	Addition/Deletion of text: For analysis of primary and secondary endpoints other than malignancy, events will be attributed to patients according to their randomized treatment group assignment through the date of their last dose of randomized study medicine plus up to 30 days, censored <u>after at the time of any</u> rescue or initiation of a nonpermitted RA treatment.	Revised for accuracy and to match with IWRS settings.

	Because malignancies may result from an extended biological process, such events will be attributed to patients through the date of their last available study visit, without regard for last dose of randomized study medicine, but censored <u>after</u> ~~at the time of any~~ rescue (for analyses of individual baricitinib dose groups) or initiation of a nonpermitted RA treatment.	
10.3.1.3. Handling of Dropouts or Missing Data	<u>Addition/deletion of text:</u> <u>Nonresponder imputation:</u> For analysis of categorical efficacy and health outcomes data ~~through Week 28~~, patients who discontinue study treatment early, are rescued, or initiate nonpermitted RA treatments will be defined as nonresponders <u>after</u> ~~from the time of~~ discontinuation, ~~the time of~~ rescue, ~~or the time of~~ new medicine initiation, respectively. <u>Mixed-model repeated measures:</u> Observed data will be analyzed with the exception that any data that occur after rescue, <u>study treatment discontinuation, or initiation of nonpermitted RA treatments</u> will be censored in order to estimate the effects of the randomized treatment.	Corrections
10.3.3.2. Secondary Analyses	Addition/Deletion of text: Similar analysis methods as described above will be used, except that patients who rescue from baricitinib 2-mg to baricitinib 4-mg will be censored <u>after</u> ~~at the time of first dose of~~ rescue ~~treatment~~.	Clarification
10.3.4.1. Analyses of Categorical Measures	Addition/deletion of text: The following outcomes will be compared between each baricitinib dose group and the TNF inhibitor group through the first ~~28~~ 52 weeks.	Correction

	A logistic regression model with factors for treatment group, <u>BMI</u> , geographic region, and prior inadequate response or intolerance to a TNF inhibitor will be used to test for treatment differences ~~at Weeks 12 and 28~~ .	
10.3.4.2. Analyses of Continuous Measures	Addition/deletion of text: The following outcomes will be compared between each baricitinib dose group and the TNF inhibitor group <u>through the first 52 weeks across all time points where data are collected</u>. An MMRM analysis method described in Section <u>10.3.1.1</u> will be used to test for treatment differences ~~through the first 28 weeks~~.	Correction
10.3.5. Interim Analyses	Addition of text: The data from Studies JAJA and JAJD will be evaluated <u>by the DMC</u> at interim analyses in order to determine if the combined evidence is sufficient to meet the studies' primary objective with respect to VTE.	Clarification
Appendix 2 Clinical Laboratory Tests	Addition/deletion of text in footnotes: ^d Fasting laboratory values for glucose and lipids will be required at baseline and at Week 12 ~~and 28~~. ^g For women of childbearing potential, urine pregnancy tests (local laboratory) will be performed at Visits 2 (prior to randomization) ~~3 and 4~~, and may be performed thereafter at the discretion of the investigator or according to local regulations or guidelines.	Updated for consistency and flexibility.

	¹ In countries where the QuantiFERON®-TB Gold test or T-SPOT®.TB test is available, either test may be used instead of the PPD TB test. The QuantiFERON®-TB Gold test ~~may~~ <u>must</u> be performed <u>locally or centrally</u> ; the T-SPOT®.TB test must be performed locally.	
--	---	--

Signature Page for VV-CLIN-067243 v3.0

Approval	PPD Medical Director 16-Oct-2024 21:50:36 GMT+0000
----------	--

Approval	PPD Statistician 16-Oct-2024 22:50:35 GMT+0000
----------	--

Signature Page for VV-CLIN-067243 v3.0