Statistical Analysis Plan 14V-JE-JAJE Version 5

A Phase 2/3, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Baricitinib in Adult and Pediatric Japanese Patients With NNS/CANDLE, SAVI, and AGS

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Approval Date: 26-Nov-2024

1. Statistical Analysis Plan: I4V-JE-JAJE: A Phase 2/3, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Baricitinib in Adult and Pediatric Japanese Patients with NNS/CANDLE, SAVI, and AGS

Baricitinib (LY3009104)

A Phase 2/3, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Baricitinib in Adult and Pediatric Japanese Patients with NNS/CANDLE, SAVI, and AGS.

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[Protocol I4V-JE-JAJE]
[Phase 2/3]

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approved on 26 Nov 2024 GMT

2. Table of Contents

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3. Revision History

SAP Version 1 was approved prior to the first patient visit of the study.

SAP Version 2 was approved prior to the database lock of primary treatment period. The overall changes and rationale for the changes incorporated in Version 2 were as follows:

Section	Revisions
6.1	To add the conversion factors of calculating Prednisone (or Equivalent) Dose
6.1.1	To remove the definition of baseline and endpoint in the pre-treatment period for CANDLE/NNS because there are no intervention in pre-treatment period.
6.4	To add summary of treatment disposition and detailed specifications of disposition listing.
6.5	To add the listing of medical history and pre-existing conditions.
6.6	To add the logic of calculating treatment compliance.
6.7	To add summary of concomitant medications.
6.8.3.1	To specify the endpoints of efficacy analyses for comparison with pre-treatment period.
6.12.2.1	To add the listing of COVID-19 related AEs .
6.14	To move the definition of protocol deviation for treatment non-compliance from section 6.6 and descrive the Trial Issue Management Plan for assessing protocol deviations.

SAP Version 3 was approved prior to the 52 week database lock. The overall changes and rationale for the changes incorporated in Version 3 are as follows:

Section	Revisions
5	To update Figure JAJE.1 using the latest version of study design figure in the protocol.
6.6	To remove the method of calculation of treatment compliance.
6.8.3	To add interferon (IFN) signature score for the analysis of biomarkers.
6.8.3	To create spaghetti plot for efficacy parameters.
6.12.2.1	To add by-patient-listing of all AEs, AEs leading to study discontinuation, AEs leading to temporary study drug interruption.
6.12.4	To add the listing of BK virus tests.
6.15	To add the interim analysis to assess efficacy and safety of baricitinib with 1 year exposure.

SAP Version 4 was approved after 52 week database lock. The change was to translate a Japanese manuscript in the Section 7 (References) into English.

SAP Version 5 will be approved before final database lock. The change is made to modify Figure JAJE.1 to be consistent with the I4V-JE-JAJE(e) Clinical Protocol.

4. Objectives and Endpoints

Table JAJE.1 shows the objectives and endpoints of the study.

Table JAJE.1 Objectives and Endpoints

Objectives	Endpoints
Primary To determine if the administration of baricitinib to patients with NNS/CANDLE, SAVI, or AGS results in reduction in the patient's mean daily diary scores compared to baseline.	At primary endpoint [a]: • Change from baseline in patient's mean daily diary scores
Secondary To determine, in patients receiving systemic corticosteroids at baseline, if administration of baricitinib to patients with NNS/CANDLE, SAVI, or AGS results in reduction in the daily dose of corticosteroids.	At primary endpoint and various time points over the primary treatment period and maintenance treatment period: • Result in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.15 mg/kg/day oral prednisone or a decrease of at least 50% of the patient's daily dose at baseline)
To determine if the administration of baricitinib to patients with NNS/CANDLE, SAVI, or AGS results in improvement with clinical measurements compared to baseline	At primary endpoint and various time points over the primary treatment period and maintenance treatment period: • Change from baseline ○ in patient's symptom specific daily diary scores ○ in Physician's Global Assessment of Disease Activity scores At various time points over the primary treatment period and maintenance treatment period: • Change from baseline in patient's mean daily diary scores[b]
To determine if the administration of baricitinib to patients with NNS/CANDLE results in improvement with clinical measurements compared to pre-treatment period[c]	At primary endpoint and various time points over the primary treatment period and maintenance treatment period: • Change from pre-treatment period ○ in patient's daily diary score ○ in Physician's Global Assessment of Disease Activity scores • Proportion of days meeting the criteria of patient's mean daily diary score <0.5
To assess the growth of pediatric patients treated with baricitinib	Mean changes in growth (height and weight) and growth velocity over the course of treatment
Exploratory To characterize the pharmacokinetic profile of baricitinib in Japanese patients with NNS/CANDLE, SAVI, or AGS and explore whether baricitinib exposure in Japanese NNS/CANDLE, SAVI, or AGS patients is comparable to the exposure in study I4V-MC-JAGA in non-Japanese	• Population PK analysis based on sparse sampling • PK comparability will be assessed visually and/or modeling approach, if appropriate.

patients receiving the weight/eGFR-adjusted dosage of baricitinib.	
To determine if the administration of baricitinib to patients with NNS/CANDLE, SAVI, or AGS results in a change in biomarkers/inflammatory markers.	At primary endpoint and various time points over the primary treatment period and maintenance treatment period: ● Change from baseline in biomarkers/inflammatory markers[d]
To determine if the administration of baricitinib to patients with NNS/CANDLE, SAVI, or AGS results in improvement with clinical measurements compared to patient's relative retrospective medical records[e]	At primary endpoint and various time points over the primary treatment period and maintenance treatment period: ● Change from the start of the patient's relative retrospective medical records

[a] At Week 20 for NNS/CANDLE patients. At Week 32 for SAVI and AGS patients.

[b] Timepoint at Week 20 for NNS/CANDLE patients and Timepoint at Week 32 for SAVI and AGS patients will be assessed as primary endpoint.

[c] 12 weeks Pretreatment period is applied to NNS/CANDLE patients (See Protocol Section 5.1).

[d] See Protocol Appendix 2.

[e] Patient's relative retrospective medical records prior to the study will be collected up to a maximum of 5 years from the point at when the patient participates in JAJE (screening visit) (See Protocol Section 9.1.2.6).

5. Study Design

5.1. Summary of Study Design

Study I4V-JE-JAJE is a Phase 2/3 multicenter, open-label study to evaluate the efficacy and safety of baricitinib in adult and pediatric Japanese patients with type 1 autoinflammatory interferonopathies expected to benefit from JAK1/JAK2 inhibition, including NNS/CANDLE, SAVI, and AGS. Patients will receive an initial dose based on weight class and eGFR. The patient's disease severity will be recorded daily in a patient diary by the patient or caregiver throughout the study. Average diary scores will characterize responses to therapy and will trigger additional dose escalation or steroid weaning (for patients who are receiving systemic corticosteroids), as appropriate.

Figure JAJE.1 illustrates the study design.

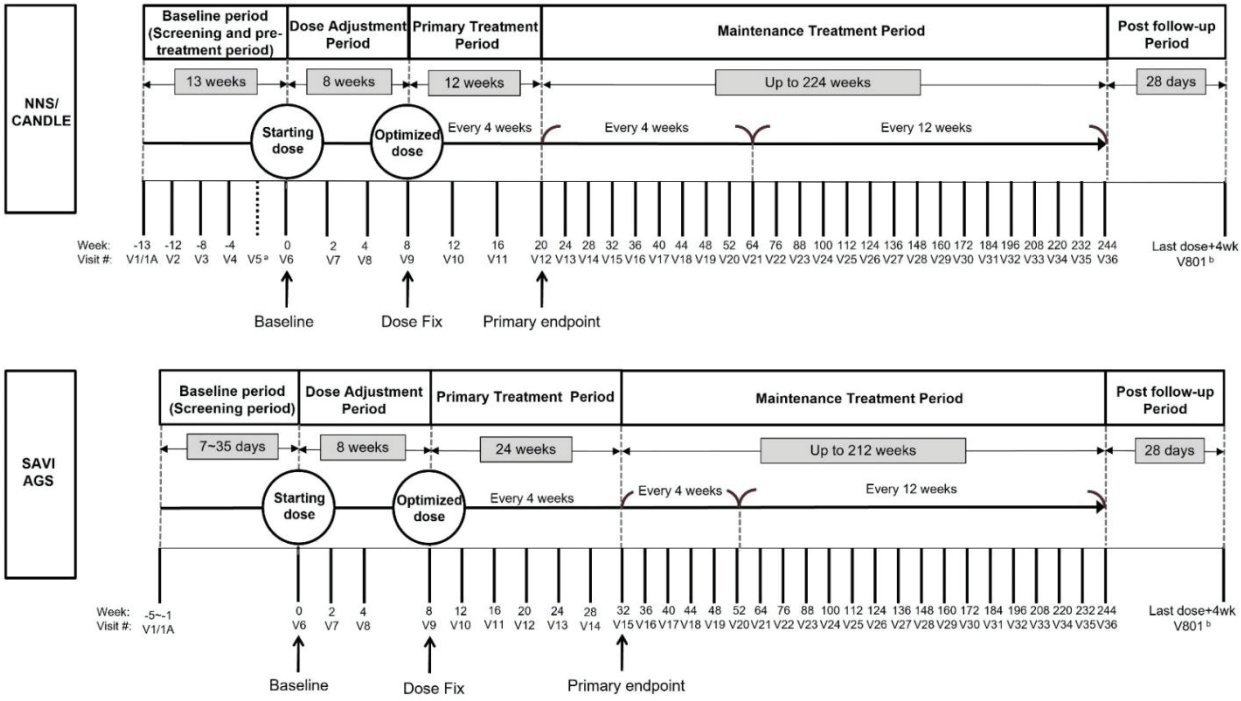
5.2. Determination of Sample Size

Because the medical conditions being treated in the study are very rare in Japan, it is anticipated that relatively few patients will be enrolled. Approximately 5 patients will be enrolled. The sponsor will try to enroll more than 1 patient per disease.

However, given the scarcity of patient population for each of these target diseases in Japan, it may be possible that the study is completed without enrolling any patient for a specific disease if no eligible patient could be found.

5.3. Method of Assignment to Treatment

All patients participating in this study will receive open-label baricitinib. Site personnel will dispense IP bottles manually. Site personnel will confirm that they have located the correct IP bottles before dispensing to the patient.



Abbreviations: AGS = Aicardi-Goutières Syndrome; NNS/CANDLE = Nakajo-Nishimura Syndrome/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; SAVI = STING-associated vasculopathy with onset during infancy; STING = stimulator of interferon genes; V = visit; wk = week.

[a] Patient can skip Visit 5 and proceed to Visit 6 instead of Visit 5 if biologic agents are not administered during pre-treatment period or an appropriate washout duration of biologic agents defined exclusion criterion #28 has already passed at Visit 5 (see Protocol Section 6.2 Exclusion criteria [28], Section 7.7.1).

[b] V801 should occur approximately 28 days after the last dose of investigational product. Patients who will transition from this study to commercial baricitinib are not required to have Visit 801.

Figure JAJE.1. Illustration of study design for Clinical Protocol I4V-JE-JAJE.

6. A Priori Statistical Methods

This plan describes a priori statistical analyses (listings and descriptive statistics) for efficacy, health outcomes, and safety data for Study JAJE.

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Because the medical conditions being treated in this study are rare, it is anticipated that relatively few patients with each condition will be enrolled. Therefore, no formal statistical analyses are planned. Instead, descriptive summaries, where applicable, and data listings will be the main tools used to summarize the results from this study. When summary statistics are deemed appropriate, continuous data will be summarized in terms of the mean, standard deviation, minimum, maximum, median, and number of observations and categorical data will be summarized as frequency counts and percentages.

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 exploratory analyses of the data will be conducted as deemed appropriate.

Patient's diary scores collected every day will be entered and stored into the clinical trial database and these data will be used for the efficacy analyses. Two types of derivations for the diary scores are planned; (1) "mean" daily diary scores and (2) proportion of days meeting threshold during treatment period. Details are described in Section 6.9.1.

(1) **mean daily diary scores**; average scores from 7 days of preceding the current visit (not including data on the day of current visit) will be used as a representative value of the visit. If more than 50% symptom scores are missing for the specified calculation, then the average diary score will not be calculated.

(2) **Proportion of days meeting threshold;** proportion of days which meets a threshold of response criteria for daily diary score will be used (e.g. daily diary score <0.5 for NNS/CANDLE). Given a interval (e.g. from previous visit to current visit, or during primary treatment period), the proportion of days will be calculated as total number of days meeting the threshold divided by total number of days with non-missing diary scores during the interval.

To allow for assessments of changes in doses of various corticosteroids, all corticosteroid doses will be standardized to an equivalent prednisone dose. Table JAJE.2 provides a summary of frequent corticosteroids and their prednisone-equivalent dose. This dose of corticosteroid will be referred to as "prednisone (or equivalent)" throughout this document.

Table JAJE.2 Conversion Factors for Calculating Prednisone (or Equivalent) Doses

Column 1	Column 2
Corticosteroid Preferred Name	**Conversion Factor for Converting to an Equivalent Prednisone Dose**
Prednisone	1
Prednisolone	1
Methylprednisolone	1.25
Triamcinolone	1.25
Cortisone	0.2
Hydrocortisone	0.25
Betamethasone	6.25
Dexamethasone	6.25
Paramethasone	2.5
Deflazacort	0.83

Listings will be sorted and presented by disease diagnosis and patient ID unless otherwise specified. Listings will include data from all visits unless otherwise specified.

All analyses will be implemented using SAS Version 9.4 or a more recent version.

6.1.1. Definition of Baseline and postbaseline Measures

The treatment period starts after administration of the first dose of baricitinib at Visit 6 (Week 0) and ends on the date of the final visit in the treatment period or the early discontinuation visit.

NNS/CANDLE, SAVI, AGS

Baseline of the baricitinib treatment period which includes dose adjustment period, primary treatment period and maintenance treatment period will be defined as the last available value before the first dose of baricitinib. In most cases, this will be the measure recorded at Week 0 (Visit 6). Change from baseline will be calculated as the visit value of interest minus the baseline value.

Endpoint of the baricitinib treatment period will be the last non-missing postbaseline measurement during the baricitinib treatment period. Major interest is the endpoint of the primary treatment period. Any measurements collected after the first dose of baricitinib will be considered a postbaseline measurement.

Baseline of the post follow-up period is defined as the date of the final visit or early termination in the treatment period. **Endpoint of the post follow-up period** is Visit 801.

NNS/CANDLE (Comparison with pre-treatment period)

In order to assess the change **from pre-treatment period** for NNS/CANDLE patients of efficacy measurements during baricitinib treatment period, average of all daily diary scores collected during pre-treatment period (i.e. from Visit 2 through Visit5) will be used as a baseline value.

6.2. Handling of Dropouts or Missing Data

If the year of birth is collected but the day and month are missing then July 1st will be used as the imputed month and day for purposes of age calculation.

For continuous measure, observed case analyses will be performed. In addition, a last observation carried forward (LOCF) imputation replaces missing data with the most recent non-missing post-baseline assessment for the endpoint of primary treatment period and maintenance treatment period.

6.3. Use of an "Efficacy Subset" of Patients

Entered population set includes those patients who sign the informed consent form directly or through their legally acceptable representatives.

Enrolled population set includes all patients who have entered the study and who are not considered screen fails at or before Visit 6 (i.e. patients not excluded due to not meeting inclusion criteria or meeting exclusion criteria during screening/pre-treatment period).

Efficacy population set includes all enrolled patients who have at least one dose of baricitinib.

Safety population set includes all enrolled patients who receive at least 1 dose of baricitinib and who did not discontinue the study for the reason "Lost to Follow-up" at the first postbaseline visit (Visit 7).

6.4. Patient Disposition

For enrolled population, a by-patient listing of the patient disposition (discontinued or completed) including the visit that occurred will be created. The listing will include the following information; patient ID, disease diagnosis, visit, disposition category (complete or the primary reasons for study discontinuation).

Frequency counts and percentages of patients who complete or discontinue early from the study will be summarized separately by disease diagnosis along with their reason for study discontinuation.

6.5. Patient Characteristics

A summary and list of demographic information and baseline characteristics of all enrolled patients will be created by disease diagnosis. The following continuous demographic and baseline characteristic variables will be summarized using descriptive statistics.

- Age at the time of study entry (in years).
- Height (cm)

- Weight (kg) (as recorded at Visit 6, unless missing, in which case the Visit 1 result will be used).

The following categorical variables will be summarized using frequency counts and percentages:

- Sex
- Weight categories (kg) (<10, ≥10 -<20, ≥20 - <30, ≥30 - <40, ≥40 - <50, ≥50 - <60, and ≥60)
- Race
- estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2)

A by-patient listing of demographic and baseline characteristics will be provided including age at study entry (years), body weight (kg), height (cm) and eGFR (mL/min/1.73 m^2). A by-patient listing of medical history and pre-existing conditions will be created.

6.6. Treatment Compliance

Treatment compliance was planned to calculate from treatment dispense and returned information from electronic CRF in the statistical analysis plan version 2. However, since these data were not collected at every visit, it was not possible to calculate the compliance by visit or treatment period. So treatment compliance will not be calculated.

Regarding the protocol deviation of treatment compliance, the information will be reported via monitoring.

6.7. Concomitant Therapy

Medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO) drug dictionary. Medication start and stop dates will be compared to the date of the first dose of study treatment (recorded on the Study Drug Administration page of the electronic case [clinical] report form [eCRF]) to allow medications to be classified as 'prior' or 'concomitant'. Medications that start and end before the first dose date will be classified as 'prior' medications. Medications that end on or after the first dose date will be classified as 'concomitant' medications. Note that medications with partial or missing start and/or stop dates will be assumed to be 'concomitant' unless there is evidence, through comparison of partial dates, to suggest otherwise. Concomitant medications will be summarized by disease diagnosis.

A by-patient listing of all non-steroid concomitant medications and steroid concomitant medications will be provided.

The total daily corticosteroid dose (mg), corticosteroid dose per weight (mg/kg), change from baseline, and percent change from baseline of corticosteroid doses will be listed.

6.8. Efficacy Analyses

6.8.1. Primary Outcome and Methodology

The primary objective is to determine if the administration of baricitinib to patients with NNS/CANDLE, SAVI, or AGS results in reduction in the patient's mean daily diary scores compared to baseline.

For change from baseline in patient's mean daily diary scores (defned in Section 6.9.1), descriptive statistics will be calculated by visit for NNS/CANDLE, SAVI, and AGS for baricitinib treatment period including dose adjustment period, primary treatment period and maintenance treatment period. Primary interest is to assess the mean change from baseline in patient's mean daily diary scores at Week 20 in NNS/CANDLE and Week32 in SAVI and AGS during primary treatment period, which is the primary endpoint of the study.

6.8.2. Additional Analyses of the Primary Outcome

Percentage of the patients who result in reduction in the patient's mean daily diary scores will be summarized by visit. Table JAJE.3 shows a threshold of reduction in patient's mean daily diary scores. Additional threshold may be added.

Table JAJE.3 Thresholds of reduction in patient's mean daily diary scores

Variables	Disease	Threshold
Mean daily diary score	NNS/CANDLE	mean daily score to <0.5
	SAVI	mean daily score to <1.0
		mean daily score excluding the respiratory/breathing symptom score to <1.0
		mean daily score to <0.5
		mean daily score excluding the respiratory/breathing symptom score to <0.5
	AGS	mean daily score to <0.5
		mean daily score excluding neurological symptoms to <0.5

6.8.3. Other Secondary Efficacy Analyses

The same statistical analyses described in Section 6.8.1 will be performed for the following efficacy/pharmacodynamic measurements.

1. Patient's symptom specific daily diary scores
2. Proportion of days which meets a threshold of response criteria (See section 6.1)
3. Physician's Global Assessment of Disease Activity scores
4. Barthel Index (for SAVI and AGS)
5. Classification of disease severity (for NNS)
6. Prednisone (or equivalent) dose of systemic corticosteroids
7. Laboratory testing (e.g. CRP, complete blood cell count, AST, ALT, gammaglutamyltransferase [GGT], creatine phosphokinase [CPK])
8. Biomarkers (IFN response gene score, IFN signature score*, Cytokine panel (serum IP-10/CXCL10, etc))
9. Inflammatory marker (High sensitivity C-reactive protein (hsCRP))

* interferon (IFN) signature score is a composite score using 6 genes of IFN response gene score. The following is a equation of the calculation of IFN signature score.

IFN signature = Median(-1.4680 + 1.1938*DDX60, 5.8581+0.6907*IFI44, 1.8415 + 0.8009*LY6E, MX1, 2.2300 + 0.8037*OAS3, 6.4731 + 0.7148*USP18) – 13.5

Regarding proportion of days which meets a threshold of response criteria, the following criteria described in Table JAJE.4 will be used. Additional threshold may be added.

Table JAJE.4 Thresholds for calculating proportion of days meeting response criteria

Variables	Disease	Threshold
daily diary score (average scores across symptoms)	NNS/CANDLE	daily score to <0.5
	SAVI	daily score to <1.0
		daily score excluding the respiratory/breathing symptom score to <1.0
		daily score to <0.5
		daily score excluding the respiratory/breathing symptom score to <0.5

	AGS	daily score to <0.5
		daily score excluding neurological symptoms to <0.5
Symptom specific daily diary score	NNS/CANDLE	daily score to 0
	SAVI	daily score to 0
	AGS	daily score to 0

Proportion of patients who result in a decrease in the daily dose of corticosteroids (systemic corticosteroids <0.15 mg/kg/day oral prednisone or a decrease of at least 50% of the patient's daily dose at baseline) by visit. Prednisone (or equivalent) for the daily dose of corticosteroids will be used for the analysis. Dose of corticosteroids taken at the visit date will be used as the representative value of the dose at the visit.

A by-visit listing of the calculated mean diary score (defined in Section 6.9.1), change in diary score, percent change in diary score, mean symptom scores, and change from baseline in each symptom score will be provided. In addition, spaghetti plot of efficacy measures including the calculatd mean diary score, Physician's Global Assessment of Disease Activity score and Prednisone (or equivalent) dose of systemic corticosteroids for the primary diseases will be provided.

6.8.3.1. Comparison against pre-treatment period (NNS/CANDLE only)

In order to assess the change from pre-treatment period for NNS/CANDLE patients of efficacy measurements during baricitinib treatment period, the same analyses for the following primary and secondary efficacy variables will be performed by using average of data during pre-treatment period as a baseline value.

- Mean daily diary score
- Patient's symptom specific daily diary scores
- Proportion of days which meets a threshold of response criteria (See section 6.1)
- Physician's Global Assessment of Disease Activity scores

Proportion of days which meets a threshold of response criteria during both pre-treatment period and primary treatment period will be calculated.

6.8.3.2. Patient's relative retrospective medical records

This study will collect case report form data for parameters that define disease symptoms retrospectively of up to a maximum of 5 years from the point at when the patient participates in

Study JAJE (screening visit). The following data will be used for by-patient listing. Graphical presentation of change from the start of the patient's relative retrospective medical records may be shown.

- Laboratory testing (e.g. CRP, complete blood cell count, AST, ALT, gammaglutamyltransferase [GGT], creatine phosphokinase [CPK])
- Classification of disease severity (e.g. classification of disease severity for NNS patients, Barthel index)

6.9. Health Outcomes/Quality-of-Life Analyses

6.9.1. Patient Diary and Diary Score

6.9.1.1. NNS/CANDLE Diary

The patient diary for NNS/CANDLE is provided for daily collection of information on patients' signs and symptoms. NNS/CANDLE patients (or caregiver) record daily symptoms of fever, rash, musculoskeletal pain, headaches, and fatigue. Each symptom is rated on a scale of 0 to 4, with 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = more severe symptoms, and 4 = severe symptoms (possible range of total score 0 to 20). At each visit, the average daily diary score is calculated as follows:

- Average score of each symptom is calculated using data from 7 days preceding the current visit (not including data on the day of current visit).
- The calculated average score for each symptom is summed up and divided by the number of assessed symptoms (ie, 5 symptoms for NNS/CANDLE) to calculate the average score for each patient.

6.9.1.2. SAVI Diary

The patient diary for SAVI is provided for daily collection of information on patients' signs and symptoms. SAVI patients (or caregiver) record daily symptoms of fever, rash, musculoskeletal pain, fatigue, respiratory symptoms, and severity of ulcers/ischemic lesions. Each symptom is rated on a scale of 0 to 4, with 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = more severe symptoms, and 4 = severe symptoms (possible range of total score 0 to 24).

At each visit, the average daily diary score is calculated as follows:

- Average score of each symptom is calculated using data from 7 days preceding the current visit (not including data on the day of current visit).
- The calculated average score for each symptom is summed up and divided by the number of assessed symptoms (ie, 6 symptoms for SAVI) to calculate the average score for each patient.

- Additionally, the average diary score is calculated as the average of the symptom scores, excluding the respiratory/breathing symptom score.

6.9.1.3. AGS Diary

The patient diary for AGS is provided for daily collection of information on patients' signs and symptoms. AGS patients (or caregiver) record daily symptoms of neurologic disability, crying, length of uninterrupted sleep, generalized seizure, fever, excessive irritability, skin findings (body), and skin findings (hands, feet, and ears). Each symptom is rated on a scale (possible range of total score 0 to 34). At each visit, the average daily diary score is calculated as follows:

- Average score of each symptom is calculated using data from 7 days preceding the current visit (not including data on the day of current visit).
- The calculated average score for each symptom is summed up and divided by the number of assessed symptoms (ie, 8 symptoms for AGS) to calculate the average score for each patient.
- Additionally, the average diary score is calculated as the average of the symptom scores excluding neurological symptoms.

6.10. Other exploratory analyses

If sample size allows, two-dimensional plots of various data may be utilized to explore the relationship between variables of interest. For example, plots of efficacy measures such as change from baseline in mean daily diary score or proportion of days meeting response criteria versus change in laboratory measures may be used to explore risk/benefit relationships.

6.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

This will be described in a separate Pharmacokinetic Analysis Plan.

6.12. Safety Analyses

All safety data will be descriptively summarized by disease diagnosis for the safety population. The safety outcomes include TEAEs, TEAEs related to study drug, adverse events of special interest (AESI), serious AEs (SAEs), laboratory analytes, and vital signs.

6.12.1. Extent of Exposure

A by-patient listing will be created including the visit, week, patient's weight, total daily dose, total daily dose per weight (mg/kg), dose frequency, the treatment start date or dose adjustment date, and so on.

Baricitinib exposure will be summarized based on duration of exposure to baricitinib, and the patient years of exposure (PYE). PYE is defined as the sum of all patient exposure time in years for the specific disease diagnosis. A by-patient listing of study drug exposure will be provided

including duration of exposure in years and separately in weeks. Duration in days of baricitinib exposure is defined as the date of last dose of baricitinib minus the date of first dose of baricitinib +1.

6.12.2. Adverse Events

Adverse events are classified based upon the Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be coded to system organ class (SOC) and Preferred Term (PT) using the MedDRA version that is current at the time of database lock. Severity of AEs is recorded as mild, moderate, or severe. Adverse events will use the safety population defined in Section 6.3.

Summaries will consist of the frequency and percent of patients experiencing each AE. For summaries, SOC will be sorted in alphabetical order and PT in decreasing frequency within SOC by the total group. Patients will only be counted once, regardless of how many conditions are included under the same SOC and PT.

All AE listings will include AE type (pre-existing condition or TEAE), SOC, PT, reported term, event start and end date, start and end day, severity, related to study drug or non-study drug treatment, SAE status, reason AE is classified as serious, and event outcome.

6.12.2.1. Adverse Events

An overview of AEs including deaths, SAEs, TEAEs, and patients discontinued from study due to an AE will be summarized for the treatment period. Treatment Period includes all of three period: Dose-adjustment period, Primary treatment period and Maintenance treatment period.

By patient listing of all AEs, AEs leading to study treatment discontinuation, AEs leading to temporary study drug interruption and COVID-19 releated AEs will be provided.

6.12.2.2. Serious Adverse Events

Consistent with the International Conference on Harmonisation (ICH) E2A guideline, an SAE is any AE that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threating experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Considered significant by the investigator for any other reason.

By-patient listing of patients who experienced any SAE will be developed.

6.12.2.3. Treatment-emergent Adverse Events

Adverse events will be considered TEAEs if the AEs begin or increase in severity after the patient receives the first dose of baricitinib and up to the last visit during the treatment period. The MedDRA Lowest Level Term (LLT) will be used in defining which events are treatment-emergent. The maximum severity for each LLT during the baseline period up to first dose of the study medication will be used as baseline. The treatment period (i.e. Dose-adustment period, Primary treatment period and Maintenance treatment period) will be included as post-baseline for the analysis. If an event is pre-existing during the baseline period but it has missing severity, and the event persists during the treatment period, then the baseline severity will be considered mild for determining any post-baseline treatment-emergence (ie, the event is treatment-emergent unless the severity is coded mild post-baseline); if an event occurring post-baseline has a missing severity rating, then the event is considered treatment-emergent. All TEAEs will be summarized by SOC and PT.

6.12.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

6.12.3.1. Adverse Events of Special Interest

Adverse events of special interest include the following:

- Infections (all MedDRA preferred terms in MedDRA SOC “Infections and infestations”)
- myelosuppressive events
    - anemia (hemoglobin <6.5 g/dL),
    - leukopenia (White blood cell [WBC] count <2000 cells/µL),
    - neutropenia (absolute neutrophil count [ANC] <1000 cells/µL),
    - lymphopenia (lymphocyte count <500 cells/µL), and
    - thrombocytopenia (platelet count <75,000/µL)
- thrombocytosis (platelet count >600,000/µL)
- malignancies (except for successfully treated basal or squamous cell skin carcinoma)
- hepatic events including elevations in alanine transaminase (ALT) or aspartate aminotransferase (AST) (>3 times upper limit of normal [ULN]) with total bilirubin (>2 times ULN)
- major adverse cardiovascular events (MACE) which was positively adjudicated
- thrombotic events (such as deep vein thrombosis and pulmonary embolism) which was positively adjudicated

By-patient listing of treatment-emergent adverse events of special interest by AESI category will be developed by disease diagnosis.

6.12.4. Clinical Laboratory Evaluation

Observed values (CN and SI) and changes from baseline for hematology, chemistry, urinalysis, and fasting lipids laboratory parameters will be listed separately for each patient, including visit, week of visit, values, units, reference ranges, and flag for low/high results.

By-patient listing of treatment-emergent abnormalities (high, low, abnormal) in laboratory results at any time postbaseline will be developed. Abnormal elevations in hepatic laboratory value will be summarized as follows:

- ALT value ≥3 X ULN at any postbaseline visit,
- ALT value ≥5 X ULN at any postbaseline visit,
- ALT value ≥10 X ULN at any postbaseline visit,
- AST value ≥3 X ULN at any postbaseline visit,
- AST value ≥5 X ULN at any postbaseline visit,
- AST value ≥10 X ULN at any postbaseline visit, and
- ALT value ≥3 X ULN and total bilirubin ≥2 X ULN at any postbaseline visit (Hy's rule).

By-patient listing of BK virus test will be developed.

6.12.5. Vital Signs and Other Physical Findings

By-patient listing of individual patient data for pulse, systolic blood pressure, diastolic blood pressure, weight, height and occipital frontal circumference measurement (children less than 3 years old) over time with associated tables of values and changes from baseline will be created. In order to assess growth velocity over the course of baricitinib treatment, normative data will be used for height and weight (Ito et al. , 2005). Patient's relative retrospective medical records will also be used for height, weight and occipital frontal circumference measurement. Graphical display of individual patient data may be produced.

6.13. Subgroup Analyses

Because the medical conditions being treated in this study are rare, it is anticipated that relatively few patients with each condition will be enrolled. Therefore, no subgroup analyses are planned.

Some AGS patients may be diagnosed as FCL (familial chilbrain lupus). If more than 1 patient is diagnosed as FCL, subgroup analyses to select the subpopulation may be performed.

6.14. 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. Important protocol deviations (IPD) are defined and documented in the Trial Issue Management Plan. Of all the IPDs identified, a subset occurring from Visit 1 to the end of primary treatment period will be

evaluated to assess the quality of the trial. Potential examples of deviations include patients who receive excluded concomitant therapy, significant non-compliance with study medication (≤80% of expected number of doses), patients incorrectly enrolled in the study, and patients whose data are questionable due to significant site quality or compliance issues. Refer to a separate document for the important protocol deviations. The Trial Issue Management Plan includes the categories and subcategories of important protocol deviations and whether or not these deviations will result in the additional analysis excluded these data. By-patient listing of all IPDs will be created.

6.15. Interim Analyses and Data Monitoring

An interim analysis is planned after all planned enrolled patients completed the primary treatment period or early discontinued at or prior to the primary treatment period. The purpose of the interim analysis is to support regulatory submission of the Study JAJE data.

Another interim analysis is also planned after all planned enrolled patients completed Week 52 (Visit 20) or early discontinued at or prior to Visit 20 in order to evaluate the efficacy and safety of baricitinib with 1 year exposure.

Adjustment to type I error is not applicable as Study JAJE is a single arm, open-label program.

6.16. Planned Exploratory Analyses

Not applicable.

6.17. Annual Report Analyses

Annual report analyses, such as the Development Safety Update Report (DSUR), will be documented in a separate analysis plan.

6.18. 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 adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and ‘Other’ Adverse Events are summarized by treatment group, by MedDRA preferred term.

- An adverse event is considered ‘Serious’ whether or not it is a treatment emergent adverse event (TEAE).

- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the 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.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects 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 for example, the CSR, manuscripts, and so forth.

7. References

Zenya Ito, Noriko Kato, Katsuhiko Tachibana, Kenji Fujieda. (translated English title) The 2000 version of “standard height table” and “standard growth curve” conforming to the height standards adopted in the medical aid program for chronic pediatric diseases of specified categories, *The Journal of Pediatric Practice* 2005; 7:1343-1351.

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