Statistical Analysis Plan I4V-MC-JAJD

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

NCT04086745

Approval date: 21-Jul-2025

1. Statistical Analysis Plan: I4V-MC-JAJD (RA-BRANCH): A Randomized, Controlled Pragmatic Phase 3b/4 Study of Baricitinib in Patients with Rheumatoid Arthritis

Baricitinib (LY3009104) Rheumatoid Arthritis

Study I4V-MC-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 venous thromboembolism (VTE) and other key safety endpoints in patients with rheumatoid arthritis (RA) receiving routine clinical care. Treatment will be open label for patients and study site personnel.

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Protocol I4V-MC-JAJD
[Phase 3b/4]

VV-CLIN-167310

Approved on 21 Jul 2025 GMT

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3. Revision History

SAP Version	Approval Date	Change
1	28 November 2019	Not applicable, original version
2	05 February 2020	The major changes incorporated in Version 2 are as follows: definition of patient noncompliance in Section 6.8 was changed from missing more than 20% of prescribed doses to missing a specific number since the last contact that depends on the assigned treatment.
3	13 May 2020	SAP Version 3 was approved after the first patient visit. The major changes incorporated in Version 3 are as follows: definition of venous thromboembolism (VTE) was updated to clarify that deep vein thrombosis (DVT) will include nonsuperficial below-knee thrombosis events. added a sensitivity analysis consisting of a Cox proportional hazards regression model with study and randomization stratification factors as stratifying variables and treatment group as an explanatory variable per the Food and Drug e)4j h e 5)request.
4	23 September 2024	The revision of Statistical Analysis Plan Version 4 is to allow the use of biosimilars within tumor necrosis factor (TNF) inhibitor treatment arm. No other changes were made to the study design and analysis.
5	See date on cover	SAP Version 5 is the final version and was approved before database lock. The major changes incorporated in Version 5 are as follows: The per protocol population and associated analyses were removed in alignment with the study protocol and the main safety objectives.

		The per-protocol analysis compares the response for treatment A for those who adhere to treatment A with the response for treatment B for those who adhere to treatment B. This estimate does not correspond to a causal estimand (Lipkovich et al. 2020) and is not consistent with the recommendation in ICH E9 (R1). Therefore, we moved this analysis. The wording regarding interim and ad hoc analysis has been aligned with the updates specified in protocol amendment (f) The Statistical Analysis Plans for studies JAJA and JAJD were homogenized Additional safety analyses have been included in the Safety assessments, as per the Program Safety Analysis Plan for Baricitinib Version 7. The section for Administrative Claims has been updated to include the impact of privacy requirements on data access.

4. Study Objectives

4.1. Primary Objective

The primary objective of the study is the following, where venous thromboembolism (VTE) is defined as deep vein thrombosis (DVT, including non-superficial below knee thrombosis) and pulmonary embolism (PE):

Objective	Endpoint
• To compare baricitinib (combined dose groups) to TNF inhibitors with respect to VTE	• Time from first dose of study treatment to first event of VTE

Abbreviations: TNF = tumor necrosis factor; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

If the accumulation of events for VTE is lagging considerably behind what was anticipated when planning study enrollment, then an unblinded assessment will occur after the CCI of the expected patient-years of exposure (PYE) for the final analysis. This is expected to account for at least CCI patient-years (PY) or CCI of the anticipated total PYE. When this unblinded assessment confirms that a 1-sided 95% confidence interval (CI) for the aggregate incidence rate excludes a rate of CCI, the study's primary objective will be modified to the following to rule out an incidence rate difference between groups of CCI provided CCI patients with events have been observed.

Objective	Endpoint
• To compare baricitinib (combined dose groups) to TNF inhibitors with respect to VTE	• Difference in incidence rate of VTE

Abbreviations: TNF = tumor necrosis factor; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

4.2. Secondary Objectives

The secondary objectives of the study are the following:

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

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; MACE = major adverse cardiovascular event; NMSC = nonmelanoma skin cancer; PE = pulmonary embolism; TNF = tumor necrosis factor; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

4.3. Exploratory Objectives

The exploratory objectives of the study are the following:

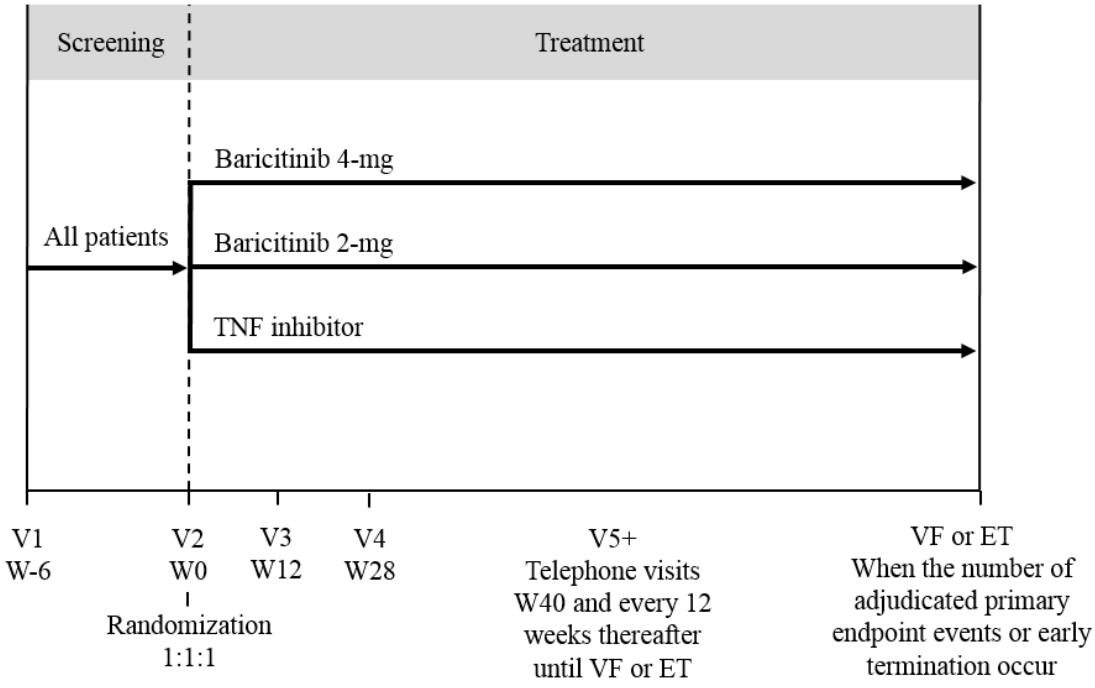
Objectives	Endpoints
To describe the effects of baricitinib (individual and combined dose groups) and TNF inhibitors with respect to other safety outcomes	Individual components of key safety outcomes o VTE o MACE ATE Malignancy (excluding NMSC) Opportunistic infection Serious infection SAEs TEAEs AEs leading to permanent study drug discontinuation

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; MACE = major adverse cardiovascular event; NMSC = nonmelanoma skin cancer; PE = pulmonary embolism; TNF = tumor necrosis factor; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

5. Study Design

5.1. 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 to tumor necrosis factor (TNF) inhibitor (adalimumab or etanercept), administered according to approved local labeling with regard to risk of VTE and other key safety endpoints in patients with rheumatoid arthritis (RA) (Figure JAJD.5.1).



Abbreviations: ET = early termination; TNF = tumor necrosis factor; V = in-person visit until V5, thereafter telephone assessment until VF or ET; VF = final visit; W = week.

Figure JAJD.5.1. Study I4V-MC-JAJD pragmatic design.

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

5.2. Determination of Sample Size

The results of this clinical trial (JAJD) will be combined analytically with another randomized trial (Study I4V-MC-JAJA [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 CCI power to demonstrate that the hazard ratio (HR) for the risk of VTE events in the combined-baricitinib group (ie, across dose groups) relative to the TNF-inhibitor group is CCI based on the upper limit of the 95% CI of the HR, assuming a true HR 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 CCI power to demonstrate that the HR for the risk of VTE in each baricitinib dose group relative to the TNF inhibitor group is CCI based on a similar approach.

Studies JAJD and JAJA, together, aim to enroll approximately 3900 patients (2600 in JAJA, 1300 or more in JAJD) in a 1:1:1 ratio among baricitinib 4-mg, baricitinib 2-mg, and TNF-inhibitor groups in order to observe the planned number of events.

5.3. Method of Assignment to Treatment

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 based on the following factors and categories:

- history of a VTE: yes versus no
- score derived from age and body mass index (BMI): >3 versus ≤3, where score is calculated as:

  Min(Max[2{Age-45}/30, 0], 2) + Min(Max[3*{BMI-20}/20, 0], 3)*
- prior inadequate response or intolerance to a TNF inhibitor: yes versus no

Randomization schemas will be generated with SAS® and uploaded into the iMednet electronic data capture (EDC) system. Assignment of patients to treatment groups will be through the iMednet randomization module.

6. A Priori Statistical Methods

6.1. General Considerations

This plan describes a priori statistical analyses for safety that will be performed.

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

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

Data collected at early termination visits or the final visit at study closure will be mapped to the next scheduled visit number for that patient. Any unscheduled visit data will be included in the patient-level listings.

All descriptive data summaries will be based on observed values only and will include means, medians, standard deviation (SD), and ranges for continuous variables and absolute/relative frequencies for categorical data. In addition, for each variable the number (count) of values that are missing may be reported. Missing data are data that are planned and can be collected but are absent. Statistics will be summarized for the study population overall and by treatment arm.

All tests of treatment effects and CIs will be conducted at a 2- otherwise stated.

For the TNF-inhibitor (administered according to the local product label) treatment group, there will be no distinctions between adalimumab and etanercept (eg, cycling between adalimumab and etanercept will be ignored). Hence, safety and other data collected on either treatment will be attributed to the TNF-inhibitor group. For the combined-baricitinib treatment group, there will be no distinction between baricitinib 4 mg and baricitinib 2 mg (e.g., rescue from 2 mg to 4 mg will be ignored, or dose reduction from 4 mg to 2 mg).

Patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at screening who are randomized to the baricitinib 4-mg dose will receive a dose of 2 mg once daily, but they will be included in the 4-mg dose group for analysis.

Estimands (FDA 2017) associated with each endpoint/analysis are documented in the following places:

Population of interest: patients with RA and meeting the protocol inclusion/exclusion criteria. Analysis populations are defined in Section 6.1.1. The analysis population corresponding to each of the safety endpoints is specified in Table JAJD.6.5.

Endpoints/variables: primary, secondary, and exploratory endpoints/variables are listed in Table JAJD.6.4.

Population-level summary: difference in time from first dose of study treatment to first event of interest and difference in response proportions for binary variables. Details are given in Table JAJD.6.5.

Handling of intercurrent event(s): specific statistical methods to be used for handling intercurrent events under different strategies are described in Section 6.3. Statistical methods corresponding to safety variables are summarized in Table JAJD.6.5.

Analyses specified in this document will be performed based on data collected in Study JAJD alone, unless otherwise specified.

6.1.1. Analysis Populations

The primary, secondary, and exploratory safety analyses will be conducted on the safety population, as described in Table JAJD.6.1.

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

Table JAJD.6.1. Analysis Populations

Population	Description
Intent-to-Treat (ITT) Population	All patients who are randomized will be included in the ITT population. Patients will be analyzed according to the investigational product to which they are randomized.
Safety Population	The safety population is defined as all randomized patients who receive at least 1 dose of investigational product and who did not discontinue from the)))) p))j -)))))) Patients will be analyzed according to the investigational product to which they are randomized.

6.1.2. Definition of Baseline and Postbaseline Measures

Table JAJD.6.2 describes the baseline and postbaseline definitions for the different types of safety analyses.

Table JAJD.6.2. Baseline and Postbaseline Definition for Safety Measures

Analysis Type	Baseline	Postbaseline
Protocol-specified treatment-emergent adverse events (TEAEs) including special topics	The entire period up to date of first study drug administration (typically at Week 0)	For the final lock, first day of study drug administration up to 30 days after the last dose of the study drug. For interim locks, first day of study drug administration up to data cut for ongoing patients and up to 30 days after the last dose of the study drug or up to the cut-off date, whichever occurs first, for patients who discontinued study drug prior to the data cut.

Baseline and Postbaseline Definition for Safety Measures

Analysis Type	Baseline	Postbaseline
Adverse events (AEs) leading to study drug discontinuation, AEs leading to study drug interruption, and serious adverse events (SAEs)	NA	For the final lock, first day of study drug administration up to 30 days after the last dose of the study drug. For interim locks, first day of study drug administration up to data cut for ongoing patients and up to 30 days after the last dose of the study drug or up to the cut-off date, whichever occurs first, for patients who discontinued study drug prior to the data cut.

Abbreviation: NA = not applicable.

6.1.3. Analysis Methods

The main analysis of time-to-event variables will use a Cox proportional hazards regression model stratified by study with treatment group and randomization stratification factors (VTE history, age/BMI combination, prior inadequate response or intolerance to a TNF inhibitor, and geographic region [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. In addition, a sensitivity analysis consisting of a Cox proportional hazards regression model with study and randomization stratification factors as stratifying variables and treatment group as an explanatory variable will be performed. In the event of a low number of observed events or substantial imbalance in event distribution across randomization stratification factors at study completion, strata may be combined or certain stratification variables excluded from the Cox proportional hazards model to enhance model stability and ensure convergence. Additionally, a pre-specified hierarchical approach will be implemented if the primary Cox proportional hazards model fails to converge.

CCI [redacted], CCI [redacted]

This same hierarchical convergence procedure will be applied consistently to individual study analyses (JAJA and JAJD analyzed separately), while Study JAJD excludes geographical region entirely (US-only study), and any supplementary analyses conducted per study to ensure uniformity in model convergence approaches across all analytical components. All convergence attempts and model modifications will be documented, with the final model specification clearly identified and any deviations from the primary analysis treated as sensitivity analyses.

Poisson regression will be used to evaluate incidence rates of adverse events (AEs), serious adverse events (SAEs), discontinuations, and other categorical safety data (Section 6.11.3.3) for between-treatment-group comparisons.

For document writing purposes for safety (other than the primary safety analysis), tests with 2-sided p-values <0.05 will be referred to as having strong statistical evidence for a treatment

difference, unless otherwise noted. However, p-values should not be overinterpreted for these safety analyses. Except for prespecified hypotheses, they correspond to data-driven hypotheses and hence are only useful as a flagging mechanism.

6.2. Adjustments for Covariates

Unless otherwise specified, the following general approach will be used with regard to inclusion of covariates:

> For time-to-event analyses of the primary and secondary objectives, the treatment, VTE history, age/BMI combination, and prior inadequate response or intolerance to a TNF inhibitor will be included as covariates. In addition, when Studies JAJA and JAJD are combined for the primary and secondary objective, the analysis will be stratified by study and include geographic region as a covariate.

6.3. Handling of Dropouts or Missing Data

Intercurrent events (ICH E9 R1) are events which occur after the treatment initiation and make it impossible to measure a variable or influence how it would be interpreted. Potential intercurrent events include: rescue from baricitinib 2 mg to 4 mg, start of a nonpermitted RA treatment (ie, initiation of any targeted synthetic disease-modifying antirheumatic drugs [tsDMARDs] or biologic DMARDs [bDMARDs] other than adalimumab or etanercept in the TNF inhibitor group, or initiation of any bDMARD or tsDMARD other than baricitinib in the baricitinib group), treatment discontinuation due to death or AEs, loss to follow-up, etc. The methods for handling these intercurrent events are described below.

6.3.1. Censoring Rules for Time-to-Event Safety Analyses

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 to baricitinib 4 mg within the baricitinib 2-mg group, or initiation of a nonpermitted RA treatment. For analyses of combined-baricitinib dose groups, censoring will not occur upon rescue from baricitinib 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 to baricitinib 4 mg within the baricitinib 2-mg group (for analyses of individual baricitinib dose groups) or initiation of a nonpermitted RA treatment.

These censoring rules can be justified based on the while-on-treatment strategy (ICH E9 R1) for handling intercurrent events.

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. In this case, the ICH E9 R1-defined treatment policy strategy is being followed. However, patients who discontinue the study early will be censored at the time of discontinuation and thus have missing data, which follows the while-on-treatment strategy. So, this supportive analysis can be justified based on the combination of the treatment policy and while-on-treatment strategies for handling intercurrent events.

6.4. Multiple Comparisons/Multiplicity

No multiplicity control will be conducted for the analyses described in this SAP other than the evaluation of the primary objective over repeated interim and final analyses (Section 6.13).

6.5. Active-Control Studies Intended to Show Equivalence

The primary objective of this study is to demonstrate that the HR for the risk of VTE events in the combined-baricitinib group (ie, across dose groups) relative to the TNF inhibitor group is CCI based on the upper limit of the 95% CI of the HR for time to first event.

6.6. Patient Disposition

Patient flow will be summarized from entry to randomization to first dosing to completion, and analysis population will be listed and summarized by treatment group.

Patient disposition from study will be listed and summarized with reasons for disposition for the intent-to-treat population. The number of patients rescued from baricitinib 2 mg to 4 mg, dose reduction from 4 mg to 2mg, or cycled between adalimumab and etanercept will be summarized as well.

6.7. Patient Characteristics

Patient demographic variables and baseline characteristics are listed in Table JAJD.6.3 and will be summarized with all treatment groups combined and by treatment groups for the safety population. No formal statistical comparisons will be made among treatment groups. In addition, a by-patient listing will be provided.

Table JAJD.6.3. Patient Characteristics

Variable	Quantitative Summary	Categorical Summary	Derivation
Demographics			
Age	Yes	< 50, ≥50 years	Age (year) = (number of months between first dose date and July 1st of birth year) / 12, and truncated to a whole-year (integer) age. If first dose date is missing, randomization date will be used.
		< 60, ≥60 years	
		<65, ≥65 years	
		<75, ≥75 years	
		<85, ≥85 years	
		<65, ≥65 to <75, ≥75 to <85, ≥85 years	
Sex	No	Male, Female	
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino, Not Applicable	
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	
Baseline Anthropometric Measures			
Height (cm)	Yes	None	Height (cm) = height (in) * 2.54
Weight (kg)	Yes	<60 kg, ≥60 kg to <100 kg, ≥100 kg	Weight (kg) = weight (lbs) * 0.454
BMI	Yes	<18.5, ≥18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35 to <40, ≥40 kg/m^2	BMI (kg/m^2) = Weight (kg) / (Height [m])^2
CCI			

Patient Characteristics

Variable	Quantitative Summary	Categorical Summary	Derivation
Baseline RA History			
Duration of RA from diagnosis (year)	Yes	None	Duration of RA from diagnosis (year) = [(Date of first dose Date of RA diagnosis) +1] / 365.25 If the year of RA diagnosis is missing, the duration will be set as missing. Otherwise, an unknown month will be taken as January, and an unknown day will be taken as 01. If first dose date is missing, randomization date will be used.
Current use of corticosteroid	Yes	Yes, No	
Number of csDMARDs previously used	No	0, 1, 2, 3	
Number of csDMARDs currently used	No	0, 1, 2, 3	
Type of csDMARDs currently used	No	No csDMARDs, MTX only, MTX + 1 other csDMARD, 1 non-MTX csDMARD only, 2 non-MTX csDMARDs only, 3 or more csDMARDs	
Number of bDMARDs previously used	No	B8)C8)D8) E	
Prior inadequate response or intolerance to TNFi	No	Yes, No	
bDMARDs previously used	No	Humira®, Enbrel®, etc.	

Patient Characteristics

Variable	Quantitative Summary	Categorical Summary	Derivation
Other Risk Factors			
Tobacco use	No	Never, current, former	
Diabetes	No	Yes, No	Prior medical history pre-specified preferred terms and lowest level terms
Prior VTE	No	Yes, No	eCRF specific entries
Prior ATE	No	Yes, No	
NSAID use	No	Yes, No	Prior and concomitant medications with pre-specified ATC codes
COX2 inhibitor use	No	Yes, No	
OCP/SERM use	No	Yes, No	
HRT	No	Yes, No	
Baseline RA Clinical Characteristics			
Tender joint count based on 28 joints (TJC28)	Yes	None	Number of tender joints in the 28 joints that are evaluated. When there are nonevaluable joints, tender joints will be prorated to 28 joints.
Swollen joint count based on 28 joints (SJC28)	Yes	None	Number of swollen joints in the 28 joints that are evaluated. When there are nonevaluable joints, tender joints will be prorated to 28 joints.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Yes	None	P)))) function is measured by HAQ-DI, which consists of 24 questions referring to 8 domains with a range of possible scores (0-3): dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Scoring will follow the index manual. Missing when there are less than 6 domains completed.
t) global assessment of disease activity (0-10) (PhGA)	Yes	None	PhGA is measured using a 0-10 numeric rating scale. Single item score reported by physician, missing if missing.
t)) assessment of disease activity, modified (0-10) (PtGAm)	Yes	None	PtGAm is measured using a 0-10 numeric rating scale. Single item score reported by patient, missing if missing.

Patient Characteristics

Variable	Quantitative Summary	Categorical Summary	Derivation
Acute phase reactant as measured by high-sensitivity C-reactive protein (hsCRP) (mg/L)	Yes	None	
Simplified Disease Activity Index (SDAI)	Yes	L)))4 CC58)) (>11 - 26), high (>26)	Measure of disease activity that integrates measures of physical examination, acute phase response, patient self-assessment, and evaluator assessment using the following variables: TJC28, SJC28, hsCRP, PtGAm, and PhGA. Calculated as: TJC28 + SJC28 + hsCRP (0.1-10.0 mg/dL) + PtGAm (0-10) + PhGA (0-10).[a] Missing if any of the component score is missing.
Clinical Disease Activity Index (CDAI)	Yes	L)))4 CB58)) (>10 - 22), high (>22)	Measure of disease activity that integrates measures of physical examination, patient self-assessment, and evaluator assessment using the following variables: TJC28, SJC28, PtGAm, and PhGA. Calculated as: TJC28 + SJC28 + PtGAm (0-10) + PhGA (0-10).[a] Missing if any of the component score is missing.
Disease activity score (DAS28-hsCRP)	Yes	Low disease activity E>D8)moderate disease activity bE>D)) L>C8)high disease activity >5.1	Measure of disease activity based on 28 joints that consists of a composite numeric score of the following variables: TJC28, SJC28, hsCRP, and PtGAm. Calculated as: $0.56(TJC28)^{1/2} + 0.28(SJC28)^{1/2} + 0.36(\ln[hsCRP +1]) + 0.014(PtGAm) + 0.96$.[b] Missing if any of the component score is missing.

Patient Characteristics

Abbreviations: ATE = arterial thromboembolic event; bDMARDs = biologic DMARDs; BMI = body mass index; csDMARDs = conventional synthetic DMARDs; COX = cyclooxygenase; DMARDs = disease-modifying antirheumatic drugs; DVT = deep vein thrombosis; HRT = hormone replacement therapy; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; OCP = oral contraceptive pill; PE = pulmonary embolism; RA = rheumatoid arthritis; SERM = selective estrogen receptor modulator; TNFi = tumor necrosis factor inhibitor; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

[a] Aletaha and Smolen 2005.

[b] Vander Cruyssen et al. 2005.

6.8. Treatment Compliance

Compliance with baricitinib and TNF inhibitors will be assessed at each study visit after randomization and recorded in the EDC system. For patients who had their treatment temporarily interrupted by the investigator, the period of time that dose was withheld will be taken into account in the compliance evaluation. A patient will be considered significantly noncompliant if they are randomized to baricitinib (2 mg or 4 mg) and miss at least 2 weeks worth of medication since the date of last contact, or if they are randomized to a TNF inhibitor and miss 1 or more doses since the date of last contact. 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.

The proportion of patients significantly noncompliant will be summarized on a yearly basis and across the entire study for both treatment groups.

6.9. Concomitant Therapy

Concomitant therapy is defined as the therapy that starts before, on, or after the first dose of study treatment and continues into the treatment period. Use of the concomitant therapies will be recorded at baseline. After baseline, collection of information on concomitant medications will focus on those used in association with protocol-specified AEs.

Concomitant therapy will be summarized using frequency counts and percentages by World Health Organization drug anatomical therapeutic chemical classification and treatment group (each treatment group separately and the combined-baricitinib group) for the safety population. Summaries at baseline will be provided separately for concomitant medications used to treat RA and concomitant medications used to treat other conditions.

6.10. Administrative Claims

The use of))4 5) to identify potentially unreported occurrences of VTE in the JAJD trial was not feasible due to contractual restrictions imposed upon the largest data source. It was recognized that claims data may contain errors and include provisional or -)))) ; hence, sites were to confirm the occurrence of any previously unreported VTE found in the claims data. This requires re-identification of information from the claims record to trace it to an identified trial participant. Although participants consented to the use of their claims records and the two claims data providers initially agreed with the planned use, the largest data provider's contracts with payers ultimately

prohibited re-identification of information from participant claims records.. While the second, smaller database remains available, the trial was not integrated within either claims database, making the combined probability of (a) linking a meaningful proportion of trial participants and (b) identifying a previously unreported VTE among these linked participants negligible.

Consequently, Lilly was unable to use claims records as an additional resource to identify VTE. As the claims data were intended to supplement the identification of the primary endpoint and were not part of the trial data, this limitation does not impact the study's execution. The JAJD trial remains a traditionally designed randomized clinical trial conducted among US participants.

6.11. Safety Analyses

6.11.1. Extent of Exposure

Duration of exposure to each study drug will be summarized for the safety population. Cumulative exposure and duration of exposure will be summarized in terms of frequency counts and percentages by category and treatment group.

Duration of exposure will be calculated as follows:

baricitinib 4-mg exposure = date of last baricitinib 4-mg treatment date of first baricitinib 4-mg dose + 1

- The baricitinib 4 mg exposure gained after rescue from patients who were originally randomized to baricitinib 2 mg will not be included.

baricitinib 2-mg exposure = date of last baricitinib 2-mg treatment date of first baricitinib 2-mg dose + 1

- For patients who were rescued from the baricitinib 2-mg dose to the 4-mg dose, their drug exposure after rescue will not be counted as baricitinib 2-mg exposure.

TNF inhibitor exposure = date of last TNF inhibitor treatment (adalimumab or etanercept) date of first TNF inhibitor dose (adalimumab or etanercept) + 1

- regardless of treatment cycling from adalimumab to etanercept or vice versa

total baricitinib exposure = date of last baricitinib (2-mg or 4-mg) treatment date of first baricitinib (2-mg or 4-mg) dose + 1

- regardless of rescue from baricitinib 2 mg to baricitinib 4 mg

For patients randomized to the baricitinib 4-mg dose group who receive a dose of 2 mg once daily due to having an eGFR <60 mL/min/1.73 m^2 at screening, exposure will be considered as exposure to 4 mg and computed as total baricitinib exposure, regardless of actual dose taken.

Missing date handling will follow the compound-level safety standards.

The number and percentage of patients in each of the following exposure ranges will be included in the summaries:

M))4DF) 58) CD))4LD) 58) DF))4CBF) 58) EM)
(156 weeks), and so on. Note that patients may be included in more than 1 category.

bB))XM) 8) M)))XCD) 8) CD)))XDF) 8) DF)))
<36 months, and so on.

The summaries will also include the overall exposure in total PY, calculated as:

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

No p-values will be reported in these tables as they are intended to describe the characteristics of the study sets.

6.11.2. Primary, Secondary, Sensitivity, and Supplementary Analyses

The general methods used to summarize safety data, including analysis population definition and analysis methods are described in Section 6.1.

Primary endpoint events (VTE) and selected secondary endpoint events, including certain arterial thromboembolisms events (ATEs), cardiovascular (CV) events incorporating major adverse cardiovascular events (MACE), and opportunistic infections, will undergo adjudication by an independent, blinded clinical endpoint committees (CECs). Only CEC-confirmed events will be included in the following endpoint analyses.

Table JAJD.6.4 includes the descriptions and derivations of the primary and secondary safety measures.

Table JAJD.6.5 provides the detailed analyses including analysis type, population, and comparisons for safety analyses.

Table JAJD.6.4. Description and Derivation of Primary and Secondary Safety Measures

Measure	Description	Calculation of Targeted Analysis Event Time	Notes	Censoring Type
Time to first VTE, time to first ATE, time to first MACE, time to first malignancy (excluding NMSC), time to first opportunistic infection, time to first serious infection	When a targeted analysis event occurs between first dose date and within 30 days of their last dose date of originally randomized treatment[a] (or date of their last available study visit for malignancies)	Event date first randomized dose date	The targeted analysis event and intercurrent event: rescue, initiation of nonpermitted RA treatment, discontinuation/completion of the study, whichever occurs first, and the corresponding time will be used in the analysis. For analysis of malignancy, the last visit date will be used. **Note:** rescue only applies to analysis of individual baricitinib 2-mg dose vs TNFi. In the combined-baricitinib dose vs TNFi analysis, rescue will not be considered in the analysis (i.e., events occurring on either dose will be attributed to the combined dose group).	Primary (in consideration of intercurrent events)
	When there is no targeted analysis event	(last dose date of the originally randomized treatment[a] + 30 days or last visit date,[b] whichever the earliest) first randomized-dose date		
	When nonpermitted RA treatment is initiated	Initiation date of the nonpermitted RA treatment first randomized dose date		
	When there is rescue	Rescue date first randomized dose date		
Time to first VTE, time to first ATE, time to first MACE, time to first malignancy (excluding NMSC), time to first opportunistic infection, time to first serious infection	When an event occurs between first dose date and date of their last available study visit	Event date first randomized dose date	All events occurring during the study will be)))) randomized treatment group regardless of any subsequent rescue, treatment discontinuation, or initiation of a nonpermitted RA treatment.	Supportive (regardless of intercurrent events)
	When there is no event	Last visit date[b] first randomized dose date		

Description and Derivation of Primary and Secondary Safety Measures

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; JAJD = I4V-MC-JAJD; MACE = major adverse cardiovascular event; NMSC = nonmelanoma skin cancer; PE = pulmonary embolism; TNFi = tumor necrosis factor inhibitor; RA = rheumatoid arthritis; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

[a] When evaluating baricitinib (vs TNFi), the originally randomized treatment refers to baricitinib. When evaluating baricitinib 4 mg or 2 mg (vs TNFi), the originally randomized treatment is that specific dose of baricitinib.

[b] For the calculation of targeted analysis event time when there is no event in patients enrolled in Study JAJD,))d))))))))targeted events, either at an in-person visit or by telephone interaction via the call center.

Table JAJD.6.5. Description of Primary, Secondary, Sensitivity, and Supplementary Analyses

Measure	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Comparison	Censoring Type	Analysis Type
Time to first VTE	Cox proportional hazards regression model	Safety (JAJA and JAJD combined)	Combined baricitinib vs TNFi	Primary	Primary
	Cox proportional hazards regression model	Safety (JAJA and JAJD combined)	Combined baricitinib vs TNFi	Supportive	Sensitivity
	Cox proportional hazards regression model	Safety (JAJD alone)	Combined baricitinib vs TNFi	Primary	Supplementary
	Cox proportional hazards regression model with study and stratification factors as stratifying variables	Safety (JAJA and JAJD combined)	Combined baricitinib vs TNF inhibitor	Primary	Sensitivity
Time to first ATE, time to first MACE, time to first malignancy (excluding NMSC), time to first opportunistic infection, time to first serious infection	Cox proportional hazards regression model	Safety (JAJA and JAJD combined)	Combined baricitinib vs TNFi	Primary	Secondary
	Cox proportional hazards regression model	Safety (JAJA and JAJD combined)	Combined baricitinib vs TNFi	Supportive	Sensitivity
	Cox proportional hazards regression model	Safety (JAJD alone)	Combined baricitinib vs TNFi	Primary	Supplementary

Description of Primary, Secondary, Sensitivity, and Supplementary Analyses

Measure	Analysis Method (Section 6.1.3)	Population (Section 6.1.1)	Comparison	Censoring Type	Analysis Type
Time to first VTE, time to first ATE, time to first MACE, time to first malignancy (excluding NMSC), time to first opportunistic infection, time to first serious infection	Cox proportional hazards regression model	Safety (JAJD alone)	Baricitinib 4 mg vs TNFi	Primary	Supplementary
	Cox proportional hazards regression model	Safety (JAJA and JAJD combined)	Baricitinib 4 mg vs TNFi	Primary	Secondary
	Cox proportional hazards regression model	Safety (JAJA and JAJD combined)	Baricitinib 2 mg vs TNFi	Primary	Secondary
	Cox proportional hazards regression model	Safety (JAJD alone)	Baricitinib 2 mg vs TNFi	Primary	Supplementary

Abbreviations: ATE = arterial thromboembolic event; DVT = deep vein thrombosis; JAJA = I4V-MC-JAJA; JAJD = I4V-MC-JAJD; MACE = major adverse cardiovascular event; NMSC = nonmelanoma skin cancer; PE = pulmonary embolism; TNFi = tumor necrosis factor inhibitor; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

6.11.3. Other Safety Analyses (Exploratory)

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 6.1. Baseline and postbaseline are defined in Table JAJD.6.2. Two analysis periods will be used depending on the analysis type: Treatment period is defined as up to 30 days after the last dose of the study treatment; study period is defined as up to the last visit of the study.

6.11.3.1. Adverse Events

The planned summaries for AEs are provided in Table JAJD.6.6 and are described more fully in the compound-level safety standards.

A treatment-emergent adverse event (TEAE) is defined as an event that either first occurred or worsened in severity after the first dose of study treatment and on or prior to the last-visit date during the analysis period. Refer to the compound-level safety standards for handling of missing severity.

Studies JAJA and JAJD may be combined for analyses of SAEs and AEs. General (nontargeted) AEs will be reported individually for Study JAJA.

Table JAJD.6.6. Summary Tables Related to Adverse Events

Analysis	Analysis Period
An overview table, with the number and percentage of patients who experienced a reported TEAE, SAE, death, discontinuation from the study due to an AE, temporary interruption from study drug due to an AE, or permanent discontinuation from study drug due to an AE	Treatment period
An overview table, with the number and percentage of patients who experienced a TE AESI including VTE, MACE, ATE, malignancy (excluding NMSC), opportunistic and serious infections	Treatment period (Study period for malignancy)
The number and percentage of patients with reported TEAEs using MedDRA PT nested within SOC	Treatment period
The number and percentage of patients with reported TEAEs using MedDRA PT (without regard to SOC)	Treatment period
The number and percentage of patients who experienced an SAE (including deaths and SAEs temporally associated or preceding deaths) during the treatment period using MedDRA PT nested within SOC	Treatment period
A listing of SAEs	Study period
A listing of death	Study period
The number and percentage of patients who permanently discontinued from study treatment due to an AE (including adverse events that led to death) during the treatment period using MedDRA PT nested within SOC	Treatment period
The number and percentage of patients who temporarily interrupted study treatment due to an adverse event during the treatment period using MedDRA PT nested within SOC	Treatment period

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

6.11.3.2. Deaths, Other Serious Adverse Events, and Temporary Study Drug Interruptions

The planned table and listing for SAEs are included in the previous section. A listing of deaths, regardless of when they occurred during the study, will also be provided as specified in the previous section.

A summary of temporary interruptions of study drug will also be provided, showing the number of patients who reported at least 1 temporary interruption and the number of temporary interruptions per patient who had an interruption. Further, the duration of each temporary interruption (in days), the cumulative duration of dose interruption (in days) using basic descriptive statistics (n, mean, SD, minimum, first quartile, median, third quartile, and maximum), and the reason for dose interruption will be provided.

6.11.3.3. Special Safety Topics

6.11.3.3.1. Infections

Infections will be defined using all the Preferred Terms (PTs) from the Infections and Infestations System Organ Class as defined in the Medical Dictionary for Regulatory Activities (MedDRA). Opportunistic infections will be adjudicated by an independent, external adjudication committee and will be summarized by PT nested under infection pathogen (or

presentation of pathogens). Events will be ordered by decreasing frequency of pathogen nested under its pathogen species (mycobacteria, bacteria, fungi, virus, parasites, other).

The planned summaries are provided in Table JAJD.6.7 and are described more fully in the compound-level safety standards.

Infections will be reported separately for Studies JAJA and JAJD.

Table JAJD.6.7. Summary Tables Related to Infections

Analysis	Analysis Period
The number and percentage of patients with reported treatment-emergent infections, serious infections, opportunistic infections and infections resulting in permanent study drug discontinuation using MedDRA PTs	Treatment period
The number and percentage of patients with reported TEAEs of infections by maximum severity using MedDRA PTs	Treatment period
The EAIR and 95% CIs by the overall period for reported infections of special interest (ie, serious infections, herpes simplex, and herpes zoster)	Treatment period
A listing of patients experiencing reported TEAE infections will be provided. The listing will include patient demographics, treatment group, treatment start and stop dates, infectious PT event, event start and stop dates, event seriousness, and event outcome.	Treatment period
The number and percentage of patients with opportunistic infection, as positively adjudicated, will be summarized by treatment group.	Treatment period
A listing of the events sent for opportunistic infection adjudication will be provided to include data concerning the MedDRA PT related to the event, the seriousness of the event, and the event outcome, along with the adjudicated result.	Study period

Abbreviations: CIs = confidence intervals; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.

6.11.3.3.2. Major Adverse Cardiovascular Events (MACE) and Other Cardiovascular Events

Major adverse cardiovascular events and other CV events will be adjudicated by an independent, external adjudication committee. All confirmed events after adjudication will be used for the analysis.

The planned summaries are provided in Table JAJD.6.8 and are described more fully in the compound-level safety standards.

Table JAJD.6.8. Summary Tables Related to MACE and Other Cardiovascular Events

Analysis	Analysis Period
The number and percentage of patients with MACE, other cardiovascular events, noncardiovascular death, and all-cause death, as positively adjudicated, will be summarized by treatment group based on the categories and subcategories as defined in the compound-level safety standards.	Treatment period
A listing of the events sent for cardiovascular adjudication will be provided to include data concerning the MedDRA PT related to the event, the seriousness of the event, and the event outcome, along with the adjudicated result.	Study period
EAIRs and 95% CIs by the overall period for positively adjudicated MACE will be summarized by treatment group.	Treatment period

Abbreviations: CIs = confidence intervals; EAIRs = exposure-adjusted incidence rates; MACE = major adverse cardiovascular events; MedDRA = Medical Dictionary for Regulatory Activities; PT =Preferred term.

6.11.3.3.3. Venous and Pulmonary Artery Thromboembolic Events

Venous thromboembolisms will be adjudicated by an independent, external adjudication committee. Venous and pulmonary artery thromboembolic events will be classified as DVT (excluding nonsuperficial below-knee thrombosis), PE, or other peripheral venous thrombosis (including nonsuperficial below-knee thrombosis). All confirmed events after adjudication will be used for the analysis.

The planned summaries are provided in Table JAJD.6.9 and are described more fully in the compound-level safety standards.

Table JAJD.6.9. Summary Tables Related to VTE Events

Analysis	Analysis Period
The number and percentage of patients with a VTE, DVT/PE, DVT, PE, and other peripheral venous thrombosis, as positively adjudicated, will be summarized separately and by treatment group.	Treatment period
A listing of the VTE events sent for adjudication will be provided to include data concerning the MedDRA PT related to the event, the seriousness of the event, and the event outcome, along with the adjudicated result.	Study period
EAIRs and 95% CIs by the overall period for positively adjudicated VTEs will be summarized by treatment group.	Treatment period

Abbreviations: CIs = confidence intervals; DVT = deep vein thrombosis; EAIRs = exposure-adjusted incidence rates; MedDRA = Medical Dictionary for Regulatory Activities; PE = pulmonary embolism; PT = Preferred Term; VTE = venous thromboembolism that consists of DVT, including nonsuperficial below-knee thrombosis, and PE.

6.11.3.3.4. Arterial Thromboembolism

Arterial thromboembolisms will be adjudicated by an independent, external adjudication committee.

The planned summaries are provided in Table JAJD.6.10 and are described more fully in the compound-level safety standards.

Table JAJD.6.10. Summary Tables Related to ATE Events

Analysis	Analysis Period
The number and percentage of patients with an ATE, as positively adjudicated, will be summarized by treatment group.	Treatment period
A listing of the ATE events sent for adjudication will be provided to include data concerning the MedDRA PT related to the event, the seriousness of the event, and the event outcome, along with the adjudicated result.	Study period
EAIRs and 95% CIs by the overall period for positively adjudicated ATE will be summarized by treatment group.	Treatment period

Abbreviations: ATE = arterial thromboembolic event; CIs = confidence intervals; EAIRs = exposure-adjusted incidence rates; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term.

6.11.3.3.5. Malignancies

Malignancies will be identified using terms from the malignant tumors Standardized MedDRA Query (SMQ). Malignancies will be reported separately for nonmelanoma skin cancers (NMSCs) and all those excluding NMSC. All the cases identified by the malignant tumors SMQ will be assessed through medical review to determine *confirmed* NMSC cases.

The planned summaries are provided in Table JAJD.6.11 and are described more fully in the compound-level safety standards.

Table JAJD.6.11. Summary Tables Related to Malignancies

Analysis	Analysis Period
The number and percentage of patients with treatment-emergent malignancies will be summarized separately for NMSCs and all those excluding NMSC by treatment group.	Treatment period
Listing of all malignancy cases with an NMSC flag	Study period
EAIRs and 95% CIs by the overall period for treatment-emergent malignancies excluding NMSC and NMSC will be summarized by treatment group. Of note, investigator-reported time will be used for the EAIR calculation.	Treatment period

Abbreviations: CIs = confidence intervals; EAIR = exposure-adjusted incidence rate; NMSC = nonmelanoma skin cancer.

6.11.3.4. Criteria for Notable Patients

Patient narratives will be provided for all patients wh)))) w) compound level safety standards for list of criteria.

6.12. Protocol Violations

Protocol deviations will be tracked by the clinical team, and their importance will be assessed by key team members during protocol deviation review meetings.

The categories and subcategories of IPDs, the source of identification for the deviation, and the statistical programming guidance for the CSR are included in the JAJD Site Management Plan document.

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

6.13. Interim Analyses and Data Monitoring

An independent data monitoring committee (DMC) will oversee the conduct of this study in conjunction with Study JAJA. The DMC will consist of members external to Lilly who have rheumatology, CV, coagulation, or statistics expertise. This DMC will follow the rules defined in the DMC charter.

The data from Studies JAJA and JAJD will be evaluated at interim analyses in order to determine if the combined evidence is sufficient to meet the studies' primary objective with respect to VTE. CCI interim data analyses are planned to occur based on the cumulative number of patients with events of VTE observed in these CCI trials: CCI analyses to evaluate safety with no consideration of the studies' primary objectives and CCI subsequent analyses to evaluate safety and whether the primary objective has been met. The first CCI analyses are planned to occur when approximately CCI of the planned total patients with VTE events are observed (across studies). The CCI analyses to evaluate the primary objectives 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. Ad hoc interim analyses may be conducted to address regulatory requests. CCI

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

When the accumulation of events for VTE is lagging considerably behind, the primary analysis will be modified to an incidence rate difference analysis. See more details in Section 4.1.

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.

More details are given in the DMC charter.

6.14. Planned Exploratory Analyses

The planned exploratory analyses are described in Section 6.11.3 through 6.11.3.3.5.

6.15. Annual Report Analyses

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

6.16. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

Summary of protocol-specified AEs, provided as a dataset which will be converted to an ≥q p) ≥))f)we i)) s)e i))))) 8)) MedDRA PT.

- e)e i))) w))))))xi e i >
- e)e i))))) s)) f it is both a TEAE and is not ≥))j))we i)) s)e i 8)))))) 8)) following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced
- g)) ≥g x >) 8) s)e i)))) 5% of patients in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures (eg, the CSR, manuscripts, and so forth).

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

7. Unblinding Plan

Refer to a separate blinding and unblinding plan document for details.

8. References

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Approval	PPD 21-Jul-2025 14:39:01 GMT+0000

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