

Protocol 14V-MC-JAJD (f)

A Randomized, Controlled Pragmatic Phase 3b/4 Study of Baricitinib in Patients
With Rheumatoid Arthritis

NCT04086745

Approval Date: 22-Mar-2024

Protocol I4V-MC-JAJD(f) (RA-BRANCH)
A Randomized, Controlled Pragmatic 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

Document ID: VV-CLIN-068404

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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
<i>Amendment e</i>	<i>03-Aug-2022</i>
<i>Amendment d</i>	<i>02-May-2022</i>
<i>Amendment c</i>	<i>12-Feb-2021</i>
<i>Amendment b</i>	<i>04-Jun-2020</i>
<i>Amendment a</i>	<i>24-Jan-2020</i>
<i>Original Protocol</i>	<i>30-Apr-2019</i>

Amendment [f]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The main rationale for the amendment is to allow the use of biosimilars within 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 Trial acronym	Additional information
1.Synopsis 5.1. Overall Design	Removed the brand names “Humira®” and “Enbrel®”	To allow for biosimilars
3.3. Benefit/Risk Assessment	Replaced “Enbrel and Humira” with “the TNF inhibitors”	To allow for biosimilars and for consistency with JAJA(e) language
5.3. Scientific Rationale for Study Design	Removed the brand names “Enbrel” and “Humira”	To allow for biosimilars
	Replaced “ENTRECOTE” with “ENTRACTE”	Correction
7.1. Treatments Administered 7.4. Dosage Modification 7.7. Concomitant Therapy	Removed the brand names “Humira” and “Enbrel”	To allow for biosimilars
7.1.1. Packaging and Labelling	Removed “(Humira or Enbrel)”	
7.2.2. Dose Adjustment for Renal Impairment	Added the sentence “When calculating eGFR, the same eGFR formula should be applied consistently for each patient throughout the study.”	To ensure consistency in renal function data
7.3. Blinding 9.4.1. Primary and Secondary Endpoints	Added "Infection Adjudication Committee (IAC)" for adjudication of opportunistic infections.	For clarification

Section # and Name	Description of Change	Brief Rationale
8.1. Discontinuation from Study Drug	Added ATE as a permanent discontinuation criterion of investigational product.	To clarify the secondary endpoint of ATE as a specific condition under which study medication must be discontinued.
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 the sentence “Serious infection is defined as all infections that meet SAE criteria (Section 9.2.1).”	To clarify definition of serious infection.
10.3.4. Interim analyses	Added sentence “Ad hoc interim analyses may be conducted to address regulatory requests. The data for ad hoc interim analyses will be submitted to the DMC in accordance with the DMC charter.”	To make provision for ad hoc interim analyses for addressing regulatory requests
Appendix 5: 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

Table of Contents

Section	Page
Protocol I4V-MC-JAJD(f) (RA-BRANCH) A Randomized, Controlled Pragmatic Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis	1
Protocol Amendment Summary of Changes Table.....	2
Table of Contents	4
1. Synopsis.....	10
2. Schedule of Activities.....	13
3. Introduction	19
3.1. Background.....	19
3.2. Study Rationale	20
3.3. Benefit/Risk Assessment.....	20
4. Objectives and Endpoints	22
5. Study Design	23
5.1. Overall Design.....	23
5.2. End of Study Definition.....	26
5.3. Scientific Rationale for Study Design	26
5.4. Justification for Dose.....	29
6. Study Population	30
6.1. Inclusion Criteria	30
6.2. Exclusion Criteria.....	32
6.3. Screen Failures	36
7. Treatments	37
7.1. Treatments Administered	37
7.1.1. Packaging and Labelling.....	37
7.2. Method of Treatment Assignment.....	37
7.2.1. Selection and Timing of Doses	38
7.2.2. Dose Adjustment for Renal Impairment	38
7.3. Blinding.....	38
7.4. Dosage Modification	39
7.5. Preparation/Handling/Storage/Accountability	39
7.6. Treatment Compliance	39
7.7. Concomitant Therapy	40
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	42
9.	Study Assessments and Procedures.....	43
9.1.	Efficacy Assessments	43
9.2.	Adverse Events	43
9.2.1.	Serious Adverse Events	44
9.2.1.1.	Suspected Unexpected Serious Adverse Reactions	45
9.3.	Treatment of Overdose	45
9.4.	Safety	45
9.4.1.	Primary and Secondary Endpoints	45
9.4.2.	Physical Examination.....	45
9.4.3.	Laboratory Tests	46
9.4.4.	Chest X-Ray and Tuberculosis Testing	46
9.4.5.	Hepatitis B Virus DNA Monitoring.....	46
9.4.6.	Safety Monitoring	46
9.4.6.1.	Venous Thromboembolic Event Assessment.....	47
9.4.6.2.	Hepatic Safety Monitoring	47
9.5.	Pharmacokinetics.....	47
9.6.	Pharmacodynamics.....	48
9.7.	Biomarkers	48
9.8.	Medical Resource Utilization and Health Economics.....	48
10.	Statistical Considerations	49
10.1.	Sample Size Determination	49
10.2.	Populations for Analyses.....	50
10.3.	Statistical Analyses.....	50
10.3.1.	General Statistical Considerations	50
10.3.1.1.	Analysis Methods.....	50
10.3.1.2.	Censoring Rules	50
10.3.1.3.	Handling of Dropouts or Missing Data	51
10.3.1.4.	Multiple Comparisons/Multiplicity.....	51
10.3.2.	Treatment Group Comparability	51
10.3.2.1.	Patient Disposition and Duration of Exposure and Follow-Up	51
10.3.2.2.	Patient Characteristics	51
10.3.2.3.	Concomitant Therapy	52
10.3.2.4.	Treatment Compliance	52
10.3.3.	Safety Analyses.....	52

10.3.3.1. Primary Analyses	52
10.3.3.2. Secondary Analyses	52
10.3.3.3. Other Safety Analyses	53
10.3.3.3.1. Adverse Events.....	53
10.3.4. Interim Analyses	53
11. References	55
12. Appendices	59

List of Tables

Table		Page
Table JAJD.1.	Schedule of Activities	13
Table JAJD.2.	Objectives and Endpoints	22
Table JAJD.3.	Treatment Regimens.....	37
Table JAJD.4.	Analysis Populations	50

List of Figures

Figure

Page

Figure JAJD.1. Study I4V-MC-JAJD pragmatic design.	23
---	----

List of Appendices

Appendix		Page
Appendix 1.	Abbreviations and Definitions.....	59
Appendix 2.	Clinical Laboratory Tests	63
Appendix 3.	Study Governance Considerations	64
Appendix 4.	Hepatic Monitoring Tests for Treatment-Emergent Abnormality	68
Appendix 5.	Provisions for Changes in Study Conduct During Exceptional Circumstances	69
Appendix 6.	Protocol Amendment History.....	74

1. Synopsis

Title of Study:

A Randomized, Controlled Pragmatic Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis

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 (Smolen et al. 2016). These patients are also at 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. 2018)
 - deep vein thrombosis (DVT) and pulmonary embolism (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; Aviña-Zubieta et al. 2012)
- overall early mortality (Muru et al. 1985; Sihvonen 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) (Fleischmann et al. 2017; Taylor et al. 2017). 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).

The present randomized, comparator-controlled pragmatic study (I4V-MC-JAJD) is to evaluate the safety of baricitinib in patients with RA receiving routine clinical care and will be conducted concurrently with a traditional randomized, comparator-controlled study I4V-MC-JAJA (JAJA). The pragmatic Study JAJD shares primary, secondary, and safety-related exploratory objectives with Study JAJA, as well as similarly adjudicated endpoints. Study JAJD is designed to capture one-third and may potentially capture one-half of the planned total VTE events to be observed between these 2 safety trials. Study JAJD will complement Study JAJA by collecting information from a real-world setting. This will broaden the generalizability of results to RA

patients receiving treatment with baricitinib who might not have participated in traditional clinical trials.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To compare the risk of VTE among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors	Time from first dose of study treatment to first event of VTE
Secondary (Not Multiplicity Controlled) To compare the risk of key safety outcomes among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors To compare the risk of key safety outcomes among patients with RA treated with each baricitinib dose to similar patients treated with TNF inhibitors	Time from first dose of study treatment to first event of: ATE MACE Malignancy (excluding NMSC) Serious infection Opportunistic infection Time from first dose of study treatment to first event of: VTE ATE MACE Malignancy (excluding NMSC) Serious infection Opportunistic infection

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

Summary of Study Design

Study I4V-MC-JAJD (JAJD) is a Phase 3b/4, multicenter, randomized, parallel-group, active-controlled, pragmatic, 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 risk of VTE and other key safety endpoints in patients with RA receiving routine clinical care. Consistent with the pragmatic intent of this study, once randomized, treatment will be provided through mechanisms available to patients in routine care and 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), unless stopped 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 years, if the study runs to its full conclusion.

Number of Patients

Approximately 1300 patients will be randomized to ensure that the planned number of patients with primary endpoint events will be observed.

Statistical Analysis:

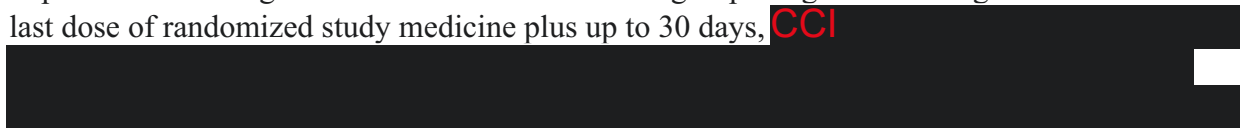
The results of this clinical study will be combined analytically with another randomized study (JAJA) running concurrently and comparing the same 3 treatment groups to estimate the relative risk of VTE for baricitinib (combined doses and individual dose groups) versus TNF inhibitors. The primary, inferential 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 JAJD and JAJA who receive at least 1 dose of study medication and have data available from at least the first postbaseline contact.

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



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 at the time of any rescue (for analyses of individual baricitinib dose groups) or initiation of a nonpermitted RA treatment. Additional analyses without censoring may also be conducted.

2. Schedule of Activities

Table JAJD.1. Schedule of Activities

	Screening	Treatment						Comments
Visit Number	V1a	V2a	V3b	V4b	V5+c	ET	FVd	Per footnote b, V3 and V4 may be conducted over the phone if COVID-related reasons preclude an in-person visit. Per footnote c, V5+ are telephone interactions. All other scheduled study visits (including ET and FV) are in-person.
Study Week		0	12	28	Week 40, and every 12 weeks thereafter	Any	-	
Permitted Window, Days	-42 to 0	1	± 7	± 7	± 14	Any	0 to + 14	
Procedures and Assessments								
Informed consent	X							Written informed consent must be obtained before any JAJD study procedures or assessments.
Demographics	X							
Consent to access claims data	X							Consents will be requested to access patient administrative claims data (a) over the study period, (b) in the year prior to entering the study.
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. Subsequent physical examinations may be symptom-directed.
Symptom-directed physical examination		X	X ^b	X ^b		X	X	Per footnote b, due to COVID-related issues V3 and V4 may be conducted over the phone with the exception of the symptom-directed physical examination. If a symptom points to an adverse event, or other reason for the patient to be seen in person, the investigator should perform the appropriate follow-up.
Height	X							

	Screening	Treatment						Comments
Visit Number	V1 ^a	V2 ^a	V3 ^b	V4 ^b	V5 ^{+c}	ET	FV ^d	Per footnote b, V3 and V4 may be conducted over the phone if COVID-related reasons preclude an in-person visit. Per footnote c, V5+ are telephone interactions. All other scheduled study visits (including ET and FV) are in-person.
Study Week		0	12	28	Week 40, and every 12 weeks thereafter	Any	-	
Permitted Window, Days	-42 to 0	1	± 7	± 7	± 14	Any	0 to + 14	
Weight	X	X						In addition to scheduled assessments, these should also be performed according to clinical standard of care.
Vital signs (blood pressure, pulse rate, temperature)	X	X						
Substance use (tobacco)	X							For patients randomized prior to addition of this activity, the substance use should be assessed at the next visit (protocol-specified or SOC) and the eCRF completed with the actual date of the assessment, despite not being assessed at Visit 1.
Tuberculosis test	X ^e							See Exclusion Criteria [18] and [19]. Acceptable TB test methods are QuantiFERON [®] -TB Gold, T-SPOT [®] .TB, or PPD test (with results assessed 48 to 72 hours after PPD placement).
Chest x-ray	X ^e							For patients with a positive screening TB test.
Previous Rheumatoid Arthritis therapy	X	X						
Review inclusion/exclusion criteria	X	X						
Preexisting conditions	X	X						
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.

	Screening	Treatment						Comments
Visit Number	V1 ^a	V2 ^a	V3 ^b	V4 ^b	V5+ ^c	ET	FV ^d	Per footnote b, V3 and V4 may be conducted over the phone if COVID-related reasons preclude an in-person visit. Per footnote c, V5+ are telephone interactions. All other scheduled study visits (including ET and FV) are in-person.
Study Week		0	12	28	Week 40, and every 12 weeks thereafter	Any	-	
Permitted Window, Days	-42 to 0	1	± 7	± 7	± 14	Any	0 to + 14	
Adverse events		X	X ^b	X ^b	X	X	X	Including SAEs, AEs leading to study discontinuation, and AEs leading to changes in study medication (permanent discontinuation or temporary interruption). Per footnote b, V3 and V4 may be conducted over the phone, if COVID related issues preclude an in-person visit. AE symptoms may determine if a symptom-directed physical requiring an in-person visit is deemed necessary by the investigator.
Concomitant medications	X	X	X	X	X	X	X	
Log into the EDC system	X	X	X	X	X	X	X	
Randomization		X						Patients will be randomized with stratification CCI  The screening eGFR result must be entered on the CRF at Visit 2 for appropriate baricitinib dose adjustment to occur if necessary (Section 5.4). If the patient is randomized to baricitinib 4 mg, the investigator is responsible for ensuring the appropriate baricitinib dose is prescribed based upon screening eGFR and dosage adjustment requirements outlined in Section 7.2.2.
Study medication compliance assessed			X	X	X	X	X	
RA Assessments								
Patient's Global Assessment of Disease Activity (GAD)		X						

	Screening	Treatment						Comments
Visit Number	V1 ^a	V2 ^a	V3 ^b	V4 ^b	V5+ ^c	ET	FV ^d	Per footnote b, V3 and V4 may be conducted over the phone if COVID-related reasons preclude an in-person visit. Per footnote c, V5+ are telephone interactions. All other scheduled study visits (including ET and FV) are in-person.
Study Week		0	12	28	Week 40, and every 12 weeks thereafter	Any	-	
Permitted Window, Days	-42 to 0	1	± 7	± 7	± 14	Any	0 to + 14	
Health Assessment Questionnaire-Disability Index (HAQ-DI)		X						
Physician's GAD		X						
Tender joint count (TJC)/Swollen joint count (SJC) (28 joints)	X	X						
Laboratory Tests								
hsCRP		X ^e						The results of this test are not required prior to randomization.
Rheumatoid Factor/ACPA	X ^e							
Hepatitis C Virus antibody testing	X ^e							For patients who are positive for HCV antibody, a follow-up test for HCV ribonucleic acid (RNA) should be performed. Patients who are positive for HCV antibody and negative for HCV RNA may be enrolled.
Hepatitis B Virus serology (HBsAg, HBcAb, HBsAb)	X ^e							For patients who are positive for HBcAb, testing for HBV DNA should be performed. Patients who are positive for HBcAb and negative for HBV DNA may be enrolled.
HBV deoxyribonucleic acid (DNA)	X ^e							As per clinical standard of care, for patients who are HBcAb positive at screening, it is recommended that patients be monitored for HBV DNA post-randomization (no less frequently than every 6 months and accompanied by liver chemistry including ALT (Section 9.4.5)).

	Screening	Treatment						Comments
Visit Number	V1 ^a	V2 ^a	V3 ^b	V4 ^b	V5+ ^c	ET	FV ^d	Per footnote b, V3 and V4 may be conducted over the phone if COVID-related reasons preclude an in-person visit. Per footnote c, V5+ are telephone interactions. All other scheduled study visits (including ET and FV) are in-person.
Study Week		0	12	28	Week 40, and every 12 weeks thereafter	Any	-	
Permitted Window, Days	-42 to 0	1	± 7	± 7	± 14	Any	0 to + 14	
Pregnancy test	X ^e							For all women of childbearing potential, a pregnancy test (urine or serum) will be performed prior to randomization.
Clinical chemistry	X ^e							In addition to scheduled assessments, these laboratory tests should also be performed according to clinical standard of care. Patients should not eat or drink anything except water for 12 hours prior to fasting lipid sample collection.
Fasting lipid panel			X					
Hematology	X ^e							

Abbreviations: ACPA = anti-citrullinated peptide antibodies; AE = adverse event; ALT = alanine aminotransferase; ATE = arterial thromboembolic event; BMI = body mass index; DMC = data monitoring committee; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; ET = early termination; FV = final visit; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; hsCRP = high-sensitivity C-reactive protein; MACE = major adverse cardiovascular events; NMSC = nonmelanoma skin cancer; PPD = purified protein derivative; RA = rheumatoid arthritis; RNA = ribonucleic acid; SAE = serious adverse event; TB = tuberculosis; TNF = tumor necrosis factor; V = visit; VTE = venous thromboembolism.

- ^a Where applicable (i.e., all pertinent inclusion/exclusion criteria can be assessed), screening and baseline Visits 1 and 2 may be combined to occur on the same day; in such cases, activities noted in the schedule at both Visits 1 and 2 do not need to be conducted twice at that visit. All baseline assessments, including laboratory sampling at Visit 2, must be conducted PRIOR to administration of the first dose of study medication for randomized patients. If Visits 1 and 2 are combined, randomization must occur on the same date as the combined visit.
- ^b Visit 3 should be scheduled to occur as close as possible to 12 weeks after the first dose of study medication, remaining within permissible visit windows. Due to COVID-related issues, Visits 3 and Visit 4 may be conducted over the phone. Take into consideration the symptom-directed physical examination cannot be conducted over the phone. If a symptom points to an AE, the investigator should determine if an in-person visit is required. Documentation of COVID-related issues that preclude an in-person visit is required for these visits to be conducted over the phone.
- ^c Telephone interactions via central call center every 12 weeks (i.e., Weeks 40, 52, 64, 76, etc., as calculated from Visit 2, Week 0; see Section 5.1) until the study reaches the planned number of adjudicated primary endpoint events. During this period and outside of the planned, scheduled in-person and telephone interactions, usual clinical visits are expected to occur according to routine practice. Patients who report experiencing one of the study endpoints during a scheduled telephone visit or show evidence of a potential event based on their administrative claims records are to be contacted by the site. As part of the confirmation or evaluation of such an event, the site or patient may determine that an in-person study visit is desired. These additional in-person study visits, outside of the scheduled activities, will be determined by the site and the participant.

- ^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 permitted window is calculated from time of Sponsor notification to the site.
- ^e Results from testing prior to study entry, but within 6 weeks of planned randomization (Visit 2) may be used, without requiring test repetition at screening.

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 (Smolen et al. 2016). Patients also have increased risk of significant nonmusculoskeletal 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. 2018)
 - 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; 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 2019; 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)
- 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
- 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 pragmatic 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.

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. The approved label recommends 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 (TBL) 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.

In line with the recommendations in the United States Package Insert (USPI), the inclusion and exclusion criteria in the protocol limit enrollment of patients who are at unacceptable risk of serious infections, hepatotoxicity, and fetal malformations, which have been identified as important potential risks or adverse drug reactions with baricitinib (Section 6.2). Testing for liver enzymes and Hepatitis B and C at baseline is being conducted to ensure patients with increased risk of hepatotoxicity are not enrolled.

Venous thromboembolic events have been classified as an adverse drug reaction for baricitinib. With long-term exposures, the incidence rate of VTE in baricitinib-treated patients with RA was similar to the background rates published in the literature for the target population. There was no evidence of increasing or decreasing risk during long-term exposures, and cases of VTE observed during baricitinib treatment were observed in patients with 1 or more recognized risk factors for VTE. Patients with recognized risk factors for VTE will be included in this study to allow evaluation of the primary study endpoint (Sections 5.4 and 6.1). 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 (Sections 6.2 and 8.1).

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of baricitinib, are to be found in the Investigator's Brochure (IB) and the USPI. More detailed information about the known and expected benefits and risks of the TNF inhibitors may be found in the USPI.

4. Objectives and Endpoints

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

Table JAJD.2. Objectives and Endpoints

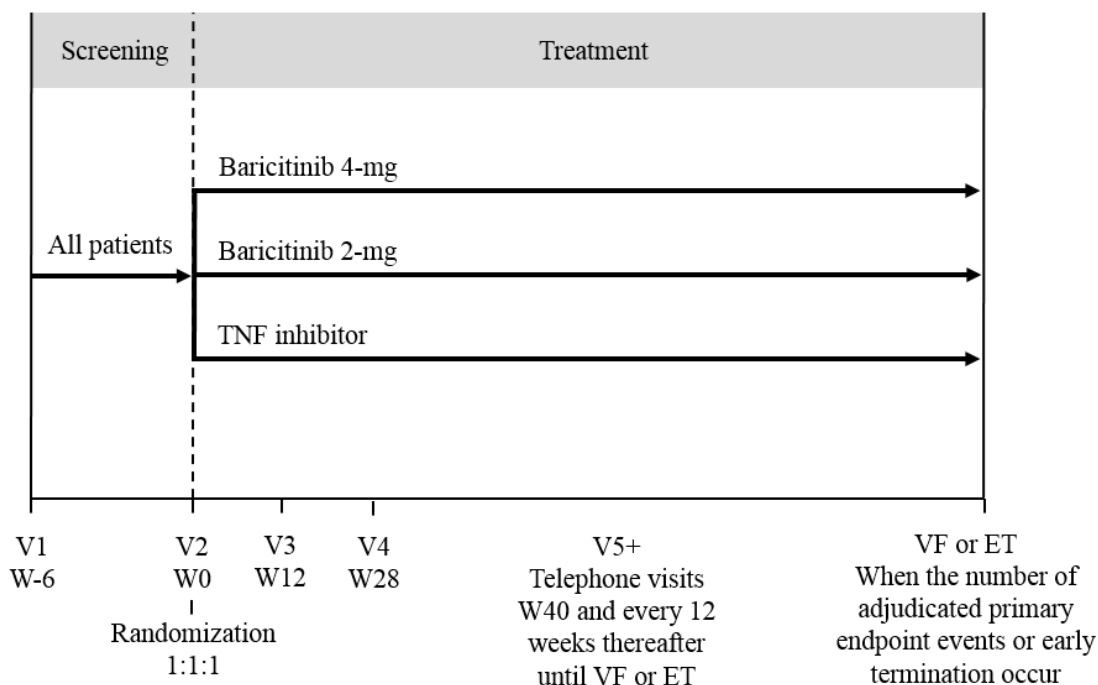
Objectives	Endpoints
Primary To compare the risk of VTE among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors	Time from first dose of study treatment to first event of VTE
Secondary (Not Multiplicity Controlled) To compare the risk of key safety outcomes among patients with RA treated with baricitinib (combined 2- and 4-mg dose groups) to similar patients treated with TNF inhibitors To compare the risk of key safety outcomes among patients with RA treated with each baricitinib dose to similar patients treated with TNF inhibitors.	Time from first dose of study treatment to first event of: ATE MACE Malignancy (excluding NMSC) Serious infection Opportunistic infection Time from first dose of study treatment to first event of: VTE ATE MACE Malignancy (excluding NMSC) Serious infection Opportunistic infection
Exploratory To describe the effects of baricitinib (individual and combined dose groups) and TNF inhibitors with respect to other safety outcomes	Individual components of key safety outcomes, including: ○ ATE ○ MACE ○ Malignancy (excluding NMSC) ○ Serious infection ○ Opportunistic infection All-cause mortality

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

5. Study Design

5.1. Overall Design

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



Abbreviations: ET = early termination; RA = rheumatoid arthritis; TNF = tumor necrosis factor; V = in-person visit until V5 (although V3 and V4 may be remote due to COVID-related issues), thereafter telephone assessment until VF or ET; VF = final visit; W = week.

Recommendations and options for management of RA disease activity are outlined in Section 7.4.

Figure JAJD.1. Study I4V-MC-JAJD pragmatic design.

Data acquisition for this study will occur primarily via conventional case report form (CRF)/SAE data entry by investigational site personnel. In addition, information obtained from patients at telephone visits and from administrative claims data, will be used to support and complement the primary investigational site-based data acquisition procedures.

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). Screening procedures will be performed according to the Schedule of Activities ([Table JAJD.1](#)). 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). 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).

Treatment Period: Eligible patients will be randomized at Week 0, Visit 2 (Table JAJD.1), and will initiate treatment with baricitinib or TNF inhibitor as outlined in Section 7.2. Treatment will be open-label for patients and study site personnel.

Patients will be stratified at randomization according to a history of VTE (DVT/PE), age and body mass index (BMI) combination, and prior inadequate response (IR) or intolerance to a TNF inhibitor. Section 7.7 describes permitted concomitant therapy.

Patients will have regularly scheduled study visits, with in-person clinic visits during the first 6 months (although V3 and V4 may be remote due to COVID-related issues) and, thereafter, telephone interactions conducted by a central call center before an in-person final or early termination visit. These telephone visits will help identify the potential occurrence of study endpoints. All potential occurrences of study endpoints will be referred to the site. Investigators will confirm and evaluate these referrals with participants, enter data, and request medical records, as necessary, for adjudication when the site has identified a study endpoint.

During telephone visits, information obtained from the patients will be used to determine whether additional site interaction is needed for patient evaluation ± recording of protocol-specified AE data (Section 9.2) via CRF ± SAE reporting/adjudication. Information about study medication compliance and concomitant medication use will also be obtained, which may also drive site interaction for data recording. During the study, usual clinic visits are expected to continue according to standard practice including the period when scheduled study visits are by telephone or routine in-person clinic attendance for management and monitoring. Additional in-person study visits may also occur, as needed.

Patients who report experiencing one of the study endpoints during a scheduled telephone visit or show evidence of a potential event based on their administrative claims records are to be contacted by the site. As part of the confirmation or evaluation of such an event, the site or patient may determine that an in-person study visit is desired. These additional in-person study visits, outside of the scheduled activities, will be determined by the site and the participant.

In addition to receiving randomized treatment, patients should be managed according to standard medical practice, using permitted background standard-of-care RA therapy (Section 6.2 and Section 7.7).

Clinical and laboratory assessments will occur according to the Schedule of Activities (Table JAJD.1). Among the assessments outlined in the Schedule of Activities (Table JAJD.1), patients will be directly queried to solicit evidence of primary and secondary endpoint events (VTE [DVT/PE], arterial thromboembolic events (ATE) and MACE, malignancy [excluding nonmelanoma skin cancer (NMSC)], opportunistic infection, and serious infection).

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.

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, with procedures as outlined in the Schedule of Activities ([Table JAJD.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 years.

All procedures to be conducted during the study, including timing of procedures, are indicated in the Schedule of Activities ([Table JAJD.1](#)).

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

Number of Participants

The results of this clinical trial will be combined analytically with another randomized trial (Study JAJA) running concurrently and comparing the same 3 treatment groups to estimate the relative risk of VTE for baricitinib (combined and individual dose groups) versus TNF inhibitors. The JAJD pragmatic trial is expected to contribute between 41 to 63 patients with events, for a combined targeted total of 123 patients with events from the combined studies.

Approximately 1300 participants will be randomized in a 1:1:1 ratio into 3 treatment groups to ensure that a sufficient number of patients with events will be observed to assess the primary and secondary objectives related to VTE. The total number of enrolled patients in this study may be increased up to 2600 without protocol amendment (for example, in cases of delayed enrollment in either the JAJD or JAJA studies or lower than expected event rates, in order to preserve adequate statistical power for the assessment of the primary objective within the planned timeframe).

Administrative Claims Data

Patients who enroll in this study are required to have health insurance coverage (both medical and prescription drug coverage) through a commercial or Medicare plan at the time of enrollment. This provides the opportunity to review administrative claims data as an additional data source to identify the occurrence of study endpoints. This review will supplement the identification of study endpoints by the call center (primary means) and by participants' rheumatologists during routine visits. To support this review, administrative claims data will be requested periodically throughout the study for patients covered by commercial or Medicare plans. When previously unreported events are identified in claims data, investigators will be notified so they can contact the participant and evaluate further. Claims data will also be used to supplement the baseline medical history by permitting the site to clarify any relevant diagnoses or prescriptions that may not have been collected previously. Claims data may also be used to identify dispensing of study medication for patients randomized to TNF inhibitors.

Linkage of study participants to claims data will be based on maximizing the total participants linked with the greatest accuracy. Patients will be queried regularly, during scheduled calls, to provide information about changes to their insurance coverage and healthcare network participation, particularly as it relates to coverage of their care related to RA. Patients who lose coverage through commercial and Medicare plans will continue to be followed through the scheduled calls and their routine rheumatology visits, as they would be in a traditional trial. Some patients may have a change in insurance plan coverage that results in a change to “in-network” providers. In such circumstances, study participation and patient follow-up will continue as long as patients receive care from a study investigator. If a patient transitions care to a non-study physician, participation in the study may continue if the patient is willing and able to return to the study site for protocol-specified visits as well as AE and/or other necessary study follow-up.

The proportion of patients insured through Medicare will be capped at a maximum one-third of study participants, based on a patient’s health insurance at the time of their enrollment. This aligns with the US population, where approximately 30% of patients with RA treated with baricitinib have health insurance through Medicare. The participation of those who transition from commercial insurance to Medicare over the course of the study, as they become age-eligible, will not be affected. This cap will increase the generalizability of results to the US population most likely to receive treatment with baricitinib, including patients at younger ages who are not Medicare-eligible. Such a focus on generalizability is consistent with the more pragmatic intent of this study.

5.2. 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 ([Table JAJD.1](#)) for the last patient.

5.3. Scientific Rationale for Study Design

The study will be active comparator-controlled and blinded to the core study team to minimize bias (Section [7.3](#)). The study is designed to more closely reflect routine care and permit broader generalization of study results to patients and/or clinics that may not typically participate in clinical trials.

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 use of TNF inhibitors are permitted to enroll, as are those with use of a single prior TNF inhibitor, as cycling between different members of this class is a common treatment strategy, and 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 outcomes of interest for this study (Smolen et al. 2017; Porter et al. 2016). 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 to the primary analysis.

The primary outcome measure of this randomized postmarketing safety study is VTE. 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) that will serve both this pragmatic trial and Study JAJA. The CEC 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 (Food and Drug Administration [FDA]/Center for Drug Evaluation and Research [CDER] Guidance 2008). A noninferiority margin of CCI 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 report results 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 toward higher risk with baricitinib.

Several measures assure that study integrity is maintained during planned interim analyses. A data monitoring committee (DMC), common to both Study JAJD and Study JAJA, who are 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  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 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: (a) would not inform the primary analysis; (b) may encourage reduced time per patient on randomized treatment for the primary analysis; and (c) may nullify other study analyses based on randomized group without censoring (for example, 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 is anticipated to occur less frequently than in the baricitinib RA development program (7% IR to comrade [csDMARD-IR] to 22% IR to bDMARD [bDMARD-IR]) in completed Phase 3 studies up to 24 weeks (FDA 2018 [Lilly briefing document for baricitinib advisory committee]). Requiring a minimum period of stability on baricitinib 2 mg before rescue to 4-mg is permissible to assure that the assessment of secondary (2 mg) objectives is not unacceptably impacted by excessive early attrition from this group through rescue. A required minimum period of 52 weeks was

selected as a relevant regulatory landmark for safety exposure. The collection of demographic information includes race and ethnicity.

5.4. Justification for Dose

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 and the USPI (baricitinib), baricitinib exposure increases with decreased renal function (Study I4V-MC-JADL [JADL]). Based on pharmacokinetic 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 should 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 may 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 at screening/enrollment:

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 during screening or within the most recent 6 months prior to study entry.
- [3] Be clinically suitable, in the investigator's opinion, to receive a targeted therapy, such as those being studied in this protocol.
- [4] 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. Visits 1 and 2 may be combined to occur on the same day; in such cases, activities noted in the Schedule of Activities at both Visits 1 and 2 do not need to be conducted twice at that visit. See Section 2 for more details. Joints with significant surgical treatment or injury cannot be counted toward the minimum number of tender and swollen joints for enrollment purposes.
- [5] Have had an IR or intolerance to at least 1 DMARD (synthetic or biologic).

Demographic Characteristics

- [6] Are male or female patients who are at least 18 years of age.
- [7] Have at least one 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

- [8] Nonpregnant, nonbreastfeeding female patient of childbearing potential:
- 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.

- Otherwise, female patients must agree to use 1 highly effective method of contraception (defined as <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.

Note: Female patients of non-childbearing potential include female patients who are infertile due to surgical sterilization, congenital anomaly, or postmenopausal.

Informed Consent

- [9] 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.
- [10] Consent is required to request access to patient administrative claims data (a) over the study period and (b) in the year prior to entering the study.

Other Inclusion Criterion

- [39] Patients must have health insurance coverage (both medical and prescription drug coverage) through a commercial or Medicare plan at the time of enrollment. Patients whose health insurance coverage is through Medicaid, including those with dual Medicare /Medicaid coverage, will not be eligible.
- The proportion of study participants who have coverage through Medicare at the time of enrollment will be capped at a maximum one-third of study participants.

6.2. Exclusion Criteria

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

Medical Conditions

- [11] 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.
- [12] Are pregnant or breastfeeding. Prior to initiation of treatment, female patients of childbearing potential must have a negative pregnancy test during screening.
- [13] 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.
- [14] 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.
- [15] Have active herpes zoster.
- [16] 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.
- [17] 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.
- [18] Have had household contact with a person with active tuberculosis (TB) and did not receive appropriate and documented prophylaxis for TB.

- [19] 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 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).

Prior/Concomitant Medications

- [20] Have received more than 1 prior TNF inhibitor that was:
 - a. discontinued for IR for RA (lack or loss of efficacy), or
 - b. discontinued for intolerance (AE) when used for any indication.
- [21] Have been treated with a bDMARD within 4 weeks of randomization (within 24 weeks of randomization for rituximab).
- [22] Are being treated with more than 2 csDMARDs.
- [23] Have been treated with a JAK inhibitor.
- [24] 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.
- [25] 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.
- [26] Are being treated with an anticoagulant (for example direct and indirect factor Xa inhibitors [including fondaparinux], direct thrombin inhibitors, heparins, enoxaparin, or vitamin K antagonists). Antiplatelet agents, such as aspirin, clopidogrel, prasugrel, are not considered anticoagulants for the purpose of this study.
- [27] Have been previously enrolled (that is, randomized or received study medication) in any baricitinib study (including this JAJD study).

Laboratory Screening Assessments

Laboratory screening should follow the USPI recommendations for both tumor necrosis factor (TNF) inhibitor and baricitinib, including liver enzymes and TBL, hemoglobin, neutrophil and lymphocyte count, eGFR, and hepatitis B and C serology. The baricitinib label criteria for exclusion apply for these parameters, except for liver parameters (not defined in label) and eGFR.

- [28] Have any of the following within 6 weeks of planned randomization (Visit 2):
- a. ALT or AST $>2 \times$ the upper limit of normal (ULN)
 - b. alkaline phosphatase (ALP) $\geq 2 \times$ ULN
 - c. TBL $\geq 1.5 \times$ 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 <30 mL/min/1.73 m²

In the case of any of the aforementioned laboratory abnormalities (Criterion [28]), the tests may be repeated once during screening, and resulting values may be accepted for enrollment eligibility if they meet the eligibility criterion.

- [29] 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.
- [30] Have hepatitis B virus (HBV) infection, defined as:
- a. positive for hepatitis B surface antigen (HBsAg), or
 - b. positive for hepatitis B virus deoxyribonucleic acid (HBV DNA)

It is recommended that patients who are positive for hepatitis B core antibody (HBcAb) be monitored for HBV DNA during the study (Refer to Schedule of Activities [[Table JAJD.1](#)]).

- [31] 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

- [32] Are currently enrolled in or have discontinued within 4 weeks of screening from any other clinical trial involving a study medication 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.

- [33] Are largely or wholly incapacitated, permitting little or no self-care, such as being bedridden.
- [34] 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.
- [35] Are unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.
- [36] 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.
- [37] Are Lilly or Incyte employees or their designee(s).
- [38] In the opinion of the investigator, are at an unacceptable risk for participating in the study for any reason.

Patients with laboratory test results which did not meet the inclusion/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/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 ([Table JAJD.1](#)), and will be assigned a new identification number.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of baricitinib 4-mg or 2-mg doses, administered orally once daily, with TNF inhibitors, administered according to the local product label. [Table JAJD.3](#) shows the treatment regimens. Provision of the 4-mg baricitinib dose is expected to occur through prescription for two 2-mg tablets.

Table JAJD.3. Treatment Regimens

Treatment Group	Treatments Administered
Baricitinib 4-mg QD ^a	2 baricitinib 2-mg tablets
Baricitinib 2-mg QD	1 baricitinib 2-mg tablet
TNF inhibitor ^b	adalimumab or etanercept administered according to the local product label

Abbreviations: eGFR = estimate glomerular filtration rate; 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 2-mg baricitinib QD until and unless the patient later qualifies for rescue to baricitinib 4 mg (see [Section 7.4](#)).
- ^b Patients who have previously been treated with a TNF inhibitor will be prohibited from receiving a TNF inhibitor that they had previously discontinued due to IR or intolerance.

Consistent with practice in routine clinical care, the investigator or their designee is responsible for the following:

- explaining the correct use of the study medication to the patient
- verifying that instructions are followed properly.

7.1.1. Packaging and Labelling

Baricitinib: will be supplied by a licensed pharmacy.

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, and prior IR, or intolerance to a TNF inhibitor, as defined in the statistical analysis plan (SAP).

Assignment to treatment groups will be determined by a computer-generated random sequence using a randomization system.

7.2.1. Selection and Timing of Doses

Following randomization at Visit 2:

Baricitinib: Patients will receive a prescription for the study medication and will obtain their medication from a pharmacy. If the patient is randomized to baricitinib 4 mg, the investigator is responsible for ensuring the appropriate baricitinib dose is prescribed based upon screening eGFR and dosage adjustment requirements outlined in Section 7.2.2. The first dose should be taken as soon as the medication is received, on or after Visit 2. Those assigned to the 2-mg dose should take 1 tablet orally each day, without regard to food, and, if possible, at approximately the same time every day. Those assigned to the 4-mg dose will proceed similarly, but should take 2 tablets orally each day instead of 1.

TNF inhibitor: Patients will receive a prescription for the study medication and will obtain their medication from a pharmacy. The first dose should be taken as soon as the medication is received, on or after Visit 2. Dosing will be according to approved labeling.

7.2.2. Dose Adjustment for Renal Impairment

The dose of baricitinib assigned may require adjustment based on the patient's eGFR value at screening. This value must be available at the time of randomization at Visit 2. Adjustment will proceed as follows:

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) are to receive a baricitinib 2-mg once-daily dose.

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

When calculating eGFR, the same formula should be applied consistently for each patient throughout the study.

The rationale for dose adjustment in patients with documented renal impairment and receiving baricitinib is detailed in Section 5.4.

Should patients receiving baricitinib 2 mg require rescue to baricitinib 4 mg later in the trial – after a minimum of 1 year of treatment with baricitinib 2 mg – the most recent eGFR value obtained must be used to determine eligibility for rescue to baricitinib 4 mg, as detailed in 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 10.3.4.

7.4. Dosage Modification

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 (if not constrained by renal function based on the most recent eGFR) (see Section 7.2.2). 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 (etanercept/adalimumab)
 - b. use of the specific TNF inhibitor to which patients had prior IR or intolerance prior to the study, is not permitted
 - c. 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

Storage and handling instructions are provided on the product packaging for baricitinib and TNF inhibitors, and should be followed. Study medication will be dispensed at pharmacies directly to patients.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed by the site during the treatment period and will be supplemented through patient reporting to the call center and with records of pharmacy co-pay cards (baricitinib and TNF inhibitor). Deviations from the prescribed dosage regimen that are identified during scheduled or usual care visits 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 study medication. Patients found to be noncompliant with the study medication 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

Patients should be assessed for use of the following medications at baseline with start and stop dates recorded (as applicable). Post-baseline, collection of information on concomitant medications will focus on those used in association with protocol-specified adverse events (Section 9.2) and any use of DMARDs, corticosteroids or opioids. In addition, administration of SARS-CoV-2 vaccines should be captured in the eCRF.

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

- JAK inhibitors or other tsDMARDs (other than baricitinib).
- bDMARDs other than TNF inhibitor study medication (etanercept/adalimumab).
- More than 2 background csDMARDs (at any time prior to permanent discontinuation of study medication; a maximum of 3 simultaneous csDMARDs may be used thereafter).
- Live vaccines (at any time prior to permanent discontinuation of study medication).
- OAT3 inhibitors (at any time prior to permanent discontinuation of study medication).
- 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.

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 for a patient to temporarily interrupt or permanently discontinue study medication during the study. Except where specific direction is provided in this protocol, please refer to the study medications' local product labels 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

Treatment that is temporarily interrupted because of an AE or abnormal laboratory value may be restarted, at the discretion of the investigator, according to the USPI recommendations. Retest timing and frequency is at the investigator's discretion, based on routine clinical practice. Baricitinib is not recommended for use in patients with estimated GFR of $<30 \text{ mL/min/1.73 m}^2$.

Permanent discontinuation

Reasons that may lead to permanent discontinuation of study medication include the following:

Subject decision

- the patient requests to discontinue study medication.

Investigator decision

- the investigator decides that the patient should be discontinued from study medication.

Serious or opportunistic infection that in the opinion of the investigator merits the study medication 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 $<30 \text{ mL/min/1.73 m}^2$ for a patient taking baricitinib 2 mg or if eGFR $<60 \text{ mL/min/1.73 m}^2$ 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)

The date of the last dose of study medication must be captured in the eCRF.

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 which require permanent discontinuation from study medication (Section 8.1).

The patient requires chronic (>30 days) treatment with an anticoagulant (Section 7.7).

If a patient prematurely permanently discontinues study medication 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 continue follow-up visits, the site and call center 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 JAJD.1, ET 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 respond to scheduled visits and is unable to be contacted by the study site. Study personnel are expected to make diligent attempts to contact patients who fail to respond to a scheduled visit or were, otherwise, unable to be followed up by the site.

9. Study Assessments and Procedures

This study relies primarily on assessments conducted in the course of routine clinical care.

[Table JAJD.1](#) 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.

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

Given that the purpose of this study is to assess specific safety concerns, AE data collection during the treatment period will focus on **protocol-specified AEs**, which must be reported to the sponsor:

- Targeted AEs (VTE, ATE, MACE and other adjudicable CV events, malignancy, potential opportunistic infection, and serious infection)

- All SAEs (Section [9.2.1](#))

- All COVID-19 infections (serious or nonserious)

- All AEs related to permanent or temporary study medication discontinuation.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any protocol-specified event.

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

The investigator remains responsible for following, through an appropriate healthcare option, AEs that are serious, or that caused the patient to discontinue the study medication before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of all preexisting conditions of each patient, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in preexisting conditions (for example, changes in severity, seriousness, or consequences, such as temporary interruption/permanent study medication discontinuation), when it is related to a protocol-specified AE, and any new protocol-specified AEs that arise during the study.

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 study medication.

The investigator will interpret and document whether or not a protocol-specified 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 study medication, study device, and/or study procedure and the AE. The investigator answers “yes”/“no” when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs, unless the underlying medical condition has worsened during the course of the study and meets the criteria for a protocol-specified AE.

If the study medication 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 discontinuation of treatment.

Where related to a protocol-specified AE, 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. Rheumatoid arthritis flares must be reported as an AE only if they fulfill one of the criteria for protocol-specified AE (e.g., SAE or result in temporary or permanent discontinuation of study medication).

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.

Adverse events occurring after signing the ICF are assessed for seriousness criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received study medication. However, if an SAE occurs after signing the ICF, but prior to receiving study medication, 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 serious hepatic AEs should have additional data collected, using the eCRF.

Pregnancy (during maternal or paternal exposure to study medication) 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.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.3. Treatment of Overdose

Refer to the IB and USPI for baricitinib and the USPI for TNF inhibitors included in this study.

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, shared with Study JAJA, will adjudicate primary endpoint events, and selected secondary events, including ATE, MACE (myocardial infarction, stroke, and cardiovascular death) and opportunistic infections. The common 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. Physical Examination

For each patient, physical examinations will be conducted according to the Schedule of Activities (Table JAJD.1). One complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1 (Screening). All remaining physical examinations throughout the study may be symptom-directed, in accordance with routine clinical practice.

9.4.3. Laboratory Tests

For each patient, laboratory tests detailed in [Appendix 2](#) should be conducted according to the Schedule of Activities ([Table JAJD.1](#)). Otherwise, the nature and frequency of laboratory testing should follow routine clinical practice.

Lilly will request available local laboratory results, as required for adjudication of study endpoints.

9.4.4. Chest X-Ray and Tuberculosis Testing

Patients will be tested at screening (Visit 1) for evidence of active or latent TB, as described in the exclusion criteria (Section [6.2](#)). For patients with a positive TB test, a posterior-anterior view chest x-ray will be obtained locally at screening (Visit 1). The chest x-ray will be reviewed by the investigator or their designee to exclude patients with active TB infection.

Investigators should follow local guidelines/product labeling for monitoring patients for TB.

9.4.5. Hepatitis B Virus DNA Monitoring

As per standard of care, enrolled patients with positive HBcAb results at screening should be monitored during the study for HBV DNA, accompanied by liver chemistry, including ALT, as outlined in the Schedule of Activities ([Table JAJD.1](#)).

Should HBV DNA be detected, consultation with a hepatologist is recommended.

9.4.6. 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 remain blinded 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. 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, as 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.

9.4.6.1. 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.

9.4.6.2. Hepatic Safety Monitoring

If an investigator observes that a study patient experiences elevated ALT $\geq 3 \times$ ULN, ALP $\geq 2 \times$ ULN, or elevated TBL $\geq 2 \times$ ULN, liver testing 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.

Additional tests ([Appendix 4](#)) should also be performed to determine the etiology of the liver abnormality, as clinically indicated. 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 ([Appendix 4](#)) 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 an SAE.

9.5. Pharmacokinetics

This study is not planned to include pharmacokinetic assessments.

9.6. Pharmacodynamics

This study is not planned to include pharmacodynamic assessments.

9.7. Biomarkers

This study is not planned to include the collection of biomarker samples.

9.8. 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 (JAJD) will be combined analytically with another randomized trial (Study JAJA), run concurrently, and compare 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 CCI 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 CCI based on the upper limit of the CCI confidence interval (CI) of the hazard ratio, assuming a true hazard ratio of CCI. Following this assumption and prorating to approximately CCI events across 2 treatment groups (1 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 CCI based on a similar approach.

Studies JAJA and JAJD, together, aim to enroll approximately 3900 patients (2600 in JAJA, 1300 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 CCI per 100 patient-years in each of the baricitinib dose groups and CCI 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 CCI. The CCI incidence rate was estimated from the baricitinib RA clinical program, using all patients treated with baricitinib through CCI, and subsetting for patients who would meet entry criteria for this study CCI.

The total number of enrolled patients in this study may be increased up to 2600 without protocol amendment in cases of reduced enrollment in Study JAJA, 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 maximum, if Studies JAJD and JAJA are not stopped early, CCI of the CCI planned patients with events between these 2 studies will come from Study JAJD. However, Study JAJD may stop early, based on the number of events estimated for the planned interim analyses (see Section 10.3.4).

Sample size and power estimates were obtained from EAST® software (Cytel, Cambridge, Massachusetts, USA) Version 6.4, 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 JAJD.4](#).

Table JAJD.4. Analysis Populations

Population	Description
Safety Population	The safety population is defined as all randomized patients who receive at least 1 dose of study medication 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 study medication 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.

All analyses will be conducted, using the safety population. 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 (CSR). 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 SAP(s).

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 IR or intolerance to a TNF inhibitor, and geographic region [used only in Study JAJA]) 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. Primary and secondary noninferiority assessments will assess whether the hazard ratio is <1.8 (for combined baricitinib groups) or <2.0 (for individual baricitinib dose groups) relative to the TNF inhibitor group.

Poisson regression will be used to evaluate incidence rates of AEs, SAEs, and discontinuations.

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 in-person and telephone visits to provide additional safety data. Data for analysis will be utilized, as indicated in the previous section on censoring rules.

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 (for example, mean and standard deviation) and distributional summaries, including Kaplan–Meier estimates. Start and stop dates for study medication will be recorded by the investigational sites. Supplemental information will also be available from telephone visits and records of co-pays made when prescriptions are dispensed. Any evidence of missed payments will be resolved by querying the patient.

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.

10.3.2.4. Treatment Compliance

Compliance with treatment for baricitinib and TNF inhibitors will be recorded by investigational sites. In addition, supplemental information may also be available from copay records. Any discrepancies for study medication will be resolved by querying the patient at the next site visit (remote or in-person visits). 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 in pooled Studies JAJD and JAJA against the TNF inhibitor group from the same 2 studies 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 IR or intolerance to a TNF inhibitor, and geographic region [used only in Study JAJA]) 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 across pooled Studies JAJA and JAJD for:

- ATE
- MACE
- malignancy (excluding NMSC)
- opportunistic infection
- 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. 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

Protocol-specified AEs (Section 9.2) will be summarized using the Medical Dictionary for Regulatory Activities (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.

10.3.4. Interim Analyses

A DMC will oversee the conduct of this study in conjunction with Study JAJA. The DMC will consist of members external to Lilly who have expertise in rheumatology, statistics, or other appropriate specialties. The 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 2 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

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

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.; 2019.
- 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.
- 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/regulatory-information/search-fda-guidance-documents/diabetes-mellitus-evaluating-cardiovascular-risk-new-antidiabetic-therapies-treat-type-2-diabetes>. 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.

- 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).
- Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol.* 1971;44(526):793-797.
- 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. *Eur Heart J*. 2018;39(39):3608-3614.
- 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, van 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.
- 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 GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, Schalm S, Murias S, Dare JA, Brown D, Stone DL, Gao L, Klausmeier T, Foell D, de Jesus AA, Chapelle 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, Nickleit 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. *J Clin Invest*. 2018;128(7):3041-3052.
- 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, Akl 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, American College of Rheumatology. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25.
- Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023-2038.

- 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, Buttgereit 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 JM, 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, Reyes Gonzaga J, 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.
- 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
ACPA	Anti-citrullinated peptide antibody
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
CDER	Center for Drug Evaluation and Research
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.
CRF	case report form
CRP	C-reactive protein

Term	Definition
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSR	clinical study report
CV	cardiovascular
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee
DNA	deoxyribonucleic acid
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
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FV	final visit
GAD	Global Assessment of Disease
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
IAC	infection adjudication committee

Term	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IL	interleukin
IR	inadequate response
IRB	institutional review board
JAK	Janus kinase
LDL	low-density lipoprotein
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NMSC	nonmelanoma skin cancer
OAT3	organic anion transporter 3
PE	pulmonary embolism
PPD	purified protein derivative
PYE	patient years of exposure
QD	once daily
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAVI	stimulator of interferon genes-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.
SJC	swollen joint count
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis

Term	Definition
TBL	total bilirubin level
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
USPI	United States Package Insert
VTE	venous thromboembolism

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology	Clinical Chemistry
Hemoglobin	Serum Concentrations of:
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Absolute count of	Direct bilirubin
Neutrophils	Alkaline phosphatase (ALP)
Monocytes	Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase
Eosinophils	Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase
Basophils	Creatinine
Platelets	Estimated glomerular filtration rate (eGFR)
	Creatine phosphokinase (CPK)
Autoantibodies	
Rheumatoid factor	Other Tests
Anticitrullinated peptide antibodies	Pregnancy test (females only) ^b
	Hepatitis B surface antigen (HBsAg)
Lipid Profile ^a	Hepatitis B surface antibody (HBsAb)
Total cholesterol	Hepatitis B core antibody (HBcAb)
High-density lipoprotein cholesterol (HDL-C)	Hepatitis C antibody ^c
Low-density lipoprotein cholesterol (LDL-C)	HBV DNA ^d
Triglycerides	HCV RNA ^e
	PPD or QuantiFERON®-TB Gold, or T-SPOT®.TB ^e

Abbreviations: HBV DNA = hepatitis B virus deoxyribonucleic acid; HCV RNA = hepatitis C virus ribonucleic acid; PPD = purified protein derivative; RBC = red blood cells; TB = tuberculosis; WBC = white blood cells.

- ^a 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.
- ^b For women of childbearing potential, pregnancy tests (local laboratory) will be performed prior to randomization and may be performed, thereafter, at the discretion of the investigator or according to local regulations or guidelines.
- ^c A confirmatory test of HCV RNA should be performed if the patient is positive for HCV antibody.
- ^d HBV DNA testing should be performed in patients who tested positive for HBcAb at screening.
- ^e Where the QuantiFERON®-TB Gold test or T-SPOT® TB test is available, either test may be used instead of the PPD TB test.

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 study medication.

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 Brochure (IB), and updates during the course of the study
- informed consent form
- other relevant documents (for example, 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.

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 (for example, 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 3.3. 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-JAJD 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-designated medical monitor.

Hepatic Monitoring Tests

Hepatic Hematology^a	Haptoglobin^a
Hemoglobin	
Hematocrit	Hepatic Coagulation^a
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	Hepatic Serologies^a
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 = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

^a Assayed by local laboratory.

Appendix 5. 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

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, assessment 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. Visit 1 and Visit 2 cannot be performed remotely, even in exceptional circumstances. Procedures performed at such visits include, but are not limited to, review of concomitant medication, assessment of weight and vital signs, assessment of adverse and targeted events, dispensation and assessment of compliance of investigational product, patient and collection of blood and urine samples. The below procedures also may be performed, but require additional qualifications and sponsor approval: Symptom-directed physical examination; Physician's GAD and Tender joint count (TJC)/Swollen joint count (SJC) (28 joints)"

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 adverse events (AEs), serious adverse events (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.

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.

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.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at V1/V2 are valid for a maximum of 60 days. Specific tests may be repeated at the discretion of the PI prior to randomization.

The following rules will be applied for active, nonrandomized participants whose participation in the study must be interrupted due to exceptional circumstances.

If screening is interrupted for less than 60 days from screening visits to randomization visit, the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 60 days from screening visit 1/2. The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the source documentation.

The site should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.

If screening is interrupted for more than 60 days from screening visits to randomization visit, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can consent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual Schedule of Activities should be followed, starting at screening visit to ensure participant eligibility by randomization visit. The screening procedures per the usual Schedule of Activities should be followed. Prior to rescreening, the principal investigator should feel confident that the exceptional circumstance will no longer prohibit collection of assessments and procedures per protocol. The medical monitor may be consulted if needed regarding the decision to move forward with rescreening

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. To maximize the possibility that these visits 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

Visit Number	Protocol Specified Day/Week	Protocol Specified Visit Interval Tolerance	Mitigation Extension of Visit Interval Tolerance	Mitigation Study Day Range
V1	≤42 days from V2	N/A	60 days	≤ 60 days from V2
V2	1	N/A	N/A	N/A
V 3	12	± 7 days	± 14 days	
V4	28	± 7 days	± 14 days	
V 5+	Week 40, and every 12 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.

Appendix 6. 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]: 03-Aug-2022

Overall Rationale for the Amendment:

The main rationale for the amendment is to update contraception language for consistency with the informed consent form.

Section # and Name	Description of change	Brief Rationale
Section 4 Objectives and Endpoints	Added all-cause mortality as an exploratory endpoint	To indicate that descriptive analysis of all-cause mortality will be performed
Section 5.1 Overall Design	Updated text regarding claims data linkage	To clarify that the administrative claims process will maximize the number of participants who can be linked with the greatest accuracy
Section 6.1 Inclusion Criteria	Updated Inclusion Criterion 8a and 8b 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	To align with the informed consent form

Amendment [d]: 02-May-2022

Overall Rationale for the Amendment:

The main rationale for the amendment is to add text regarding dose reduction of patients from baricitinib 4 mg to 2 mg dose based on renal constraint post-baseline.

Section # and Name	Description of Change	Brief Rationale
Section 2 Schedule of Activities	Added collection of tobacco use	The use of tobacco is a risk factor for study endpoints and is important to collect for final analyses when studies are combined so that baseline risk is

Section # and Name	Description of Change	Brief Rationale
	Updated text related to randomization for baricitinib 4 mg patients Updated footnote a	assessed in the same manner between Study JAJD and JAJA Clarified that the investigator is responsible to prescribe the correct dose of baricitinib based upon eGFR results (that is, if patient is randomized to baricitinib 4 mg but eGFR <60 mL/min/1.73 m², then for safety reasons the investigator must prescribe the 2 mg dose) Clarified that if V1 and V2 are combined, then randomization must occur on the same date as the combined visit
Section 5.1 Overall Study design	Added text related to handling of patients who have a change in rheumatoid arthritis care during the study	Clarified that patients who transition care to a non-study physician than the principal investigator during the study may continue to participate, provided they are willing to return to the site, as needed, for study assessments
Section 5.3 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 5.4 Justification for Dose	Added text regarding randomization of patients to baricitinib 4 mg and 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 6.1 Inclusion Criteria	Updated criterion [39] to clarify proportion of study participants with	For consistency with the Medicare cap that is denoted in Section 5.1

Section # and Name	Description of Change	Brief Rationale
	coverage through Medicare at time of enrollment	
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 7.2.1 Selection and Timing of Doses	Updated text regarding randomization of patients to baricitinib 4 mg with renal function constraints at time of randomization	Clarified that the investigator is responsible to prescribe the correct dose of baricitinib based upon eGFR results (that is, if patient is randomized to baricitinib 4 mg but eGFR < 60 mL/min/1.73 m ² , then for safety reasons the investigator must prescribe the 2 mg dose)
Section 7.4 Dosage Modification	Updated text regarding the 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	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 list of concomitant medications required to be reported on the eCRF Updated use of prohibited concomitant therapy to indicate that use of anticoagulants for >30 days is not permitted	The CRF instructions indicate that use of DMARDs, corticosteroids or opioids should be captured in the eCRF. In addition, administration of SARS-CoV-2 vaccines should be captured in the eCRF based upon regulatory guidance that impacts of the pandemic should be reported in the final CSR Chronic use of anticoagulant therapy contravenes the primary endpoint of the study. Therefore, clarification of the use of anticoagulants was provided

Section # and Name	Description of Change	Brief Rationale
Section 8.1 Discontinuation from Study Treatment	Updated circumstances for permanent discontinuation of study medication Deleted sub-section on inadvertently enrolled patients	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	Updated list of protocol-specified AEs to include COVID-19 Added clarification about reporting RA flares as AEs	Based upon regulatory guidance since the beginning of the pandemic, the sponsor must summarize impact of COVID-19 on the study within the final CSR, and thus these data must be captured in the clinical database Clarify that although generally RA flares would represent lack of efficacy rather than an AE, there may be 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	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 and 2 mg dose based on renal constraint	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

Section # and Name	Description of Change	Brief Rationale
	will not be censored from the 4-mg dose group	

Amendment [c]: 12-Feb-2021

Amendment Summary for Protocol I4V-MC-JAJD Amendment (c)

Section # and Name	Description of Change	Brief Rationale
Section 2. Schedule of Activities	Added language to clarify that the results of hsCRP testing are not required prior to randomization.	Clarification added due to prior confusion at sites regarding the need for results versus the protocol requirement to collect labs at Visit 2.
Section 5. Study Design Section 6.1. Inclusion Criterion [39]	Updated language to clarify that patients who enroll in this study are required to have health insurance coverage, including medical and prescription drug coverage.	Specification of insurance requirements to avoid confusion and enrollment of patients without this mandatory condition.
Section 5. Study Design	Updated language to indicate that request of administrative claims data for patients covered by commercial or Medicare plans will occur periodically rather than specifying twice per year.	Clarification to allow flexibility based on the state of the trial.
Section 6.2. Exclusion Criteria [19]	Updated details within criterion [19] to exclude patients who have evidence of active TB or untreated/inadequately/inappropriately treated for latent TB.	Detailed criterion for clarity and alignment with the study I4V-MC-JAJA.
Throughout the protocol	Minor formatting and editorial changes.	Minor, therefore not detailed.

Revised Protocol Sections

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

Section 2. Schedule of Activities

	Screening		Treatment							Comments
Visit Number	V1 ^a	V _{2a}	V _{3b}	V _{4b}	V5+ ^c	ET	FV ^d			
Study Week		0	12	28	Week 40, and every 12 weeks thereafter	Any	-			Per footnote b, V3 and V4 may be conducted over the phone if COVID-related reasons preclude an in-person visit.
Permitted Window, Days	-42 to 0	1	± 7	± 7	± 14	Any	0 to + 14			Per footnote c, V5+ are telephone interactions. All other scheduled study visits (including ET and FV) are in-person.
Laboratory Tests										
hsCRP		X								<u>The results of this test are not required prior to randomization.</u>

ET = early termination; FV = final visit; V = visit

- ^a Where applicable (i.e., all pertinent inclusion/exclusion criteria can be assessed), screening and baseline Visits 1 and 2 may be combined to occur on the same day; in such cases, activities noted in the schedule at both Visits 1 and 2 do not need to be conducted twice at that visit. All baseline assessments, including laboratory sampling at Visit 2, must be conducted PRIOR to administration of the first dose of study medication for randomized patients.
- ^b Visit 3 should be scheduled to occur as close as possible to 12 weeks after the first dose of study medication, remaining within permissible visit windows. Due to COVID-related issues, Visits 3 and Visit 4 may be conducted over the phone. Take into consideration the symptom-directed physical examination cannot be conducted over the phone. If a symptom points to an AE, the investigator should determine if an in-person visit is required. Documentation of COVID-related issues that preclude an in-person visit is required for these visits to be conducted over the phone.
- ^c Telephone interactions via central call center every 12 weeks (i.e., Weeks 40, 52, 64, 76, etc., as calculated from Visit 2, Week 0; see Section 5.1) until the study reaches the planned number of adjudicated primary endpoint events. During this period and outside of the planned, scheduled in-person and telephone interactions, usual clinical visits are expected to occur according to routine practice. Patients who report experiencing one of the study endpoints during a scheduled telephone visit or show evidence of a potential event based on their administrative claims records are to be contacted by the site. As part of the confirmation or evaluation of such an event, the site or patient may determine that an in-person study visit is desired. These additional in-person study visits, outside of the scheduled activities, will be determined by the site and the participant.
- ^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 permitted window is calculated from time of Sponsor notification to the site.
- ^e Results from testing prior to study entry, but within 6 weeks of planned randomization (Visit 2) may be used, without requiring test repetition at screening.

Section 5. Study Design

Administrative Claims Data

Patients who enroll in this study are required to have health insurance coverage (both medical and prescription drug coverage) through a commercial or Medicare plan at the time of enrollment. This provides the opportunity to review administrative claims data as an additional data source to identify the occurrence of study endpoints. This review will supplement the identification of study endpoints by the call center (primary means) and by participants' rheumatologists during routine visits. To support this review, administrative claims data will be requested periodically throughout the study for patients covered by commercial or Medicare plans ~~administrative claims data will be requested twice per year. For patients covered by Medicare, claims data will be requested annually to coincide with the availability of updates to Medicare data for patients covered by commercial plans, administrative claims data will be requested twice per year.~~ When previously unreported events are identified in claims data, investigators will be notified so they can contact the participant and evaluate further.

Section 6.1. Inclusion criteria

Other Inclusion Criterion

- [39] Patients must have health insurance coverage (both medical and prescription drug coverage) through a commercial or Medicare plan at the time of enrollment. Patients whose ~~main~~ health insurance coverage is through Medicaid, including those with dual Medicare /Medicaid coverage, will not be eligible.
- a. The proportion of study participants who have coverage through Medicare at the time of enrollment will be capped at approximately 1/3.

Section 6.2. Exclusion Criteria

- [19] 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 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).

~~Have evidence of active TB or untreated/inadequately/inappropriately treated latent TB, based on TB testing and clinical and chest x-ray features.~~

~~Exceptions:~~

- ~~a. Patients with a history of active or latent TB who have documented evidence of appropriate treatment, have no history of re-exposure since their treatment was completed, 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 at screening.~~

~~b. 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.~~

Signature Page for VV-CLIN-068404 v2.0

Approval	PPD 22-Mar-2024 12:28:44 GMT+0000
----------	--------------------------------------

Approval	PPD 22-Mar-2024 13:16:17 GMT+0000
----------	--------------------------------------

Signature Page for VV-CLIN-068404 v2.0