Protocol 14V-JE-JAJE Amendament (e)

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

NCT04517253

Approval Date: 04-Sep-2023

Protocol I4V-JE-JAJE(e)
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)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (d)	*07-Apr-2022*
Amendment (c)	*09-Dec-2020*
Amendment (b)	*28-Jul-2020*
Amendment (a)	*18-Jun-2020*
Original Protocol	*15-May-2020*

Overall Rationale for the Amendment:

The primary reason for amending the JAJE protocol is to extend the duration of maintenance treatment period.

Amendment Summary for Protocol I4V-JE-JAJE Amendment (e)

Section # and Name	Description of Change	Brief Rationale
1.Synopsis	Update visit and week numbers for maintenance treatment period from visit 30 (Week 172) to Visit 36 (Week 244)	To update visit and week numbers accordingly
2.Schedule of Activities	Added maintenance treatment period visits 31 through 36 Revised visit numbers to relevant footnotes to reflect changes on the added maintenance period visits (footnote k and w)	To extend maintenance treatment period For retaining consistency of visit additions
5.1. Overall Design	Update visit and week numbers for maintenance treatment period from visit 30 (Week 172) to Visit 36 (Week 244) Updated Figure JAJE. 1.	To update visit and week numbers accordingly To reflect changes made to the schedule of activities
9.4.6.1. Hepatitis B Virus DNA Monitoring	Added relevant visits	To reflect changes made to the schedule of activities
Appendix 6. Protocol Amendment History	Added the protocol amendment history of amendment (a) to (d)	To reflect the changes as required on the latest protocol template

Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

Appendix **Page**

1. Synopsis

Title of Study:
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.

Rationale:
Baricitinib belongs to the pharmacological class of Janus kinase (JAK) inhibitors. Janus kinases are a family of 4 protein tyrosine kinases (JAK1, JAK2, JAK3, tyrosine kinase 2 [TYK2]) that play an important role in cytokine signal transduction. Baricitinib is a JAK1/JAK2 inhibitor demonstrating selectivity for and balanced inhibition of JAK1 and JAK2, with lower potency towards inhibition of JAK3 or TYK2 (Fridman et al. 2010).

In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, TYK2, and JAK3 with half-maximal inhibitory concentration values of 5.9, 5.7, 53, and >400 nM, respectively (Fridman et al. 2010). Janus kinases are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation, and immune function (eg, interleukin [IL]2, IL6, IL12, IL15, IL23, interferons, and granulocyte-macrophage colony-stimulating factor) (O'Shea et al. 2015). Within the intracellular signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signaling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, reducing the phosphorylation and activation of STATs, and thereby reducing inflammation, cellular activation, and proliferation of key immune cells (O'Shea et al. 2013).

The rationale for the current study is to evaluate the efficacy and safety profile of oral baricitinib when administered to pediatric and adult Japanese patients with Nakajo-Nishimura syndrome /chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (NNS/CANDLE), stimulator of interferon genes- (STING) associated vasculopathy with onset in infancy (SAVI), and Aicardi-Goutières syndrome (AGS). The safety and tolerability data from this study are intended to establish an understanding of the benefit/risk relationship for baricitinib in patients with NNS/CANDLE, SAVI, and AGS. These diseases are categorized as a group of conditions called the Type I interferonopathies. They are genetically defined autoinflammatory disorders with a strong Type I interferon-stimulated gene signatures, suggesting that interferon amplification contributes to the disease manifestations and that JAK inhibition by baricitinib could provide a new treatment option to these diseases.

Objective(s)/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

Abbreviations: AGS = Aicardi Goutières syndrome; CANDLE = chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; NNS = Nakajo-Nishimura syndrome; SAVI = STING-associated vasculopathy with onset in infancy; STING = stimulator of interferon genes.

[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] A 12-week pretreatment period is applied to NNS/CANDLE patients (see Section 5.1).

Summary of Study Design:

Study I4V-JE-JAJE (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 I autoinflammatory interferonopathies expected to benefit from JAK1/JAK2 inhibition, including NNS/CANDLE, SAVI, and AGS.

After marketing authorization of baricitinib for any of the indications in Japan, the study will be considered a postmarketing clinical trial (Phase 4 study).

Treatment Arms and Duration:

Study JAJE consists of 6 periods:

- screening period,
- pretreatment period (NNS/CANDLE only),
- dose-adjustment period,
- primary treatment period,
- maintenance treatment period, and
- posttreatment follow-up period.

Screening Period

The duration of screening period is different among diseases. For SAVI and AGS patients, the duration of the screening period is at least 7 days and up to 35 days prior to baseline (Visit 6). For NNS/CANDLE patients, they will enter the pretreatment period after screening period. Data at Visit 6 is used for baseline in all patients. Screening procedures will be performed according to the Schedule of Activities (Section 2).

All inclusion and exclusion criteria are provided in Sections 6.1 and 6.2, respectively. Patients with SAVI or AGS who meet all of the inclusion and none of the exclusion criteria will continue to Visit 6. Patients with NNS/CANDLE will continue to pretreatment period after screening visit.

Pretreatment Period (NNS/CANDLE only)

The pretreatment period is a 12-week period beginning at Visit 2 and natural history data with NNS/CANDLE patients will be collected through the pretreatment period. This applies only to NNS/CANDLE patients. The data through the pretreatment period is used for the baseline of the pretreatment period when results in the primary/maintenance treatment period are compared to that of the pretreatment period.

Dose Adjustment Period

Patients who meet all eligibility criteria will enter an 8-week dose-adjustment period. The initial dose prescribed at Visit 6 will be determined based on weight class and estimated glomerular filtration rate (eGFR) (see Table JAJE.5). After Visit 6, the dose-adjustment period will evaluate the optimal baricitinib dosage to the patients with NNS/CANDLE, SAVI, or AGS based on

clinical response. Steroid weaning may begin for patients who are receiving systemic corticosteroids. The detailed instructions are described in Section 5.1.1.

Primary Treatment Period

After completing dose adjustment at Visit 9, each patient will receive an optimized dosage of baricitinib that was determined throughout the dose-adjustment period. Patients should maintain their optimized baricitinib dosage during the primary treatment period as much as possible.

Primary treatment period is set for each patient as follows:

- NNS/CANDLE patients: 12 weeks [after Visit 9 (Week 8) to Visit 12 (Week 20)]
- SAVI or AGS patients: 24 weeks [after Visit 9 (Week 8) to Visit 15 (Week 32)]

Maintenance Treatment Period

After completing the primary treatment period at Visit 12 for NNS/CANDLE and at Visit 15 for SAVI and AGS respectively, patients will enter the maintenance treatment period.

Each patient will continue to receive baricitinib at their optimized dosage until whichever occurs first:

- Visit 36 (Week 244) during the maintenance treatment period, **OR**
- baricitinib is commercially available for NNS/CANDLE, SAVI, and/or AGS. All patients will move to early termination visit (ETV) within 6 months after marketing authorization of baricitinib.

Patients should maintain their optimized dosage during the maintenance treatment period as much as possible. If dose modification is conducted, the investigator must notify Lilly or its designee as soon as possible.

Post-Treatment Follow-Up Period

Patients discontinuing from study treatment who have received at least 1 dose of baricitinib will continue to the early termination visit. Patients who discontinue study treatment, or who complete the study treatment, will have a posttreatment follow-up visit (Visit 801) approximately 28 days after the last dose of baricitinib. As an exception, patients who will transition from this study to commercial baricitinib are not required to have Visit 801. Other therapy for NNS/CANDLE, SAVI, or AGS, as determined to be appropriate by the investigator, is allowed during the post-treatment follow-up period.

Number of Patients

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 patients for a specific disease if no eligible patients could be found.

Statistical Analysis

Because the medical conditions being treated in this study are rare, it is anticipated that relatively few patients 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.

2. Schedule of Activities

Table JAJE.1. Schedule of Activities (Screening Period and Pretreatment Period)

	NNS/CANDLE						SAVI and AGS	
	Screening and Pretreatment						Screening	
	Screening		Pretreatment					
Visit #	**1**	**1A**	**2**	**3**	**4**	**5 [a]**	**1**	**1A**
Study Week	**-13**		**-12**	**-8**	**-4**		**N/A**	**N/A**
Number of days at visit	**-91**		**-84**	**-56**	**-28**		**-35 to -7**	
Visit tolerance interval (days)			**±3**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Informed consent/Assent (per local requirements)	X						X	
Review inclusion/exclusion criteria[b,c]	X						X	
Demographic characteristics	X						X	
Confirmation of genetic mutation related to NNS/CANDLE, SAVI and AGS	X						X	
Habits: alcohol, tobacco and caffeine	X						X	
Medical history/Preexisting conditions	X						X	
Obtain patient's historical data[d]	X						X	
Immunization record[e]	X		X	X	X	X	X	
Concomitant medications	X		X	X	X	X	X	
Administer PPD/QuantiFERON®-TB Gold/ T-SPOT®.TB[f]	X						X	
Read PPD[f]		X						X
Chest x-ray[g]	X						X	
Physician's Global Assessment of Disease Activity	X		X	X	X	X	X	
Diary Scores (for NNS/CANDLE, SAVI or AGS)	X		X	X	X	X	X	
Adverse events	X		X	X	X	X	X	

	NNS/CANDLE						SAVI and AGS	
	Screening and Pretreatment						Screening	
	Screening		Pretreatment					
Visit #	**1**	**1A**	**2**	**3**	**4**	**5 [a]**	**1**	**1A**
Study Week	**-13**		**-12**	**-8**	**-4**		**N/A**	**N/A**
Number of days at visit	**-91**		**-84**	**-56**	**-28**		**-35 to -7**	
Visit tolerance interval (days)			**±3**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Physical Evaluation								
Vital signs (blood pressure, pulse)	X		X	X	X	X	X	
Physical examination[h]	X		X	X	X	X	X	
Height	X						X	
Weight	X			X	X	X	X	
Occipital frontal circumference measurement in children less than 3 years of age	X			X	X	X	X	
Electrocardiogram	X						X	
Laboratory tests[i]								
Hematology	X			X	X	X	X	
Clinical chemistry[j]	X			X	X	X	X	
Urinalysis[y]	X						X	
HBsAg, HBcAb, HBsAb	X						X	
HBV DNA[k]	X						X	
Hepatitis C antibody	X						X	
HIV	X						X	
Thyroid stimulating hormone	X						X	
Follicle stimulating hormone[l]	X						X	
Serum pregnancy test[m]	X						X	
Urine pregnancy test[m]				X	X			
Samples for biomarkers			X					
hsCRP	X			X	X	X	X	

Table JAJE.2. Schedule of Activities (Dose-Adjustment Period, Primary Treatment Period, Maintenance Treatment Period)

		NNS/CANDLE																		
		Dose-Adjustment Period[n]				Primary Treatment Period			Maintenance Treatment Period											
		SAVI and AGS																		
		Dose-Adjustment Period[n]				Primary Treatment Period						Maintenance Treatment Period								
Visit #		6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Study Week		0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	64	76	88	100
						Every 4 weeks											Every 12 weeks			
Number of days at visit		1	15	29	57	85	113	141	169	197	225	253	281	309	337	365	449	533	617	701
Visit tolerance interval (days)			±3	±3	±3	±3						±7								
Review inclusion/exclusion criteria[b,c]		X[c]																		
Immunization record[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray[g]																				
Physician's Global Assessment of Disease Activity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Classification of disease severity (for NNS/CANDLE)		X														X				X
Barthel Index (for SAVI, AGS)		X									X					X				X
Diary Scores (for NNS/CANDLE, SAVI, AGS)		X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP dispensed[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP returned and compliance assessed[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Evaluation																				
Vital signs (blood pressure, pulse)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

		NNS/CANDLE																		
		Dose-Adjustment Period[n]				Primary Treatment Period			Maintenance Treatment Period											
		SAVI and AGS																		
		Dose-Adjustment Period[n]				Primary Treatment Period						Maintenance Treatment Period								
Visit #		**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Study Week		**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**100**
						Every 4 weeks											**Every 12 weeks**			
Number of days at visit		**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**449**	**533**	**617**	**701**
Visit tolerance interval (days)			**±3**	**±3**	**±3**	**±3**						**±7**								
Height		X				X			X			X			X		X	X	X	X
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Occipital frontal circumference measurement in children less than 3 years of age		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests[i]																				
Hematology		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid panel[q]		X				X				X				X				X		X
Urinalysis[y]		X		X		X			X			X			X		X	X	X	X
HBV DNA[k]						X			X			X			X	X	X	X	X	X
BK virus quantitative PCR, plasma		X				X					X					X				X
BK virus quantitative PCR, urine[y]		X				X					X					X				X
Urine pregnancy test[m]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Iron studies (iron, TIBC and ferritin)		X				X			X			X			X		X	X	X	X
Plasma baricitinib concentration[r]			X				X	X												

		NNS/CANDLE																		
		Dose-Adjustment Period[n]				Primary Treatment Period			Maintenance Treatment Period											
		SAVI and AGS																		
		Dose-Adjustment Period[n]				Primary Treatment Period						Maintenance Treatment Period								
Visit #		**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Study Week		**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64**	**76**	**88**	**100**
						Every 4 weeks											**Every 12 weeks**			
Number of days at visit		**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**449**	**533**	**617**	**701**
Visit tolerance interval (days)			**±3**	**±3**	**±3**	**±3**						**±7**								
Samples for biomarkers[s]		X						X[t]			X[u]					X				X
hsCRP		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetic (DNA) collection[v]		X																		

	NNS/CANDLE, SAVI, and AGS											
	Maintenance Treatment Period											
Visit #	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
Study Week	**112**	**124**	**136**	**148**	**160**	**172**	**184**	**196**	**208**	**220**	**232**	**244**
	Every 12 Weeks											
Number of days at visit	**785**	**869**	**953**	**1037**	**1121**	**1205**	**1289**	**1373**	**1457**	**1541**	**1625**	**1709**
Visit tolerance interval (days)	**±7**											
Immunization record[e]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment of Disease Activity	X	X	X	X	X	X	X	X	X	X	X	X
Classification of disease severity (for NNS/CANDLE)				X				X				X
Barthel Index (for SAVI, AGS)				X				X				X
Diary Scores (for NNS/CANDLE, SAVI, AGS)	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
IP dispensed[p]	X	X	X	X	X	X	X	X	X	X	X	
IP returned and compliance assessed	X	X	X	X	X	X	X	X	X	X	X	X
Physical Evaluation												
Vital signs (blood pressure, pulse)	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[h]	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Occipital frontal circumference measurement in children less than 3 years of age	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests[i]												
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry[j]	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid panel[q]		X		X		X		X		X		X
Urinalysis[y]	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA[k]	X	X	X	X	X	X	X	X	X	X	X	X

	BK virus quantitative PCR, plasma				X				X				X
	BK virus quantitative PCR, urine[y]				X				X				X
	Urine pregnancy test[m]	X	X	X	X	X	X	X	X	X	X	X	X
	Iron studies (iron, TIBC and ferritin)	X	X	X	X	X	X	X	X	X	X	X	X
	Samples for biomarkers[s]				X								
	hsCRP	X	X	X	X	X	X	X	X	X	X	X	X

Table JAJE.3. Schedule of Activities (Early Termination, Post-follow-up Period)

	NNS/CANDLE, SAVI, and AGS	
	Early Termination	**Posttreatment Follow-Up Period**
	ETV[w]	**801[x]**
Visit #		
Study Week	—	**Last dose+4 weeks**
Number of days at visit	**N/A**	**N/A**
Visit tolerance interval (days)	**–**	**±5**
Immunization record[e]	X	X
Concomitant medications	X	X
Physician's Global Assessment of Disease Activity	X	X
Classification of disease severity (for NNS/CANDLE)	X	
Barthel Index (for SAVI, AGS)	X	
Diary Scores (for NNS/CANDLE, SAVI, AGS)	X	X
Adverse events	X	X
IP returned and compliance assessed	X	
Physical Evaluation		
Vital signs (blood pressure, pulse)	X	X
Physical examination[h]	X	X
Height	X	
Weight	X	X
Occipital frontal circumference measurement in children less than 3 years of age	X	X
Laboratory tests[i]		
Hematology	X	X
Clinical chemistry[j]	X	X
Fasting lipid panel[q]	X	X
Urinalysis[y]	X	X
HBV DNA[k]	X	X
BK virus quantitative PCR, plasma	X	
BK virus quantitative PCR, urine[y]	X	
Urine pregnancy test[m]	X	X
Iron studies (iron, TIBC and ferritin)	X	
Samples for biomarkers[s]	X	
hsCRP	X	X

Footnotes for Table JAJE.1, Table JAJE.2, and Table JAJE.3.

Abbreviations: AGS = Aicardi-Goutières Syndrome; DNA = deoxyribonucleic acid; eGFR = estimated glomerular filtration rate; ETV = early termination visit; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity c-reactive protein; IP = investigational product; IRG-S = interferon response gene score; N/A = not applicable; NNS/CANDLE = Nakajo-Nishimura Syndrome/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature PCR = polymerase chain reaction; PK = pharmacokinetic(s); PPD = purified protein derivative; RNA = ribonucleic acid; SAVI = STING-associated vasculopathy with onset during infancy; STING = stimulator of interferon genes; TB = tuberculosis; TIBC = total iron-binding capacity; V = visit.

[a] Visit 5 is only for patients who undergo washout period. Patients who are not administered biologic agents which need wash out (see Section 7.7.1) or who have already passed an appropriate washout duration of biologic agents can skip Visit 5 and proceed to Visit 6. The patients who are required to go to Visit 5 will proceed to Visit 6 after washout of biologic agents.

[b] Site personnel needs to notify Lilly or its designee of patient registration at Visit 1 and initiation of IP dosing at Visit 6.

[c] The most recent laboratory test results prior to IP administration will be confirmed in order to judge the eligibility criteria before patients with NNS/CANDLE move to Visit 6. The most recent visit prior to Visit 6 is defined as Visit 4 for patients without a biologic agent wash-out or Visit 5 for patients requiring biologic agent wash-out.

[d] The 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 the study (See Section 9.1.2.6).

[e] All immunization records will be collected in pediatric patients (<18 years of age). Immunization records for the BCG vaccine, varicella-zoster virus (VZV) vaccine, and Herpes zoster (HZ) vaccine will be collected for all patients.

[f] TB test(s), including PPD, QuantiFERON®-TB Gold, and T SPOT®. PPD tests must be read 48 to 72 hours after screening. If results are available from testing within 3 months, then the patient will not have to be retested.

[g] A posterior-anterior chest x-ray is required if it has not been performed in the 6 months prior to screening visit. For the patients who are concerned about a risk of radiation exposure, a chest x-ray will be required at the investigator's discretion if patients have a history of active or latent TB with documented evidence of appropriate treatment or patients have a positive or repeated not-negative TB test(s) (either PPD, QuantiFERON®-TB Gold, and/or T-SPOT®). In addition, chest radiography may be performed at any time during the study, including the follow-up period, if medically necessary, in the opinion of the investigator.

[h] One complete physical examination (excluding pelvic and rectal examinations) will be performed at Visit 1. All subsequent physical examinations may be symptom directed. A complete physical examination may be repeated at the investigator's discretion at any time. Fundoscopy may be completed as part of the physical examination, as necessary if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients. Pulmonary function monitoring for SAVI patients may be completed if medically necessary in opinion of the investigator.

[i] In cases where required blood samples cannot be collected due to blood volume limitation relative to patient size/age, the investigator must consult with the Lilly-designated medical personnel to determine which samples to collect. Even if required samples are not collected, it will not be considered a protocol violation, but will need to be documented in the medical record.

[j] Clinical chemistry will include eGFR. Patients will receive an initial dose based on weight class and eGFR according to Table JAJE.5. for patients less than 2 years of age (eGFR based on the Bedside Schwarz 2009 formula),

- for patients between 2 years and 18 years of age inclusive (eGFR based on the Japanese Society for pediatric Nephrology formula),
- for patients greater than 18 years of age (eGFR based on Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine 2009 equation)

[k] Patients who are positive for HBcAb or HBsAb and negative for HBV DNA may be enrolled. Any enrolled patient who is HBcAb- or HBsAb-positive must undergo HBV DNA testing at Visit 10, Visit 13, Visit 16, Visit 19, Visit 21, Visit 22, Visit 23, Visit 24, Visit 25, Visit 26, Visit27, Visit 28, Visit 29, Visit 30, Visit 31, Visit 32, Visit33, Visit 34, Visit 35, Visit 36, ETV, and V801 (Section 9.4.6). Unscheduled visits may be used for monitoring of HBV DNA, when necessary.

[l] Women >40 years old. For women >55 years old and 12 months of amenorrhea, FSH testing is not required.

[m] For female patients of child-bearing potential: a serum pregnancy test will be performed at Visit 1 and a urine pregnancy test (local laboratory) will be performed at Visit 6 to determine study eligibility. At subsequent visits, a urine pregnancy test will be performed. Females ≥10 years old of age will be considered to have child-bearing potential if menarche has been reached or if there is reason to believe the patient is sexually active. Females <10 years old of age may have pregnancy tests performed at the discretion of investigator, as needed.

[n] Study dose for each patient is adjusted from Visit 6 to Visit 9. Dose adjustment will be conducted according to Table JAJE.5.

[o] At least 1 consecutive week of diary scores are required prior to beginning IP.

[p] If there is still sufficient left in the patient's IP bottle until the next visit, the bottle will not be returned to site and the patient will take the IP from the same bottle. In this case, a new IP bottle will not be dispensed.

[q] Fasting lipid profile: Patients should not eat or drink anything except water for 4 to 12 hours, depending on weight and age, as specified below. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Recommended fasting times by age and weight are as follows:

- Patients ≥12 years: fast for 12 hours prior to laboratory sampling;
- Patients 8 to <12 years and weighing >50 kg: fast for 12 hours prior to laboratory sampling;
- Patients 8 to <12 years and weighing ≤50 kg: fast for 8 hours prior to laboratory sampling;
- Children <8 years and weighing 25 to ≤50 kg: fast for 8 hours prior to laboratory sampling;
- Children <8 years and weighing 10 to <25 kg: fast for 6 hours prior to laboratory sampling; and
- Children <8 years and weighing <10 kg: fast for 4 hours prior to laboratory sampling.

[r] Baricitinib concentration samples will be collected, as described in Section 9.5. Additional unscheduled PK samples may be collected after Visit 6, as needed, for safety monitoring in patients with eGFR <60 mL/min/1.73 m^2.

[s] Biomarkers may include IP-10/CXCL10 and IRG-S (Appendix 2). Samples for IRG-S will be collected in RNA PAXgene tube.

[t] NNS/CANDLE only.

[u] SAVI and AGS only.

[v] Pharmacogenetic sample is collected at Visit 6. However, sample collection timing can be rescheduled to any other visit, if blood volume is limited at Visit 6.

[w] An early termination visit is required if the patient discontinues from study treatment before Visit 36. All patients will move to ETV within 6 months after marketing authorization of baricitinib.

[x] Patients who achieve either study completion or early discontinuation will have a posttreatment safety follow-up visit (V801) approximately 28 days after the last dose of IP. Patients who will transition from this study to commercial baricitinib are not required to have Visit 801. In this case, it will not be considered a protocol violation if the post treatment follow up period is not performed.

[y] If a urine sample is unable to be collected in patients, particularly those who have not been toilet trained or those who have physical impairment caused by primary disease, this will not be considered to be a protocol violation provided that the site maintains appropriate documentation of why the sample is missing.

Note: Sites should make every attempt to schedule patient visits within the defined window. Exceptions to these windows may be granted under certain circumstances with prior approval of the Lilly clinical research physician or designee.

3. Introduction

3.1. Study Rationale

The purpose of this open-label treatment protocol is to evaluate the efficacy and safety of baricitinib in patients with a confirmed genetic diagnosis of Nakajo-Nishimura Syndrome / chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (NNS/CANDLE), stimulator of interferon (IFN) genes- (STING-) associated vasculopathy with onset during infancy (SAVI), and Aicardi-Goutières-Syndrome (AGS) who are eligible for treatment under this protocol. Baricitinib is an orally administered inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2).

3.2. Background

Janus-Associated Kinase Pathway and Baricitinib

The JAKs are the principal family of kinases associated with signal transducers and activators of transcription (STAT) phosphorylation and activation. The receptor-associated STATs are phosphorylated by JAKs, resulting in their activation. Activated STATs are transcription factors that drive the expression of multiple genes important for cell activation, localization, survival, and proliferation (Valentino and Pierre 2006). The JAK/STAT pathway is used to transduce intracellular signals to relevant cell types following the binding of over 40 different cytokines to their respective receptors (Valentino and Pierre 2006). Representative JAK/STAT-dependent cytokines involved in the inflammation associated with innate and adaptive immunity include type I and II IFNs, interleukin- (IL-) 2, IL6, IL12, IL23, and granulocyte macrophage colony-stimulating factor. Evaluation of JAK inhibitors in clinical studies has validated JAK as a promising therapeutic target by demonstrating clinically meaningful efficacy in patients with rheumatoid arthritis (RA) and psoriasis (Boy et al. 2009; Kremer et al. 2009).

Baricitinib has been investigated for the treatment of inflammatory diseases, including RA, systemic lupus erythematosus, atopic dermatitis, and alopecia areata. Baricitinib has been administered to healthy subjects as single doses ranging from 1 mg to 40 mg, and as multiple doses of up to 20 mg once daily (QD) for 10 days, 10 mg QD for 28 days, or 5 mg twice daily (BID) for 28 days. Baricitinib has been administered as a single 10-mg dose to subjects with mild or moderate renal impairment, as a single 5-mg dose to subjects with severe renal impairment, and as a single 5-mg dose to subjects with end-stage renal disease. In patients with RA, baricitinib has also been administered at doses up to 15 mg QD for approximately 1 month and doses up to 10 mg QD for 24 weeks. In a Phase 2b study of baricitinib in patients with RA, baricitinib at doses of up to 8 mg QD were administered for up to 76 weeks.

In clinical studies, baricitinib has been generally safe and well-tolerated in single doses ranging from 1 mg to 40 mg and in repeat oral doses ranging from 1 mg to 20 mg. The most commonly reported treatment-emergent adverse events (TEAEs) in patients with RA are in the Medical Dictionary for Regulatory Activities (MedDRA) Infections and Infestations system organ class (SOC). The most common alterations in laboratory values involve decreases in hemoglobin,

hematocrit, total red blood cells, and white blood cells ([WBCs]; neutrophils and other white cell lines), and increases in platelet counts, high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglycerides.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) may be found in the Investigator's Brochure. Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the Investigator's Brochure.

Autoinflammatory Diseases

Autoinflammatory disorders differ from autoimmune diseases in that they primarily result from perturbations in the innate immune system rather than in adaptive immunity, although overlapping features may occur (McGonagle and McDermott 2006; Henderson and Goldbach-Mansky 2010). Autoinflammatory diseases are immune dysregulatory conditions that typically present in early childhood with fever and disease-specific patterns of organ inflammation (Masters et al. 2009; Henderson and Goldbach-Mansky 2010; de Jesus et al. 2015). These diseases can present in adults, with examples including gout and pseudogout. They can also present during childhood and infancy with multiple organ involvement including urticaria-like rash, arthralgia, frequent fevers, and neutrophil infiltration of the target organs (ie, skin).

The genetics of many of the autoinflammatory diseases have been elucidated over the past several years. Genetic mapping has identified a series of familial mutations that display a monogenic autosomal mode of inheritance. The most extensively characterized and understood autoinflammatory diseases involve mutations resulting in inflammasome activation and the increased production of mature IL1. Cryopyrin-associated periodic syndromes (CAPS) describe a spectrum of IL-1-dependent autoinflammatory diseases, including Muckle-Wells syndrome, familial cold autoinflammatory syndrome, and neonatal-onset multisystem inflammatory disease. Most of these diseases include fever, urticaria-like rash, and arthralgia, and are associated with gain-of-function- (GOF) mutations in the inflammasome, including, but not limited to, mutations in the NLRP3 gene (McGonagle and McDermott 2006). Patients with these forms of autoinflammatory disease have responded well to interventions targeting this pathway, with rapid responses seen to the IL-1 receptor antagonist (anakinra) or other IL-1 intervention strategies, including monoclonal antibodies (canakinumab [Ilaris®; Novartis]) (Goldbach-Mansky et al. 2006) and the IL-1 receptor-immunoglobulin fusion protein (rilonacept) (Hoffman et al. 2008; Goldbach-Mansky 2009; Lachmann et al. 2009).

While mutations in the IL-1 pathway have been reported for some autoinflammatory diseases, there are reports of diseases that have not mapped to this pathway nor have responded to IL-1 intervention strategies. To this extent, loss-of-function (LOF) mutations in the proteasome subunit beta type-8 (PSMB8) gene encoding the β5i catalytic subunit of the immunoproteasome, a T75M substitution, have been described in patients with systemic inflammation characterized by lipodystrophy, joint contractures, muscle atrophy, and elevated levels of circulating IFN-γ, IL-6, and IL-2 receptor (Agarwal et al. 2010). Furthermore, 9 patients have been reported with atypical neutrophil skin infiltrates, systemic inflammation, and recurrent fevers as a new

autoinflammatory syndrome with the acronym CANDLE (Liu et al. 2012). These patients also had mutations that mapped primarily to the β5i subunit of the immunoproteasome rather than to genes associated with IL-1β or its processing.

CANDLE typically presents clinically before 6 months of age with fever, repeated attacks of erythematous and violaceous, annular cutaneous plaques, persistent periorbital erythema and edema, finger or toe swelling, hepatomegaly, and variable elevation of acute-phase reactants. Another prominent clinical feature is progressive loss of peripheral fat (lipodystrophy). Patients fail to thrive and lymphadenopathy and hypochromic or normocytic anemia may be seen (Ramot et al. 2011; Torrelo et al. 2010).

In an international collaborative effort, 9 patients with the clinical diagnosis of CANDLE were studied (Liu et al. 2012). Genetic analyses showed that 7 out of 9 patients harbor a genetic mutation in PSMB8 of the immunoproteasome complex (i-proteasome). After the original report of CANDLE in 4 children, a syndrome diagnosed in 3 adult patients with joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy was reported under the acronym "JMP" for joint contractures, muscle atrophy, and panniculitis (Garg et al. 2010). Patients with JMP were recently demonstrated to carry a PSMB8 mutation (Agarwal et al. 2010). Five patients were homozygous for the same mutation (T75M). Two patients were heterozygous for the T75M mutation, 1 patient was homozygous for a nonsense PSMB8 mutation (C135X), and 1 patient with clinical CANDLE was PSMB8-mutation negative, suggesting genetic heterogeneity and the possibility of other defects in the i-proteasome or the disease-associated pathway.

CANDLE patients have some overlapping features with JMP patients, including a cutaneous eruption and lipodystrophy (Garg et al. 2010). Although the patients reported as having JMP had more prominent joint contractures and muscle atrophy than patients described as having CANDLE, the detection of the same, and additional, mutations in PSMB8 unifies these disorders as proteasome-associated autoinflammatory syndromes (PRAAS). CANDLE patients present with recurrent febrile episodes, elevated acute-phase reactants, and a characteristic neutrophilic dermatosis with a mononuclear interstitial infiltrate including "immature" neutrophils in the dermis that seems pathognomonic for CANDLE (Torrelo et al. 2015). In fact, 2 patients have been misdiagnosed with acute cutaneous myelogenous leukemia.

While data in young children illustrate manifestations of early severe, and potentially lethal, disease and alert to the fact that muscle involvement and joint contractures may not present until later in life, these findings in the adult patients illustrate the natural course of the disease in untreated or partially treated patients (Kitano et al. 1985; Garg et al. 2010).

CANDLE patients do not respond to disease-modifying anti-rheumatic drugs (DMARDs), IL-1 or IL-6 blocking agents or tumor necrosis factor- (TNF-) inhibitors and have inconsistent responses to corticosteroids with rebound symptoms with tapering (Torrelo et al. 2010; Liu et al. 2012; Wang et al. 2014). The estimated mortality based on reported cases is 30% before the age of 40 (Kim et al. 2016).

Other conditions that exhibit strong IFN-mediated gene expression signatures on gene expression studies from peripheral blood have recently been identified.

- **SAVI.** Using whole exome sequencing, a *de novo* mutation in *TMEM173* (STING) at position c.461A>G, p.N154S was identified that causes limb-threatening vasculopathy and interstitial lung disease (Liu et al. 2014). Four other unrelated children (total of 5 children) with similar clinical phenotypes have been identified to have mutations in the same gene using targeted sequencing of the candidate gene (Liu et al. 2014). Two unrelated patients were found to have the same *de novo* mutation in *TMEM173*. One of the patients succumbed to the illness at the age of 14 years. One patient, who died at the age of 15 years, harbored a *de novo* mutation at position c.463G>A, p.V155M (Liu et al. 2014 supplement). Another patient harbors a *de novo* mutation at position c.439 G>C, p.V147L. All mutations are in exon 5 of the gene. In the 3 living patients in the cohort, gene expression from whole blood was systematically evaluated. STING ligand, cyclic guanosine monophosphate- adenosine monophosphate (cGAMP) was used in stimulation assays of fibroblasts taken from patients and controls. Transfection studies of STING constructs with disease-causing mutations in HEK293T cells were performed.

  HEK293T cells transfected with disease-causing mutant constructs show spontaneous upregulation of IFN-β transcription and much stronger response to STING ligand cGAMP stimulation compared with wild type. Similarly, stimulation of patient fibroblasts with cGAMP resulted in much stronger upregulation of IFN-β transcription, even at low concentrations that triggered no response in control fibroblasts from healthy or disease controls. Increased transcription at 4 hours is restricted to IFN-β and not seen in IFN-α4, IFN-α7, IL-1, IL-6, or TNF. The clinical phenotype and the increased IFN response gene expression in the peripheral blood suggest a GOF in the STING gene. This is hypothesized to result in a severe autoinflammatory phenotype with interstitial lung disease progressing to interstitial fibrosis, with focal emphysema and acral vasculopathy, resulting in necrosis and loss of fingers/toes, ulcerating skin lesions, fevers, and elevated inflammatory markers. This condition is described as SAVI (Liu et al. 2014).

- **AGS.** AGS is a monogenic disorder resulting from LOF mutations in any of several distinct genes, resulting in a type 1 interferonopathy associated with both peripheral manifestations and devastating neurologic consequences (Crow and Manel 2015). AGS is an inflammatory disease particularly affecting the brain (causing severe damage to the white matter as well as the deposition of calcium in both white and grey matter) and the skin (resulting in so-called chilblain lesions affecting the toes, fingers, and ears in particular), but also demonstrating systemic features (eg, glaucoma, cardiomyopathy, neuropathy, endocrinological problems) in many patients.

  Characteristically, AGS manifests as an early-onset encephalopathy that results in severe intellectual and physical handicap. A subgroup of infants with AGS present at birth with abnormal neurologic findings, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia, a picture highly suggestive of congenital infection. Otherwise, most

affected infants present at variable times after the first few weeks of life, frequently after a period of apparently normal development. Typically, affected infants demonstrate the subacute onset of a severe encephalopathy characterized by extreme irritability, a loss of previously acquired skills, and a slowing of head growth. Over time, as many as 40% develop chilblain-like skin lesions on the toes, fingers, and ears.

AGS is a genetically heterogeneous Mendelian disease, occurring due to mutations, such as LOF or GOF, in any of the genes encoding:

- the DNA exonuclease TREX1 (TREX1; LOF),
- the 3 non-allelic components of the RNase H2 endonuclease complex (RNASEH2A, RNASEH2B, and RNASEH2C; LOF),
  - the deoxynucleoside triphosphate triphosphohydrolase SAMHD1 (SAMHD1; LOF), the double-stranded RNA editing enzyme, adenosine deaminase, RNA-specific (ADAR; LOF/GOF), and
- the double-stranded RNA cytosolic sensor IFIH1/MDA5 (IFIH1; GOF).

The proteins defective in AGS are all associated with nucleic acid metabolism/sensing. It is hypothesized that 6 of these proteins are involved in limiting the accumulation (TREX1, the 3 RNase H2 complex components, SAMHD1, and the mature ADAR), of intracellular nucleic acid species, a failure of which results in triggering of an innate immune response that is more normally induced by viral nucleic acids. The seventh protein, IFIH1/MDA5, is also involved in nucleic acid metabolism, being a receptor for cytosolic dsRNA. This understanding defines a novel cell-intrinsic mechanism for the initiation of autoimmunity by IFN-stimulatory nucleic acids, and offers an elegant mechanistic explanation for the phenotypic overlap of AGS with congenital infection and systemic lupus erythematosus. That is, in the absence of AGS-related protein activity, endogenous nucleic acids accumulate and are sensed as viral or "non-self," leading to the induction of an IFNα-mediated immune response and, sometimes, the production of antibodies against self-nucleic acids.

AGS is associated with increased levels of IFN-α in the cerebrospinal fluid and serum. However, IFN-α levels, and white cell counts, in the cerebrospinal fluid have been reported to fall over the first few years of life, perhaps corresponding with an apparent clinical "burning-out" of the encephalopathic period. Unfortunately, due to the obvious difficulties of repeat cerebrospinal fluid sampling, very few serial data are available (that is, systematic IFN-α activity profiling beyond infancy has not been undertaken). Indeed, data acquired more recently on more than 200 AGS patients using quantitative polymerase chain reaction (qPCR) analysis of IFN-stimulated genes indicates the presence of a so-called "interferon signature" at any age in most patients with mutations in TREX1, RNASEH2A, RNASEH2C, SAMHD1, ADAR, and IFIH1 (Crow et al. 2015). Around 30% of patients with RNASEH2B mutations demonstrated no such upregulation—but as IFN-stimulated gene sampling in these studies was usually performed many years after initial diagnosis, it is possible that all patients exhibit a positive IFN signature in the early stages of the disease. Whatever the case, these

findings are important in indicating an ongoing biochemical disease process which is likely lifelong in most patients.

Although some children are affected by the time of birth (ie, the disease has an in utero onset), most experience the onset of disease at some point postnatally, often after a period of apparently normal development. Moreover, disease progression is subacute, reflected in a progressive loss of skills occurring over several months. Thus, a window of opportunity exists during which treatments might be efficacious. Maximum benefit will likely be afforded when effective treatment is started as early as possible after disease onset. However, long-term/later-onset morbidities also occur (eg, chilblains), so children of any age might potentially benefit from efficacious treatment.

As discussed above, previously, the diagnosis of AGS has usually been made in the context of an early-onset encephalopathy characterized by basal ganglia calcification and white matter abnormalities. However, a much wider spectrum of disease presentation, progression, and outcome is now recognized. Of specific note, mutations in ADAR have recently been described in a clinically distinct phenotype characterized by bilateral striatal necrosis. Furthermore, mutations in RNASEH2B, ADAR, and IFIH1 can cause non-syndromic spastic paraparesis in the presence of completely normal brain and spinal imaging, indicating that type I IFNs can have a neurotoxic effect at the cellular level in the absence of obvious neuroimaging changes. Most recently, IFIH1 GOF mutations have been shown to cause a phenotype variably characterized by dental anomalies (early-onset periodontitis and root resorption), aortic and valvular calcification, glaucoma, psoriasis, contractures, and acro-osteolysis.

AGS was originally defined as an early-onset progressive brain disease mimicking the sequelae of in utero viral infection, but it is now known to have an expanded phenotype that includes chilblains, other lupus-like- symptoms, and glaucoma. An estimated 20% of patients with AGS develop severe neurologic dysfunction diagnosed soon after birth, manifesting as spasticity, dystonia, seizure, cortical blindness, and progressive microcephaly (Eleftheriou and Brogan 2017).

As a related disease with AGS, familial chilblain lupus [FCL] does not develop observed neurological symptoms, but other manifestations, including chilblain-like lesions and gene mutations in TREX1, SAMHD1 or STING, similarly as AGS. Lesions are characterized by cold-induced, bluish-red lesions on the hands, feet, and ears that may ulcerate, occasionally leading to significant tissue loss. The skin lesions are similar to those seen in patients with AGS with neurologic involvement and in some patients with non-genetic forms of systemic lupus erythematosus (Eleftheriou and Brogan 2017).

As several of these patients have shown limited or no clinical improvement with other disease-modifying therapies, a therapy designed to target multiple cytokine pathways, rather than a monospecific approach, would be appropriate for consideration, especially when evidence exists for activation of non-IL-1 pathways. In particular, there is a growing group of autoinflammatory syndromes with IFN pathway dysregulation that could be expected to benefit from inhibition of

IFN signaling, such as through JAK1/JAK2 inhibition. It is anticipated that baricitinib, a JAK1/JAK2 inhibitor, will inhibit the production, as well as the signaling, of cytokines associated with chronic autoinflammatory syndromes that are not IL-1 mediated.

Summary

Mutation positive NNS/CANDLE, SAVI, and AGS (including FCL) patients with inadequate response to conventional symptom-modifying therapies are eligible. In these patients, systemic inhibition of JAK signaling pathways is expected to favorably impact both innate and adaptive immunologic processes. Therefore, baricitinib is a reasonable option for patients with NNS/CANDLE, SAVI, and AGS for whom biologics have proven to be ineffective, and/or there are no other treatments, thereby, offering these patients an alternative therapeutic option.

3.2.1. Concept of Autoinflammation

3.2.1.1. The Role of IL-1 in Autoinflammatory Diseases

The discovery that single-gene mutations in the NLRP3 inflammasome cause the disease spectrum of CAPS provided a molecular mechanism that links intracellular stress recognition with the initiation of a cytokine response. The pivotal role of IL-1 in cryopyrinopathies was confirmed in clinical studies using IL-1 blocking therapies (Sanchez et al. 2013). Further, this inflammatory pathway is not only constitutively activated in CAPS, but is also activated through cellular "danger molecules," including uric-acid crystals in gout (Dalbeth and So 2010), ceramide, oxidized low-density lipoprotein, and glucose in type 2 diabetes mellitus (De Nardo and Latz 2011), and cholesterol crystals in coronary artery disease (Goldbach-Mansky 2009; Duewell et al. 2010).

Although the role of IL-1 has clinically been confirmed in other autoinflammatory diseases (Goldbach-Mansky 2011), it has become clear that blocking IL-1 in children who present with presumed autoinflammatory disorders is not effective in all patients (Canna and Goldbach-Mansky 2015). Novel autoinflammatory conditions with poor responses to IL-1 blocking therapies suggest a role of cytokine dysregulation beyond IL-1 (Sanchez et al. 2013).

3.2.2. Functional Data Supporting a Rationale to Block IFN Signaling

Empiric treatment with targeted agents to TNF, IL-1, and IL-6 have been unsuccessful in patients with CANDLE. To characterize the inflammatory pathway and to identify therapeutic targets, the cytokine profile, transcriptome, and signaling pathways in these patients has been assessed. Interestingly, interferon inducible protein 10/C-XC motif chemokine 10 (IP-10/CXCL10) serum levels, were on average over 77-fold higher than controls. Very high levels of IP-10/CXCL10 suggested excessive IFN responses in CANDLE patients. Since STAT-1 is a downstream mediator of IFN-α/β and γ signaling, STAT-1 phosphorylation in the monocytes in response to IFN-γ stimulation has been studied. Compared with monocytes from healthy controls and a patient with neonatal-onset multisystem inflammatory disease (an IL-1 mediated autoinflammatory syndrome), monocytes from CANDLE patients showed stronger STAT-1

phosphorylation in response to all IFN-γ- concentrations used for stimulation (from 0.1 to 100 IU).

To probe for further evidence of excessive IFN signaling in CANDLE patients in vivo, the transcriptome in whole-blood microarray analysis in 4 CANDLE patients and 4 age- and gender-matched healthy controls were compared. CANDLE patients had 507 genes (650 transcripts) that were more than 2-fold differentially expressed compared to healthy controls ($p<0.05$), 238 of which were upregulated. Differentially expressed genes (DEGs) were analyzed by the Ingenuity Pathway Analysis program to identify dysregulated canonical pathways, and the IFN pathway was the most differentially regulated in CANDLE patients ($p=4.73^{E-06}$). Of the 238 upregulated DEGs, 41 (17.2%) were IFN-induced. Of the DEGs on the IFN-induced gene list in Ingenuity Pathway Analysis, all were IFN-γ induced (n = 42, 100%) and 6 (14.2%) were also regulated by IFN-α/β. The genes were plotted on a color-coded heat map, and the patterns of increased and decreased DEGs were strikingly similar among CANDLE patients, regardless of the presence or absence of detectable PSMB8 mutations. IP-10/CXCL10, which is highly expressed in the patients' serum, was among the IFN-induced upregulated genes. The DEG list from patients with CANDLE was compared with IFN-regulated genes published in www.interferome.org, and 119 of the 507 DEGs were found to be IFN regulated.

To assess the effect of various treatments on IFN-induced genes, blood samples from multiple visits were obtained in 2 patients, including 1 patient treated at different times with anti-TNFα and anti-IL-6 therapy. Although temporary clinical improvement was seen with anti-TNF-α and anti-IL-6 treatment (Goldbach-Mansky et al. 2009), the "IFN signature" did not improve. IL-6 blocking therapy normalized IL-6 inducible genes and C-reactive protein (CRP) levels; however, skin lesions, fatigue, or joint pain did not improve substantially and peripheral fat loss progressed, suggesting a possible association between the IFN signature and disease activity. Interestingly, in an active SAVI patient, STAT-1 was maximally phosphorylated and could not have been further activated (Liu et al. 2014). Preliminary data using tofacitinib in cells of SAVI patients suggest that the IFN response genes can be downregulated when blocking with tofacitinib (Liu et al. 2014), supporting the hypothesis that patients with SAVI may respond to JAK1/JAK2 inhibition.

3.2.3. In Vitro Data on Loss of I-Proteasome Function in Psmb8/Lmp7 Knockout Mice

The 26S proteasomes are multi-subunit protein complexes critical for degradation of Polyubiquitinated proteins within cells. The 20S core complex consists of 2 α rings and 2 β rings, each having 7 different α or β subunits. The i-proteasomes are expressed in hemopoietic cells after IFN induction, in which the β1, 2, and 5 subunits are replaced with iβ1, iβ2, and iβ5 subunits. PSMB8 encodes β5i, a catalytic subunit of an i-proteasome. The functions of the i-proteasomes have been studied in vitro and in animal models. The i-proteasome can generate antigenic peptides for major histocompatibility complex class I presentation (Yewdell 2005), but recent data in *psmb8/lmp7* knockout mice (Moebius et al. 2010) suggest an important additional role in maintaining cell homeostasis by removing accumulating proteins marked for degradation

from the cells (Seifert et al. 2010). Cellular stress, such as infections or radiation, lead to type I IFN-induced production of reactive oxygen species and newly synthesized proteins that are particularly sensitive to oxidation (Reits et al. 2006; Lelouard et al. 2007; Medicherla and Goldberg 2008). Failure to process/degrade protein will result in formation of ubiquitin-rich cytoplasmic aggregates or inclusions and consequently increase cellular sensitivity to apoptosis (Seifert et al. 2010). It is thought that the excessive demand for protein processing/degradation is mainly met by cytokine-mediated upregulation of the ubiquitination machinery and increased assembly of the highly efficient i-proteasome (Strehl et al. 2008; Voigt et al. 2010).

There is evidence that the patients' cells have accumulated polyubiquitinated proteins, an indication of decreased proteasome activity (Arima et al. 2011). The persistent IFN signature in CANDLE patients on microarray and the increased STAT-1 phosphorylation in monocytes from CANDLE patients in response to IFN-γ stimulation could reflect ongoing "cellular stress." In concordance with the current understanding of the i-proteasome function, a disease model which proposes that defects in i-proteasome function may lead to accumulation of damaged proteins resulting in more cellular stress and a vicious cycle of increased IFN signaling has been proposed. Interestingly, CANDLE flares are observed with infections and other stressful events. Some cells, such as fat or muscle cells, may be subject to cellular apoptosis due to accumulation of damaged proteins. In fact, a Japanese patient with severe fat loss, muscle atrophy, and suspected CANDLE died of cardiac failure at the age of 47 years. Histological examination of skeletal muscle on autopsy revealed intramitochondrial paracrystalline inclusions and cytoplasmic and myeloid bodies in muscle cells (Oyanagi et al. 1987). The idea that such inclusions result from the accumulation of oxidant damaged/aggregated proteins that cause cell death is an attractive hypothesis to account for muscle loss later in life, but studies on the cell-specific effect of the i-proteasome deficiency are needed to explain the observed visceral effects of the mutations.

3.2.4. In Vitro Evidence for Using a JAK Inhibitor

Janus kinases are critical signaling molecules mediating IFN signaling on the IFN receptors. To determine the effect of a JAK inhibitor, tofacitinib, on the excessive IFN response in CANDLE patients, its inhibiting effect on STAT-1 phosphorylation in patients' monocytes stimulated with IFN-γ was studied. Tofacitinib decreased STAT-1 phosphorylation in a dose-dependent manner in both CANDLE patients and healthy control monocytes. Tofacitinib also inhibited IP-10/CXCL10 production in a dose-dependent manner, and at 0.5 μM, the IP-10/CXCL10 blockade was more efficient than with the IL-1 receptor agonist anakinra or anti-IL-6 blockade with tocilizumab (Liu et al. 2012).

3.2.4.1. Preclinical findings in induced pluripotent stem (iPS) cells

Recently, in vitro disease modeling using patient-derived iPS cells for NNS was reported to be applied to discover effective drugs, including baricitinib (Honda-Ozaki et al. 2018). Effects of a series of anti-inflammatory compounds in the in vitro disease modeling using NNS-type mutant iPS cell-derived monocytes were evaluated and baricitinib showed inhibition of the secretion of IP-10/CXCL10, IL-6, and monocyte chemoattractant protein 1 (MCP1) in a dose-

dependent- manner. These findings support promising effectiveness of baricitinib to control inflammation in patients with NNS/CANDLE.

3.2.5. Baricitinib study results in an expanded access program

To assess the effect of JAK1/JAK2 inhibition in patients with autoinflammatory interferonopathies, patients with CANDLE (N=10), SAVI (N=4), or other interferonopathies (N=4) were treated with baricitinib in an expanded access program (Sanchez et al. 2018). These patients were treated for a mean duration of 3 years and benefit was assessed by reductions in daily disease symptoms and corticosteroid requirement. Quality of life, organ inflammation, changes in IFN-induced biomarkers, and safety were longitudinally assessed. Biomarkers of IFN signaling, serum levels of the chemokine IP-10/CXCL10, and the IFN response gene score significantly decreased during treatment with baricitinib. Further, the reduction in IFN biomarkers correlated with the improvement of clinical signs and symptoms and with the ability to taper the corticosteroid dose, indicating a causative role for chronic IFN signaling in disease pathogenesis in patients with type I IFN-mediated diseases. Five (50%) CANDLE patients achieved remission with no disease symptoms (disease-specific daily symptom score <0.15) and normal CRP, despite discontinuation of corticosteroids. The patients' CRP was below 5 mg/L in 84.6% of the subsequent visits, and the IFN response gene scores were normal in 66.7% of visits at the last follow-up, which encompassed a mean of 654.4 (range: 581 to 822) days after the patients first achieved remission criteria until data analysis, suggesting durable remission. CRP levels continuously decreased with treatment with CRP returning to normal in 5 out of 10 patients. The clinical responses were most pronounced in patients with CANDLE, while in patients with SAVI, the vasculitis flares improved but still occurred, albeit with reduced duration and severity; none of the SAVI patients experienced further loss of digits. The 25 gene IRG-S and serum IP-10 levels significantly correlated with each other and were correlated significantly with daily symptoms. The IRG-S correlated with the ability to taper corticosteroid dose. The IRG-S decreased on treatment with baricitinib and normalized in 5 out of 10 CANDLE patients who achieved clinical remission criteria. IFNα–stimulated STAT-1 phosphorylation was measured to assess type I IFN receptor responsiveness during baricitinib treatment. The IFN-α stimulation–induced STAT-1 phosphorylation was reduced to the lower tertile measured in healthy controls. While patients with CANDLE were hyper-responsive to IFN-α stimulation before treatment with baricitinib, most patients with SAVI had maximal STAT-1 phosphorylation and did not respond to IFN-α stimulation. On baricitinib, the IFN response in patients with SAVI recovered to the levels detected in patients with CANDLE. Other cytokines that significantly decreased in baricitinib-treated patients included MCP1, granulocyte macrophage CSF (GM-CSF), IL-15, and IL-5.

3.3. Benefit/Risk Assessment

There is high unmet medical need for the treatment of auto-inflammatory type 1 interferonopathies. These diseases are poorly responsive to conventional and biologic immune-modulating therapies, such as biologic DMARDs that target proinflammatory cytokines (ie, IL-1, TNF, and IL-6) or to conventional DMARDs (Kuijpers 2002; De Laet et al. 2005; D'Arrigo et al. 2008; Orcesi et al. 2008; Yao et al. 2009; Kamei et al. 2013; Liu et al. 2014;

Brehm et al. 2015; Henrickson and Wang 2017; Rice et al. 2018; An et al. 2018). No effective or approved therapies exist for NNS/CANDLE, SAVI, or AGS. Many NNS/CANDLE and SAVI patients require high-dose corticosteroids to control systemic symptoms although these drugs are less widely used in AGS. However, the deleterious impact of long-term corticosteroid use on growth and development is well documented in pediatric patient populations. If left untreated or poorly managed with existing therapies, these diseases have devastating consequences on the lives of the affected patients.

I4V-MC-JAGA (JAGA) is an expanded access program that included patients with chronic autoinflammatory syndromes targeting the IFN pathway. JAGA specifically enrolled patients with CANDLE, CANDLE-related- conditions, SAVI, severe juvenile dermatomyositis, and AGS, who were not responsive to conventional/ biologic therapies and who required treatment with high doses of steroids to control systemic signs and symptoms of their condition.

The primary efficacy objective of the expanded access program for CANDLE, SAVI, and AGS was to determine if the administration of baricitinib resulted in reduction in the patient/parent-reported mean daily diary scores to condition-specific, protocol-defined levels (to <0.5 for CANDLE and AGS, and to <1.0 for SAVI exclusive of respiratory/breathing symptoms with an increase <1.0 in respiratory/breathing symptoms scores from baseline). The patient's disease severity for condition-specific clinical features was recorded daily in a diary by the patient or caregiver throughout the study.

Condition-specific decreases in patient/parent-reported- mean daily diary scores: At last observation, the majority of patients with CANDLE (63.6%) and SAVI (75.0% with and without respiratory and breathing symptom scores) met the predefined primary objective. No patients with AGS met the objective when their neurological symptom score was included. The investigator hypothesized that the AGS daily diary was not sensitive to change due to significant neurologic damage at baseline. Despite the overall limitation of the AGS mean daily diary endpoint, statistically significant improvements were demonstrated in some of the individual symptom-specific daily diary scores (such as crying, sleep, and irritability) in AGS patients.

Reduction in systemic corticosteroid use: The percentages of patients with CANDLE, SAVI, and AGS (post hoc analysis for AGS) taking corticosteroids at baseline and meeting this pre-defined secondary objective at last observation were 80% (8 of 10 patients), 50% (2 of 4 patients), and 83% (5 of 6 patients), respectively (Sanchez et al. 2018).

Biomarker changes related to autoinflammatory Type 1 interferonopathies: Biomarker data in CANDLE, SAVI, and AGS patients are supportive of the beneficial effects of baricitinib in autoinflammatory type 1 interferonopathies and support the hypothesis for using JAK inhibition in this disease pathology. Significant reduction in the 25-gene IFN response gene score (IRG-S) was observed most prominently in CANDLE and in some SAVI patients after treatment with baricitinib and correlated with the reduction in corticosteroid dose and remission in CANDLE patients. Changes in CANDLE and SAVI daily diary scores were correlated with changes in IRG-S, IP-10/CXCL10, and acute phase reactants (CRP and erythrocyte sedimentation rate). IRG-S significantly decreased in AGS patients after initiation of baricitinib (Kim et al. 2018).

Safety: Based on the safety analysis in JAGA for this patient population with serious underlying conditions and associated comorbidities (especially in the context of their possible immunocompromised state and concomitant steroid use), no new safety signals for baricitinib were identified. The safety profile is comparable to the known adverse reactions in the existing global labels for baricitinib in the treatment of adult patients with RA. The observed safety profile from JAGA was as expected for patients with these serious conditions monitored over an extended duration of study (up to 7 years).

Therefore, based on the efficacy of baricitinib demonstrated in JAGA and the observed safety profile, the probability of a positive benefit/risk warrants this study to be conducted, given the unmet need in patients with NNS/CANDLE, SAVI and AGS.

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

4. Objectives and Endpoints

Table JAJE.4 shows the objectives and endpoints of the study.

Table JAJE.4. 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 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	• Population PK analysis based on sparse sampling • PK comparability will be assessed visually and/or modeling approach, if appropriate.

Objectives	Endpoints
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 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 Section 5.1).

[d] See 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 Section 9.1.2.6).

5. Study Design

5.1. Overall 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. After marketing authorization of baricitinib for any of the indications in Japan, the study will be considered a postmarketing clinical trial (Phase 4 study).

The study consists of 6 periods:

Screening Period

The duration of screening period is different among diseases. For SAVI and AGS patients, the duration of the screening period is at least 7 days and up to 35 days prior to baseline (Visit 6). For NNS/CANDLE patients, they will enter the pre-treatment period after screening period. Data at Visit 6 is used for baseline in all patients. The patient or the patient's parent or a legal guardian (hereafter, "parent" refers to "parent or legal guardian") will sign the informed consent form (ICF) and assent from the patient will be obtained when appropriate (see Appendix 3) prior to any study assessments, examinations, or procedures being performed at Visit 1. Screening procedures will be performed according to the Schedule of Activities (Section 2).

Patient diaries will be provided for daily collection of information regarding the patient's signs and symptoms. Patient diary collection will begin at screening and each patient (or caregiver) will complete the diary at approximately the same time every day during the screening period and for the duration of the study. Ideally, the same person will complete the diary each day. It will not be considered a protocol violation even if record time or assessor for the diary is different.

Patients who receive a purified protein derivative (PPD) skin test at screening will need to return within 48 to 72 hours later to read the skin test (Visit 1A).

Concomitant therapy for primary diseases during the study is permitted as described in Section 7.7. Patients who have previously been treated with JAK inhibitors or biologic agents are eligible for the study. However, treatment must have been discontinued according to exclusion criterion #27 (Section 6.2).

Investigators should review the vaccination status of their patients at screening. Immunization records will be collected in pediatric patients (<18 years of age). Immunization records for the BCG vaccine, varicella-zoster virus (VZV) vaccine, and herpes zoster (HZ) vaccine will be collected for all patients. Investigators ensure that patients are up to date with all immunizations, and follow the local requirements for vaccination guidelines and schedule for immunosuppressed

patients. No changes in start or resumptions of a vaccine is required, pediatric patients follow the Japanese immunization guidelines, with the exception of live vaccines.

All inclusion and exclusion criteria are provided in Sections 6.1 and 6.2, respectively. Patients with SAVI or AGS who meet all of the inclusion and none of the exclusion criteria will continue to Visit 6. Patients with NNS/CANDLE will continue to pre-treatment period after screening visit.

Pre-treatment Period (NNS/CANDLE only)

Pre-treatment period is 12 weeks period beginning at Visit 2 and natural history data with NNS/CANDLE patients will be collected through pre-treatment period. This applies only to NNS/CANDLE patients.

Patients who meet all of the inclusion and none of the exclusion criteria will continue to pre-treatment period. However, results of some tests (eg, laboratory tests) may not be available at Visit 2. In the case, patients will be performed procedures for pre-treatment period according to the Schedule of Activities (Section 2). If a patient is identified not to meet enrollment criteria in accordance with screening test results, the patient should be discontinued from the study.

Patients will remain on their treatments for NNS/CANDLE therapy (excluding JAK inhibitors) during pre-treatment period based on investigator's discretion (see Section 7.7.1). Patient can skip Visit 5 and proceed to dose adjustment period (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 #27 has already passed at Visit 5 (see Section 6.2 Exclusion criteria [27], Section 7.7.1). The patients who are required Visit 5 will proceed to Visit 6 after washout of biologic agents.

Patients will be confirmed the eligibility again using the most recent laboratory test results prior to Visit 6 (see exclusion criterion #22).

The data through pre-treatment period is used for baseline of pre-treatment period when results in primary/maintenance treatment period are compared to that of pre-treatment period.

Dose Adjustment Period

Patients who meet all eligibility criteria will enter an 8-week dose adjustment period. The initial dose prescribed at Visit 6 will be determined based on weight class and eGFR (see Table JAJE.5). After Visit 6, the dose adjustment period will evaluate the optimal baricitinib dosage to the patients with NNS/CANDLE, SAVI, or AGS based on clinical response. If the patient's weight changes during the study and requires a change in the dosing regimens as outlined in Table JAJE.5, the dose may be adjusted to meet the dosing regimen based on current weight. Steroid weaning may begin for patients who are receiving systemic corticosteroids (Section 7.7.2). The detailed instructions are described in Sections 5.1.1.

Primary Treatment Period

After completing dose adjustment at Visit 9, each patient will receive an optimized dosage of baricitinib that was determined throughout the dose adjustment period. Patients should maintain their optimized baricitinib dosage during the primary treatment period as much as possible.

Primary treatment period is set for each patient as following:

- NNS/CANDLE patients: 12 weeks [after Visit 9 (Week 8) to Visit 12 (Week 20)]
- SAVI or AGS patients: 24 weeks [after Visit 9 (Week 8) to Visit 15 (Week 32)]

Dose modification: If the patient's weight changes during the study and requires a change in the dosing regimens as outlined in Table JAJE.5, the dose may be adjusted to meet the dosing regimen based on current weight.

Dose modification may be allowed if needed for appropriate medical management. In case of dose modification, the investigator must notify Lilly or its designee as soon as possible.

- Dose reduction may occur due to safety concerns.
- Dose increase is possible due to continuous inadequate response if the patient's optimized dosage does not reach the maximum total daily dose as specified in Table JAJE.5.

Maintenance Treatment Period

After completing the primary treatment period at Visit 12 for NNS/CANDLE and at Visit 15 for SAVI and AGS respectively, patients will enter the maintenance treatment period. Patients should maintain their optimized dosage during the maintenance treatment period as much as possible.

Each patient will continue to receive baricitinib at their optimized dosage until whichever occurs first:

- at Visit 36 (Week 244) during maintenance treatment period, **OR**
- when baricitinib is commercially available for NNS/CANDLE, SAVI, and/or AGS. All patients will move to ETV within 6 months after marketing authorization of baricitinib.

Dose modification: If the patient's weight changes during the study and requires a change in the dosing regimens as outlined in Table JAJE.5, the dose may be adjusted to meet the dosing regimen based on current weight.

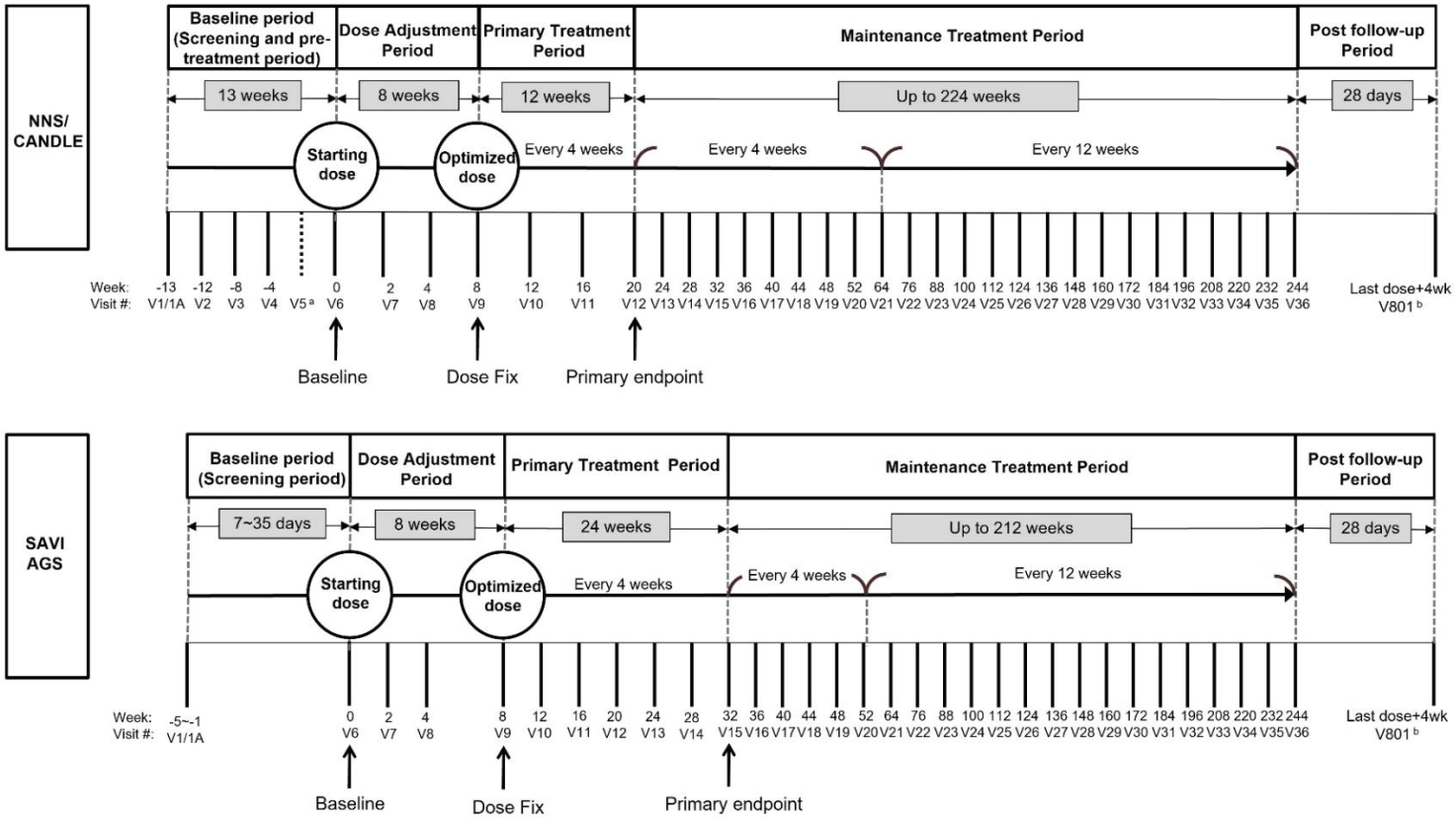
Dose modification may be allowed if needed for appropriate medical management. In case of dose modification, the investigator must notify Lilly or its designee as soon as possible.

- Dose reduction may occur in case of safety concerns.
- Dose increase is possible in case of continuous inadequate response if the patient's optimized dosage does not reach the maximum total daily dose as specified in Table JAJE.5.

Post-Treatment Follow-Up Period

Patients discontinuing from study treatment who have received at least 1 dose of baricitinib will continue to the early termination visit. Patients who discontinue study treatment, or who complete the study treatment, will have a post-treatment follow-up visit (Visit 801) approximately 28 days after the last dose of baricitinib. As an exception, patients who will transition from this study to commercial baricitinib are not required to have Visit 801. In this case, it will not be considered a protocol violation if the post-treatment follow-up period is not performed. Other therapy for NNS/CANDLE, SAVI, or AGS, as determined to be appropriate by the investigator, is allowed during the post-treatment follow-up period.

Note: Sites should make every attempt to schedule patient visits within the defined window. Exceptions to these windows may be granted under certain circumstances with prior approval of the Lilly clinical research physician or designee.



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 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.

5.1.1. Treatment Dose

5.1.1.1. Treatment Dose During Dose Adjustment Period

To find a patient's optimal dose, baricitinib dose adjustment will be conducted within 8 weeks from Visit 6. The 8-week dose adjustment period was set based on the results of Study I4V-MC-JAGA (JAGA).

Initial dose (Visit 6)

Baricitinib will be dosed by patient weight range and eGFR. Initial dose at Visit 6 will be determined based on weight class and eGFR. Data at the following visit will be used for the initial dose setting:

	Weight	eGFR
NNS/CANDLE	Visit 6	Visit 4, or Visit 5 (if applicable)
SAVI, AGS	Visit 6	Visit 1

Dose adjustment (Visit 7, 8, and 9)

If patients do not show adequate response to treatment, every effort should be made to follow the dose escalation schedule shown in Table JAJE.5. When patients have their dose escalated, they must receive an escalated dose for at least 72 hours from the last dose. For all patients, maximum total daily dose must not exceed the dose by weight and eGFR in Table JAJE.5.

Adequate response

Adequate response is defined as below.

Threshold:

- NNS/CANDLE patients: average diary score <0.5 in CANDLE diary
- SAVI patients: average diary score <1.0 in SAVI diary
- AGS patients: no quantitative score

  Note: For AGS patients, there is no quantitative score derived from the AGS diary that defines the threshold for adequate response. Treatment response will be confirmed at the discretion of the investigator.

If the patient is responding adequately to treatment,

1. **current baricitinib dose may be continued** and the patient does not necessarily have to proceed with dose escalation.

   If there are no safety concerns that would preclude increasing the dose in patients who have met the threshold, dose escalation, according to Table JAJE.5 can be performed up to the maximum total daily dose.

2. **steroid weaning** may begin after bariticinib dose initiation (Visit 6) throughout the treatment period for patients who are receiving systemic corticosteroids.

   If the patient is responding to treatment but has not met the threshold and is experiencing new or worsening clinically significant adverse effects from steroids (including, but not limited to, cataracts, vertebral fractures due to osteoporosis, Cushingoid habitus, substantial weight gain, avascular necrosis, dyslipidemia, hypertension, opportunistic infections, or stunted growth), the steroid weaning may begin when, in the opinion of the investigator, an adequate response has been achieved. The reason for steroid weaning will be documented in the medical record.

   Steroid re-increase after the weaning is permitted if medically necessary in the opinion of the investigator. In this case, it is recommended that the dose of steroid is not greater than that of baseline (dose at Visit 6). However, it is allowed to exceed the dose of baseline temporarily if the patient is experiencing unacceptable or worsening symptoms of NNS/CANDLE, SAVI, or AGS. The reason for steroid dose change will be documented in the medical record (see Section 7.7.2).

Table JAJE.5. Dose Escalation Schedule by Weight and Renal Function

Weight Class [a]	Morning Dose	Noon Dose	Afternoon Dose	Evening Dose	Total Daily Dose[b]	Dosing Frequency
eGFR ≥ 60 mL/min/1.73 m²						
5-<10 kg	1 mg	1 mg	0 mg → 1 mg	1 mg	3 mg → 4 mg	TID - QID
10-<20 kg	2 mg	2 mg	0 mg → 2 mg	2 mg	6 mg → 8 mg	TID - QID
20-<40 kg	3 mg	—	0 mg → 2 mg	3 mg	6 mg → 8mg	BID - TID
≥40 kg	4 mg → 5 mg → 6 mg	—	—	4 mg → 5 mg → 6 mg	8 mg →10mg →12 mg	BID
eGFR < 60 mL/min/1.73 m²						
5-<10 kg	0.5 mg	0.5 mg	0 mg → 0.5 mg	0.5 mg	1.5 mg → 2 mg	TID - QID
10-<20 kg	1 mg	1 mg	0 mg → 1 mg	1 mg	3 mg → 4 mg	TID - QID
20-<40 kg	2 mg	—	—	1 mg → 2 mg	3 mg → 4 mg	BID
≥40 kg	2 mg → 3 mg	—	—	2 mg → 3 mg	4 mg → 6 mg	BID

BID = twice daily, eGFR = estimated glomerular filtration rate, QID = 4 times daily, TID = 3 times daily.

a If the patient's weight changes during the study and requires a change in the dosing regimens, the dose may be adjusted to meet the dosing regimen based on current weight. (See Section 5.1.1.3.)

b If dose adjustment occurs, total daily dose must be changed step-by-step (e.g. patient with eGFR>60 mL/min/1.73 m2 and ≥40 kg; initial dose is 8 mg, and dose escalation will be conducted 8 mg → 10 mg → 12 mg gradually. Dose adjustment is expected to conduct at regular visits for JAJE. However, it may be allowed if a patient's condition warrants an accelerated dose escalation schedule. A patient must receive a dose for at least 72 hours before a dose escalation can occur to obtain samples and results from safety blood test assessments prior to dose increase.

5.1.1.2. Treatment dose during primary treatment period and maintenance period

After completing dose adjustment at Visit 9, each patient will receive an optimized dosage of baricitinib that was determined throughout the dose adjustment period. Patients should maintain their optimized baricitinib dosage during the primary and maintenance treatment periods as much as possible.

5.1.1.3. Dose modification during treatment period

In any of following dose modification, the reason for dose modification will be documented in the medical record.

Weight changes:

If the patient's weight changes during the study and requires a change in the dosing regimens as outlined in Table JAJE.5, the dose may be adjusted to meet the dosing regimen based on current weight.

- If a patient gains weight during the study and the increase in weight results in a change in weight range, the investigator may opt to increase the dose based on the patient's new weight range. The investigator should ensure that the increase in weight is not related to fluid retention.
- If the patient loses weight during the study, the investigator may opt to keep the patient on their current dose.

Dose reduction or increase:

Dose modification may be allowed if needed for appropriate medical management. In case of dose modification, the investigator must notify Lilly or its designee as soon as possible.

- **Dose reduction by safety concern**
  In the event of AEs possibly attributable to the study drug, the dose may need to be reduced. Dose reductions, interruptions, or discontinuations may also occur based on review of the patient's clinical and pharmacokinetic (PK) data (if available). Except in cases of emergency, it is recommended that the investigator consult with Lilly or its designee before interrupting or discontinuing therapy. The investigator must obtain approval from Lilly or its designee before restarting.
- **Dose increase by continuous inadequate response after dose adjustment period**
  If a patient continues to have an inadequate response to the baricitinib dose as evidenced by an elevated diary score or ongoing clinical disease activity reflected by increased symptoms or elevated markers of inflammation, the dose may be increased in the dose escalation steps shown in Table JAJE.5. When patients have their dose escalated, they must receive an escalated dose for at least 72 hours from last dose.
  If a patient reaches the maximum total daily dose as specified in (Table JAJE.5) and has an inadequate response to treatment, the patient may be discontinued from the study to pursue other treatment options. However, if the investigator determines that it is in the best interest of the patient to continue treatment, the patient may continue in the study. This will not be considered a protocol violation.

5.1.1.4. Pharmacokinetic Sampling

Blood samples will be collected to determine baricitinib concentrations. Samples will be collected according to the Section 9.5.

5.1.2. Patient Diary and Diary Score

Patient diaries will be provided for daily collection of information regarding the patient's signs and symptoms. Diaries are specific to individual indications or conditions (ie, NNS/CANDLE, SAVI, or AGS). The patient diaries are shown in Section 9.1.1. Each patient (or caregiver) will complete the diary at approximately the same time every day during the screening period and for the duration of the study. Ideally, the same person will complete the diary each day. It will not be considered a protocol violation even if record time or assessor for the diary is different.

Patients with NNS/CANDLE or SAVI:

For patients with NNS/CANDLE or SAVI, the patient or caregiver will be instructed to rate each symptom (fever, rash, musculoskeletal pain, and fatigue [all diaries], headache [NNS/CANDLE diary only], respiratory/breathing problems, and ulcers/ischemic lesions [SAVI diary only]) in the diary on a scale from 0 to 4 (where a score of 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = more severe symptoms, and 4 = severe symptoms [equivalent to "worst" symptoms])(See Section 9.1.1.1 and 9.1.1.2).

Importantly, these ratings should evaluate the *impact* of each symptom on the patient, and not the severity of the symptom itself. For example, to assess the symptom of fever, the patient or their caregiver should assess the impact fever has on the patient, regardless of whether the actual temperature of the patient is known. If no fever is apparent and the patient does not have any limitations on daily activities, the fever score for that day would be 0. If the patient has a transient fever that minimally impacts daily activities, the fever score for that day would be 1, and so on. A fever score of 4 would indicate that the patient has a fever with high impact on the patient, for example, being bedridden.

Patients with AGS:

For patients with AGS, the patient (or caregiver) will be instructed to rate each symptom (neurologic disability, crying, length of uninterrupted sleep, generalized seizure, fever, excessive irritability, skin findings [body], and skin findings [hands, feet, and ears]) as defined in the diary (See section 9.1.1.3).

The diary is to be completed daily throughout the study. The diary score is used to confirm patient eligibility, assess disease activity and inform the need for an additional dose increase (up to the maximum allowed dose as detailed in Table JAJE.5) or initiation of steroid weaning (if the patient is receiving steroids) as described in the section 5.1.1. At required visits, site personnel will calculate the average score for each symptom being collected on the diary (that is, the average of 7 days prior to the visit, correcting for any day for which diary scores were not

recorded). The site personnel will take the average scores for each symptom, sum them, and divide by the number of assessed symptoms to calculate the average diary score for a patient.

The investigator should review the entire diary and average diary scores at required visits. If there is a trend in the diary scores, (ie, initial high scores resolve by the end of the diary period or lower scores become higher by the end of the diary period), the investigator has the option of escalating or not escalating the patient's dose of baricitinib.

Method of calculation for the average diary score by site personnel:

The average 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, 6 symptoms for SAVI, or 8 symptoms for AGS) to calculate the average score for each patient.

Site personnel will be required to calculate the average score at least for eligibility (Visit 2, Visit 6) and dose adjustment (Visit 7, 8, 9). The calculation may be performed at any time during the study if necessary in the opinion of the investigator. The calculated average score will be documented in the source document.

5.2. Number of Patients

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. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

This study is a Phase 2/3, multicenter, open-label, single-arm design intended to provide baricitinib to patients with NNS/CANDLE, SAVI, or AGS. Patients will receive an initial dose that may be escalated using dose escalation tables to an effective and tolerable dose during the dose adjustment period. Patients should maintain their optimized baricitinib dosage during the primary treatment period and the maintenance treatment period.

Continued ongoing inflammation causes organ damage and results in significant morbidity and mortality. There are no approved drugs for NNS/CANDLE, SAVI, or AGS in Japan or anywhere else in the world. Many patients require high dose corticosteroids to control systemic

symptoms. However, the chronic high doses of steroids frequently required for treatment further contributes to the morbidity and mortality associated with these syndromes. Given the serious and life-threatening nature of these syndromes, no standard of care, and unsustainable chronic doses of steroids, an open-label study is deemed appropriate.

5.5. Justification for Dose

Patients will receive an initial dose based on weight class and eGFR and may have their dose escalated to determine a tolerable dose. Dose escalation according to Table JAJE.5 will be performed up to the maximum allowable dose level, as long as there are no safety concerns that would preclude increasing the dose.

Initial dose escalation parameters were supported by PK results following baricitinib treatment of the first 2 CANDLE patients in Study JAGA as well as results from a Phase 2b study in RA patients. Improvements in patients with RA, including significant improvement in American College of Rheumatology responses, were achieved at a dose of 4 mg which approximates a dose of 0.05 mg/kg. In the first 2 CANDLE patients in Study JAGA, initial improvements in clinical status were only observed upon achieving a stable daily dose of 2 mg approximating a 0.1 mg/kg dose. The requirement for a higher dose to achieve efficacy is likely due to 2 distinct reasons. The first reason is the nature of the diseases that results from auto-inflammatory syndromes appears to require higher concentrations of disease-modifying anti-rheumatic drugs (Goldbach-Mansky et al. 2006) for adequate disease management. The second reason is based on the generally shorter half-life of baricitinib observed in CANDLE patients in Study JAGA that requires higher mg/kg dosing in order to achieve therapeutic exposures.

With a 1 mg dose, the assumed maximal concentration at 1.5 hours is between 10 and 40 nM based on the first 2 patients. With whole blood half maximal inhibitory concentration (IC_{50}) values for inhibition of IL-6 induced STAT-3 phosphorylation of 104 ±14 nM (n=5) (Baricitinib Investigator's Brochure) exposure data would suggest that the dose will need to be greater than 2 mg (or 0.1 mg/kg) to approach therapeutic levels.

As baricitinib PK information and the associated clinical response in the JAGA CANDLE and SAVI patient population became available, the dose-escalation- scheme was modified accordingly (Kim et al. 2018). Based on observed dose titration and stable dose in the 18 JAGA patients seen at the National Institutes of Health up to 04 March 2016 and the PK analyses from these patients (Kim et al. 2018) in JAGA, cut off values of 20 kg and 40 kg for weight and of 120 mL/min/1.73 m^2 for eGFR were used for dose adjustment and are reflected in the JAGA protocol amendments.

In the updated population PK analysis which was recently available, baricitinib PK were further characterized with plasma concentration data available from 71 patients in JAGA. Overall, the mean AUC over 24 hours at steady state ($AUC_{0\text{-}24,ss}$) for all JAGA patients taking baricitinib doses of 3-12 mg daily was 896 ng*h/mL (90% CI = 473-1490 ng*h/mL). The mean $AUC_{0\text{-}24,ss}$ is 1.9-fold greater than the mean baricitinib exposures in adult patients with RA receiving doses of 4 mg once daily.

The analysis confirmed renal function estimated by eGFR as a significant covariate on CL/F. Due to the minimum effect size characterized of eGFR on AUC and C_{max} in the eGFR range greater than 60 mL/min/1.73 m^2, the eGFR cutoff of 120 mL/min/1.73 m^2 is considered unnecessary. In addition, little data is available to evaluate PK in patients with eGFR in the range of 30-60 mL/min/1.73 m^2. It is recommended that the dose is reduced by half for patients in this renal function category based on data from adult RA and the understanding of the elimination mechanism of baricitinib.

The analysis also confirmed body weight as a significant covariate on apparent clearance (CL/F) and apparent volume of distribution (V/F). Simulations were conducted to identify an optimal dosing regimen for patients with WT ≤10 kg, based on a target concentration range which is defined as the 90% confidence intervals for daily average concentrations (C_{av}) at the final stable doses for all CANDLE patients who achieved disease control. The results suggested a dosing regimen of 1 mg TID as starting dose and 1 mg QID as escalated dose provided exposures better in line with the target concentration range and most comparable to the other body weight groups.

If a patient gains weight during the study and the increase in weight results in a change in weight range, the investigator may opt to increase the dose based on the patient's new weight range according to Table JAJE.5 for patients with eGFR ≥60 mL/min/1.73 m^2 and for patients with eGFR <60 mL/min/1.73 m^2. The investigator should ensure that the increase in weight is not related to fluid retention. If the patient loses weight during the study, the investigator may opt to keep the patient on their current dose.

6. Study Population

Patients enrolled into this study will have been diagnosed with an autoinflammatory disorder such as NNS/CANDLE, SAVI, or AGS.

Patients who meet all of the inclusion criteria (Section 6.1) and do not meet any of the exclusion criteria (Section 6.2) may enter the study (that is, sign consent or assent). In addition, patients must meet the enrollment criteria (Section 6.1) in order to be eligible to receive baricitinib.

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

6.1. Inclusion Criteria

Patients are eligible for entry into the study only if they meet all of the following criteria at Visit 1 (screening) and Visit 6 (enrollment,baseline) unless otherwise specifically defined:

Type of Patient and Disease Characteristics

[1] Have systemic signs and symptoms of inflammation as manifested by the presence of 2 or more signs or symptoms as defined in CANDLE/SAVI/AGS diary (investigator must assess patient eligibility using a patient diary related to their disease; see Section 9.1.1.1, 9.1.1.2, and 9.1.1.3)

[2] Have been diagnosed with NNS/CANDLE, SAVI, or AGS (including FCL) with the confirmation with genetic diagnosis.

[3] Have the designated daily diary score assessed over the designated period during the screening and pretreatment period. Average daily diary score will be calculated using data from 7 days preceding the current visit (not including data on the day of current visit) (see Section 9.1.1.1)

Average daily diary score at Visit 2 (only for NNS/CANDLE patients) and Visit 6 (for all patients):

- NNS/CANDLE patients: average daily diary score of ≥0.5,
- SAVI patients: average daily diary score of ≥1.0,
- AGS patients: average daily diary score of ≥0.5.

Note: SAVI and AGS patients are required to collect daily diary score over at least 7 days prior to Visit 6. If scores are missing and the total number of daily diary score is <7 days, the eligibility for moving to Visit 6 may be considered after consultation with Lilly or its designee. NNS/CANDLE patients are required to collect daily diary score through 13 weeks according to the screening and pre-treatment period.

If the average daily diary score does not meet the criterion, but the patient's condition warrants appropriate assessment in this study, moving to Visit 6 may be allowed after consultation with Lilly or its designee. The eligibility for moving to Visit 6 will be judged by Lilly or its designee.

Patient Characteristics

[4] are male or female patients:

[4a] Female patients:

Women not of child-bearing potential or nonbreastfeeding:

- 12 months of amenorrhea for women >55, with no need for FSH

OR

- 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that induced amenorrhea)

OR

- Women who are congenitally or surgically sterile (ie, have had a hysterectomy or bilateral salpingectomy or bilateral oophorectomy).

Women of child-bearing potential:

- Must test negative for pregnancy prior to Visit 6 as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

AND either of the following:

- Must agree to either remain abstinent, if complete abstinence is their preferred and usual lifestyle, or remain in same-sex relationships, if part of their preferred and usual lifestyle, without sexual relationships with males. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

OR

- Must agree to use a reliable method of birth control when engaging in sexual intercourse with a male partner while enrolled in the study and for at least 4 weeks following the last dose of baricitinib.
  Each of the following is considered a highly effective method of birth control:
  - oral contraceptives
  - condom with a spermicide
  - intrauterine device
  - vasectomized male (with appropriate post vasectomy documentation of the absence of sperm in the ejaculate). For female patients in the

study, the vasectomized male partner should be the sole partner for that patient.

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Note: Female patients of child-bearing potential will be defined as ≥10 years old and have reached menarche, or if there is a reason to believe that the patient is sexually active. At the discretion of the investigator, female patients who are <10 years old may also be tested as needed.

[4b] Male patients:

Must agree to use the above highly effective birth control (see inclusion criterion 4a) while engaging in sexual intercourse with female partners of childbearing potential while enrolled in the study and for at least 4 weeks following the last dose of baricitinib.

[5] Are the following age, based on each disease type:

[5a] NNS/CANDLE and SAVI patients: Are ≥17.5 months of age,

[5b] AGS patients: Are ≥6 months of age.

[6] Are ≥5 kg in body weight.

Informed Consent

[7] Have the ability to provide informed consent or have a legal guardian who is willing and able to provide written informed consent, provided that assent is obtained from patients per local requirements.

Note: Full date of birth will be collected from patients <18 years old.

Note: During clinical trials, adequate informed consent for continued participation will be obtained from pediatric patients once a child reaches the age of legal consent.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at Visit 1 (screening) and Visit 6 (enrollment, baseline) unless otherwise specifically defined:

Medical Conditions

[8] Have had symptomatic herpes zoster infection within 12 weeks prior to Visit 1.

[9] Have a history of disseminated/complicated herpes zoster (eg, multidermatomal involvement, ophthalmic zoster, central nervous system involvement, post-herpetic neuralgia-).

[10] Have symptomatic herpes simplex at the time of Visit 1.

[11] Have evidence of active infection at the time of Visit 1 or during the screening period that, in the opinion of the investigator, would pose an unacceptable risk for participating in the study.

[12] Have had a serious systemic or local infection (including an infectious mononucleosis-like illness or herpes zoster) within 12 weeks prior to Visit 1 or during the screening -period.

Note: Exceptions include SAVI patients with infected ulcerative skin lesions, which in the opinion of the investigator, would not pose an unacceptable risk for participating in the study.

[13] Have a risk of TB:

[13a] Have had household contact with a person with active TB and did not receive appropriate and documented prophylaxis for TB.

[13b] Have evidence of active TB or have previously had evidence of active TB defined in this study as the following and did not receive appropriate and documented treatment.

- a positive purified protein derivative (PPD) test (≥5 mm induration between approximately 2 and 3 days after application, regardless of vaccination history), and/or QuantiFERON®-TB Gold test or T-SPOT®.TB test (as available and if compliant with local TB guidelines) may be used instead of the PPD test.
    - If the test is not negative, the test may be repeated. If the repeat test results are again not negative, the patient will be considered to have latent TB (for purposes of this study).
- medical history, and
- chest x-ray at screening.

If documented evidence of active TB or have previously had evidence of active TB are available from testing:

- within 3 months before Visit 1 for PPD test, QuantiFERON®-TB Gold test, and/or T-SPOT®.TB test,
- within 6 months before Visit 1 for chest x-ray,

then the patient will not have to be retested at Visit 1.

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

[14] Have evidence of, or a positive test for, hepatitis B virus (HBV) infection which is defined as:

- positive for hepatitis B surface antigen (HBsAg),
- positive for hepatitis B core antibody (HBcAb) and detectable HBV DNA,
- positive for hepatitis B surface antibody (HBsAb) and detectable HBV DNA,
- Detectable HBV DNA.

Note: Patients who are positive for HBcAb or HBsAb and negative for HBV DNA may be enrolled in the study. Patients who are HBcAb-, HBsAb+ with a documented history of Hepatitis B vaccination will not be required to undergo HBV DNA testing/monitoring (Section 9.4.6). If results are available from testing within 3 months prior to Visit 1, then the patient will not have to be retested.

[15] Have hepatitis C virus (HCV; positive for anti-hepatitis C antibody with confirmed presence of HCV); have evidence of HIV infection, and/or positive HIV -antibodies.

Note: If results are available from testing within 3 months prior to Visit 1, then the patient will not have to be retested.

[16] Are immunocompromised and, in the opinion of the investigator, are at an unacceptable risk for participating in the study. Additionally, patients with a confirmed diagnosis of *Pneumocystis* pneumonia will be excluded. Patients who have a history of *Pneumocystis* pneumonia will be also excluded if the investigator judges it to be an unacceptable risk.

[17] Have or have had a history of:

- lymphoproliferative disease,
- signs or symptoms suggestive of possible lymphoproliferative disease, or active primary or recurrent malignant disease, or
- been in remission from clinically significant malignancy for <5 years.

Note: Patients with resolved cervical dysplasia, or no more than 3 successfully treated basal-cell- carcinoma of the skin, may participate in this study.

[18] Have any history of venous thromboembolic event (VTE) (deep vein thrombosis [DVT]/pulmonary embolism [PE]) prior to screening.

[19] Have a serious and/or unstable illness that, in the opinion of the investigator, poses an unacceptable risk for the patient's participation in the study.

[20] Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator in consultation with Lilly or its designee, would pose an unacceptable risk to the patient if participating in the trial.

[21] Have screening laboratory test values outside the reference range that, in the opinion of the investigator, pose an unacceptable risk for the patient's participation in the study.

[22] Have any of the following specific abnormalities on screening laboratory tests (patients with NNS/CANDLE will be confirmed the eligibility again using the most recent laboratory test results prior to Visit 6.

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × the upper limit of normal (ULN),
- Hemoglobin <10 g/dL (100 g/L),
- Total WBC count <2500 cells/μL,
- Neutropenia (absolute neutrophil count [ANC] <1200 cells/μL),
- Thrombocytopenia (platelets <100,000/μL).

Note: The most recent visit prior to Visit 6 is defined as Visit 4 for patients without a biologic agent wash-out or Visit 5 for patient requiring biologic agent wash-out)

Note: A patient with NNS/CANDLE, SAVI, or AGS condition may be enrolled with any of the above specific abnormalities on laboratory tests if these laboratory abnormalities are considered a feature of the disease. If the laboratory abnormality is a feature of the underlying disease must be evaluated, in conjunction with the investigator, and documented; the investigator must also consult with Lilly or its designee before the patient can be enrolled.

[23] Have an eGFR based on serum creatinine at Visit 1 of <40 mL/min/1.73 m^2:

- for patients less than 2 years of age (eGFR based on the Bedside Schwarz 2009 formula),
- for patients between 2 years and 18 years of age inclusive (eGFR based on the Japanese Society for pediatric Nephrology formula),
- for patients greater than 18 years of age (eGFR based on CKD-EPI Creatinine 2009 equation)

[24] Have screening thyroid-stimulating hormone and/or thyroxine values outside of the laboratory's reference range and are assessed, in conjunction with the investigator, to be clinically significant.

Note: If results are available from testing within 1 month prior to initial screening, then the patient will not have to be retested. Patients who are receiving thyroxine as replacement therapy may participate in the study, provided stable therapy has been administered for ≥3 months and thyroid-stimulating- hormone is within the laboratory's reference range.

Note: In the case of any of the aforementioned laboratory abnormalities (Exclusion criteria [21], [22], [23], and [24]), laboratory tests may be repeated once during the screening period or pretreatment period (only for NNS/CANDEL patients), and values resulting from repeat testing may be accepted for enrollment eligibility if they meet the eligibility criterion.

[25] Have screening electrocardiogram (ECG) abnormalities that, in the opinion of the investigator, are clinically significant and indicate an unacceptable risk for the patient's participation in the study.

[26] Have a history of chronic alcohol abuse, intravenous drug abuse, or other illicit drug abuse within the 2 years prior to Visit 1.

Prior/Concomitant Therapy

[27] Have previously been treated with the following therapies:

a. immunosuppressive biologic agent/monoclonal antibody such as:

- etanercept, infliximab, tocilizumab, certolizumab, adalimumab, golimumab, canakinumab or abatacept within 28 days of Visit 6,
- rituximab within 6 months of Visit 6.

Use of intravenous immune globulin is permitted.

Note: If patients have been treated with any biologics which are not listed above, the investigator must consult with Lilly or its designee. The usage of them may be allowed after discussion with Lilly or its designee.

b. Any oral JAK inhibitor within 28 days of Visit 6 for SAVI and AGS patients. Patients with NNS/CANDLE must discontinue any oral JAK inhibitor from Visit 1.

c. Organic Anion Transporter 3 (OAT3) inhibitors with a strong inhibition potential such as probenecid, at the time of Visit 6 that cannot be discontinued for the duration of the study.

[28] Have been exposed to a live vaccine within the following time period prior to Visit 6

- 12 weeks for Typhoid and Bacillus Calmette-Guérin (BCG) live vaccines
- 4 weeks for other live vaccines

OR

Are expected to need/receive a live vaccine during the course of the study .

Note: Young patients who are not yet vaccinated and will be unable to receive live vaccines while receiving baricitinib may be included after discussion with Lilly or its designee.

Note: Booster vaccination for measles, mumps, and rubella or varicella-zoster virus may be considered if it is essential based on the local guideline and/or in the opinion of the -investigator.

Prior/Concurrent Clinical Trial Experience

[29] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[30] Have previously been enrolled (received treatment) in this study or any other study investigating baricitinib.

[31] Have discontinued within 30 days of study entry (Visit 1) from any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

Other Exclusions

[32] Are investigator or site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[33] Are Lilly employees or their designees.

[34] Are unwilling or unable to make themselves available for the duration of the study and/or are unwilling to follow study restrictions/procedures.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the inclusion/exclusion criteria in this study (screen failure) may be rescreened. Individuals may be rescreened up to 3 times. The interval between screening failure and rescreenings should be at least 1 week. Each time rescreening is performed the individual must sign a new ICF or assent form (as applicable) and will be assigned a new identification number.

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

7. Treatments

7.1. Treatments Administered

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

- Tablets containing 1 mg of baricitinib
- Tablets containing 2 mg of baricitinib
- Tablets containing 4 mg of baricitinib
- Liquid suspension containing baricitinib at 2 mg/mL strength

Baricitinib will be dosed as tablets or oral suspension based on patient weight and eGFR. The dosages will be adjusted according to Table JAJE.5. Tablets are not to be split for the purpose of dose adjustment. Patients with weight <40 kg will receive baricitinib tablets or oral suspension orally based on patient choice. Patients with weight ≥40 kg are recommended to receive tablets only. Patients need to use same formulation (tablet or suspension) throughout the study, but formulation change may be considered after discussion with Lilly or its designee depending on the reason.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the patient, parent/caregiver, or legal guardian,
- verifying that instructions are followed properly,
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless Lilly and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law (see Section 7.5)

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

7.1.1. Packaging and Labeling

Baricitinib packaging will be labeled with a unique identifier for drug accountability. Baricitinib tablets and oral suspension will be provided in bottles. Baricitinib suspension will be supplied as a ready to use oral suspension and doses will be delivered to the patient using an oral syringe. Lilly will provide an instructions for use document that describes the process for administration of the suspension. The investigator or appropriate site personnel should review the instructions for use with the patient and parent/caregiver to ensure understanding of the correct administration procedure for the suspension.

Clinical study materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

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. Depending upon the prescribed dose and/or the visit frequency, baricitinib will be dispensed for sufficient supply until the next visit. If there is still a sufficient amount left in the patient's IP bottle until the next visit, the bottle will not be returned to site and the patient will take the IP from the same bottle. In this case, a new IP bottle will not be dispensed. The oral suspension formulation has a stability of 100 days after opening (breaking the seal).

7.2.1. Selection and Timing of Doses

The mean half-life of baricitinib is 12.5 hours in adult patients with RA. Early clinical pharmacology studies in adults showed that doses of 5 to 10 mg QD resulted in a mean daily time of baricitinib concentrations that exceed the IC_{50} of IL-6 mediated STAT-3 phosphorylation of 2.5 to 7 hours. This suggests that in adults daily dosing will result in not only some daily time above the IC_{50}, but also some daily time without significant target engagement. As discussed in Section 9.4, the half-life- of baricitinib appears to be shorter in children compared with adults.

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Refer to Section 5.1.1.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

All investigational product (used and partially used) will be returned to Lilly or destroyed at the site level with Lilly's written approval. In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Follow storage and handling instructions on the IP packaging.

7.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit during the treatment period (dose adjustment period, primary treatment period and maintenance treatment period). Compliance will be assessed by counting returned tablets or weighing a returned bottle for liquid suspension.

Patients treated with baricitinib will be considered noncompliant if they miss ≥20% of the prescribed doses during the study (unless the patient's investigational product was withheld by the investigator for safety reasons).

Similarly, patients will be considered noncompliant if they are judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of study medication. Patients found to be noncompliant per investigator judgment should be assessed to determine the reason for noncompliance and educated and/or managed as deemed appropriate by the investigator to improve compliance.

Patients will be counseled by study staff on the importance of taking the investigational product as prescribed, as appropriate.

Patient compliance will be further defined in the statistical analysis plan.

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication electronic case report form (eCRF).

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

Additional drugs are to be avoided unless required to treat AEs or for the treatment of an ongoing medical condition. If the need for other concomitant medications arises, discontinuation of the patient from the investigational product or the study will be at the discretion of the investigator in consultation with Lilly or its designee (Section 8.2).

Treatment with concomitant therapies for NNS/CANDLE, SAVI, or AGS during the study is permitted, but treatments as prohibited in the section of exclusion criteria (Section 6.2) are still prohibited during the study.

For patients who discontinued or completed study treatment and have entered the post-treatment follow-up period, particular therapies for NNS/CANDLE, SAVI, or AGS (ie, immunosuppressive biologic agent, monoclonal antibody, JAK inhibitor) should not be used during the post-treatment follow-up period. However, their therapies are allowed if the investigator determines them to be appropriate.

7.7.1. Concomitant Therapy during pre-treatment period for NNS/CANDLE patients

Patients will remain on their treatments for NNS/CANDLE therapy (excluding JAK inhibitors) during pre-treatment period based on investigator's discretion. For NNS/CANDLE patients who have previously been treated with JAK inhibitors and/or biologic agents/monoclonal antibodies therapy prior to the study, JAK inhibitors are stopped at Visit 1. Biologic agents/monoclonal antibodies are stopped with an appropriate washout duration prior to Visit 6 (see Section 6.2 Exclusion criteria [27]).

7.7.2. Systemic corticosteroid

The use of systemic corticosteroid for NNS/CANDLE, SAVI, or AGS is permitted through the study. Steroid weaning may begin at Visit 6 according to Section 5.1.1. Even if the steroid weaning is conducted, the dose of steroid is permitted to increase after the weaning if medically necessary in the opinion of the investigator. In this case, it is recommended that the dose of steroid is not greater than that of baseline (dose at Visit 6). However, it is allowed to exceed the dose of baseline temporarily if the patient is experiencing unacceptable or worsening symptoms of NNS/CANDLE, SAVI, or AGS. The reason for steroid dose change will be documented in the medical record.

7.8. Treatment after the End of the Study

After end of the study, continued access to baricitinib will not be provided.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

In rare instances, it may be necessary for a patient to permanently discontinue (definitive discontinuation) study intervention. When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will remain in the study and follow procedures for remaining study visits, as shown in the Schedule of Activities (see Section 2).

Possible reasons leading to permanent discontinuation of investigational product:

Laboratory test results

Hepatic event or Liver test abnormality. A patient who is discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a patient meets one of the following conditions after consultation with Lilly or its designee:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks after temporary interruption of investigational product
- ALT or AST >3 × ULN and total bilirubin (TBL) >2 × ULN or international normalized ratio (INR) >1.5
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) >3 × ULN that is deemed to be of liver origin and drug related
- ALP >2.5 × ULN and TBL >2 × ULN
- ALP >2.5 × ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Other Laboratory Abnormality Results

Discontinuation of the investigational product should be considered by the investigator when a patient meets one of the following conditions after consultation with Lilly or its designee:

- WBC count <1000 cells/µL
- ANC <500 cells/µL
- lymphocyte count <200 cells/µL
- hemoglobin <6.5 g/dL

Note: If any of the above specific abnormalities are considered a feature of the disease (NNS/CANDLE, SAVI, or AGS) and the investigator determines that it is in the best interest of the patient to continue treatment, patients may continue the investigational product. The reason for the decision will be documented in the medical record after discussion with Lilly or its designee.

Note: Temporary interruption rules (see Section 8.1.2) must be followed where applicable. However, if, in the opinion of the investigator, the laboratory abnormality is due to concurrent illness such as cholelithiasis or another identified factor, laboratory tests may be repeated. Only when the laboratory value meets resumption thresholds (Table JAJE.6) following the recovery from the concurrent illness or other identified factor may the investigator restart investigational product, after consultation with Lilly or its designee.

Other circumstances

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

- The patient enrolls in any other clinical trial involving an investigational product or in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision:
    - An SAE or a clinically significant change in a laboratory value occurs that, in the opinion of the investigator, merits the investigational product being discontinued and appropriate measures being taken. In this case, Lilly or its designee is notified immediately. Refer to Safety Evaluations (Section 9.2).
    - The investigator decides that the patient should be withdrawn from the study.
    - The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication; discontinuation from the study occurs prior to introduction of the new agent.
- Parent, legal guardian, or patient decision:
    - The parents, legal guardian, or patient requests to be withdrawn from the study.
- Sponsor Decision:
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
        - Investigational product will no longer be supplied if Lilly stops development of the compound for any reason at any time.
- Compliance:
    - Patients found to be noncompliant with investigational product should be assessed to determine the reason for noncompliance. Education as deemed appropriate by the investigator may be provided to improve compliance. Persistent noncompliance may result in the patient being discontinued from the study.
- Pregnancy (see Section 9.2.1).
- Malignancy.

- Develop a VTE event (DVT/PE) during the study.
- HBV DNA is detected with a value above the limit of quantitation (see Section 9.4.6).
- Confirmed diagnosis of *Pneumocystis* pneumonia during the study.

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up- procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

On occasion, the investigator may find it necessary to temporarily interrupt or prematurely permanently discontinue investigational product administration following the occurrence of an AE or an abnormal laboratory finding. Except in cases of emergency, it is recommended that the investigator consult with Lilly or its designee before temporarily interrupting or prematurely permanently discontinuing therapy. Based on investigator discretion, if significant changes from baseline in eGFR are observed, the lab test should be repeated and confirmed on 2 separate occasions and Lilly or its designee must be contacted to discuss and document the appropriate course of action which may include a nephrology evaluation.

As listed in Table JAJE.6, certain situations necessitate a discussion with Lilly or its designee about whether treatment should be continued, either at the same dose or with a dose decrease, or if treatment should be temporarily withheld. Although Table JAJE.6 outlines guidance for certain situations, a discussion with the Sponsor should occur about the best course of action and decisions should be documented. Follow-up- laboratory tests to monitor the abnormal finding should be done promptly and frequently at the discretion of the investigator. The investigator must obtain approval from Lilly or its designee before restarting investigational product that was temporarily interrupted for an AE or for an abnormal laboratory finding.

Table JAJE.6. Guidance on Interruption of Investigational Product

Hold investigational product if the following laboratory test results occur, unless continuation of investigational product is approved by Lilly or its designee with documentation:	**If investigational product was stopped, it may be restarted after discussion with Lilly or its designee or when:**
WBC count <2,000 cells/μL[a]	WBC count ≥2,000 cells/μL
ANC <1,000 cells/μL[a]	ANC >2,000 cells/μL (Patients with baseline ANC counts between 1000 and 2000 cells/μL may restart investigational product when values return to baseline.)
Lymphocyte count <500 cells/μL[a]	Lymphocyte count ≥500 cells/μL
Platelet count <75,000/μL[a]	Platelet count >100,000/μL (Patients with baseline platelet counts between 75,000 and 100,000/μL may restart investigational product when values return to baseline.)
Patients with eGFR <60 mL/min/1.73 m^2 at assignment of initial dose eGFR <30 mL/min/1.73 m^2 [b] Patients with eGFR ≥60 mL/min/1.73 m^2 at assignment of initial dose eGFR <40 mL/min/1.73 m^2	 eGFR ≥40 mL/min/1.73 m^2 eGFR ≥50 mL/min/1.73 m^2
ALT or AST >5 × ULN or ALT or AST >3 × ULN and total bilirubin >2 × ULN	ALT and AST return to <2 × ULN, and investigational product is not considered to be the cause of enzyme elevation.
Hemoglobin <8 g/dL[a]	Hemoglobin ≥8 g/dL
Symptomatic HZ	All skin lesions have crusted and are resolving
Infection that, in the opinion of the investigator, merits the IP being interrupted	Resolution of infection
Clinical features of VTE (such as deep venous thrombosis or pulmonary embolism) are present[c]	After confirmation that DVT/PE is not present

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DNA = deoxyribonucleic acid; DVT = deep vein thrombosis; eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; IP = investigational product; PE = pulmonary embolism; ULN = upper limit of normal; VTE = venous thromboembolic event; WBC = white blood cell.

[a] Investigational product can be continued if decrease in WBC, ANC, lymphocyte count, platelet count, or hemoglobin is determined to be disease related. The investigator must also consult with Lilly or its designee to continue the investigational product. For patients with hemoglobin values <8 g/dL who were previously evaluated by a hematologist and approved for enrollment by Lilly or its designee, interruption of the investigational drug will be considered if a decrease of >1.5 g/dL from the lowest recorded baseline hemoglobin occurs.

[b] For patients with preexisting renal impairment, a lower threshold for interruption may be considered after discussion with Lilly or its designee.

[c] Evaluate promptly and institute appropriate treatment. If upon evaluation VTE is ruled out and no other temporary or permanent discontinuation criteria are met, then investigational product may be resumed.

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

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If Lilly or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and Lilly or its designee agree it is medically appropriate to continue, the investigator must obtain documented approval from Lilly or its designee to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

Safety follow-up- is required as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- subject decision
- the patient or the patient's designee, for example, parents or legal guardian, requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up- per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

Discontinuation is expected to be uncommon.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

Study procedures and their timing are summarized in the Schedule of Activities (Section 2). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary measure of effectiveness for this study is a decrease in the appropriate diary scores.

9.1.1.1. 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 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.

9.1.1.2. 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 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.

9.1.1.3. 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 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.

9.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments will include the following:

9.1.2.1. Steroid Weaning

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) is assessed in patients receiving steroids at baseline.

9.1.2.2. Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity is used to assess the patient's current disease activity, as it relates to their signs and symptoms. The instrument uses a 21-circle VAS ranging from 0 to 10 (using 0.5 increments) where 0 = "no activity" and 10 = "maximum activity" (Filocamo et al. 2010).

9.1.2.3. CANDLE Diary /SAVI Diary/ AGS Diary

The paper patient diary is provided to patients with CANDLE, SAVI, and AGS respectively. The change from baseline in patient's mean daily diary scores by symptom is assessed.

9.1.2.4. Classification of disease severity for NNS patients

Each patient with NNS will be assessed on their severity of the disease on a scale of 0 to 3 for each of the following disease symptoms as indicated on the Schedule of Activities (Section 2):

- fever attack,
- rash,
- lipomuscular atrophy and joint contractures,
- organ disorder (heart, lungs, liver).

This scoring system follows the disease severity classification process defined by the Japanese Intractable Diseases Information Center (JIDIC 2019). NNS patients residing in Japan are annually assessed based on this scale to be an acknowledged patient for this particular intractable disease.

9.1.2.5. Barthel Index

Barthel Index is used commonly for the assessment of activity of daily living for patients with intractable diseases (Mahoney 1965). The index consists of the assessment of the severity of feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers (bed to chair and back), mobility (on level surfaces) and stairs, yielding an overall score of 0 for the most severe degree to 100 for no assistance needed. Patients with SAVI and AGS will be assessed using the index at visits indicated in the Schedule of Activities (Section 2).

9.1.2.6. Collection of patient's relative retrospective medical records

The 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). Target parameters include the following:

- Height /Weight
- Occipital frontal circumference measurement (children less than 3 years old)
- Laboratory testing (eg, CRP, complete blood cell count, AST, ALT, gamma-glutamyltransferase [GGT], creatine phosphokinase [CPK])
- Classification of disease severity (eg, classification of disease severity for NNS patients, Barthel index)

These data originate from a record of assessments that NNS/CANDLE, SAVI, and AGS patients residing in Japan undergo to be officially diagnosed with a Japan Intractable Disease or a Specific Pediatric Chronic Disease via a specific submission process. In cases where the assessment/tests were done over multiple of days, data obtained closest to the date of submission will be recorded for this retrospective collection. If a patient is not yet acknowledged at the time of screening, the past data from his/her annual checks will be collected. Additional data on dermal symptoms will be used to understand the pattern of changes in dermal symptoms at an individual level for SAVI and AGS patients.

9.1.3. Exploratory Efficacy Assessments

Biomarkers of interferon signaling (serum IP-10/CXCL10 level and IFN response gene score) and acute phase reactants (high sensitivity C-reactive protein) will be collected from patients with NNS/CANDLE, SAVI, and AGS. The change from baseline in serum IP-10/CXCL10 level, IFN response gene score, and high sensitivity C-reactive protein is assessed throughout the study.

9.1.4. Appropriateness of Assessments

The use of the NNS/CANDLE, SAVI, and AGS diary score as 1 of the measurements of treatment response, trigger for dose escalation, and trigger for steroid weaning is based on precedent in similar studies in type I autoinflammatory interferonopathies conducted by investigators at the National Institutes of Health (NNS/CANDLE and SAVI diary) and at the Children's Hospital of Philadelphia, Philadelphia, PA (AGS diary). (Sanchez et al. 2018)

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

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

Investigators must document their review of each laboratory safety report.

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

The investigator will record all relevant AE and SAE information in the eCRF. After the ICF and Assent Form (as applicable) are signed, study site personnel will record via electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. The investigators should record their assessment of the potential relatedness of each AE to protocol procedure and/or investigational product, via electronic data entry.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, and/or study procedure and the AE.

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

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

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death,
- initial or prolonged inpatient hospitalization,
- a life-threatening experience (that is, immediate risk of dying),
- persistent or significant disability/incapacity,
- congenital anomaly/birth defect,
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

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

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

sponsor will comply with country-specific- regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the investigator's brochure and will notify the IRB, if appropriate according to local requirements.

Pregnancy

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

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Pregnancy itself is not considered to be an AE or SAE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 9.2.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Investigator's Brochure and that the investigator identifies as related to investigational product or procedure. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Events of Special Interest

Adverse events of special interest include the following:

- infections (including TB, HZ, or opportunistic infections),
- myelosuppressive events of anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia,
- thrombocytosis (defined as a platelet count >600,000/µL.),
- malignancies (except for successfully treated basal or squamous cell skin carcinoma),
- hepatic events (see Section 9.4.6.2),
- major adverse cardiovascular events (MACE) (see Section 10.3.6.1),
- thrombotic events (such as deep vein thrombosis and pulmonary embolism).

Sites will provide details on these AEs as instructed on the eCRF and may be asked for additional description by Lilly.

9.2.3. Complaint Handling

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a trial intervention.

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

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

AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 9.2.

Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the Sponsor during all periods of the study in which the drug is used.

If the investigator learns of any product complaint at any time after a patient has been discharged from the study, and such problem is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the Sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the Sponsor by fax.

Follow-up of Product Complaints:

Follow-up- applies to all patients, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

9.3. Treatment of Overdose

Baricitinib single doses up to 40 mg and multiple doses of up to 20 mg daily for 10 days have been administered in clinical studies without dose-limiting- toxicity. Pharmacokinetic data of a single dose of 40 mg in healthy volunteers indicate that >90% of the administered dose is expected to be eliminated within 24 hours.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately,
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until baricitinib can no longer be detected systemically (at least 3 days).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the patient.

9.4. Safety

Any clinically significant findings from ECG testing, physical examination, vital signs measurements, or laboratory measurements that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF. Any physical complaints/symptoms that present prior to initiation of treatment with investigational product will be collected as preexisting conditions on the eCRF. Signs and symptoms collected on the patient diary need not be reported as a preexisting condition/AE on the eCRF unless the signs and symptoms are considered strictly drug related or associated with an outcome defining an SAE. Information regarding use of concomitant medications will also be collected on the eCRF.

See Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 2) for the timing and frequency.

9.4.1. Electrocardiograms

A single 12-lead standard ECG will be locally collected at screening and read by a qualified physician (the investigator or qualified designee) at the site to determine whether the patient meets entry criteria. Electrocardiograms may be collected at additional times, when deemed clinically necessary.

9.4.2. Physical Examination

One complete physical examination (excluding pelvic and rectal examinations) will be performed at screening. This examination will determine whether the patient meets the criteria required to participate in the study and will also serve as a monitor for preexisting conditions and as a baseline for TEAE assessment. Body weight and height will also be recorded. Additional limited physical examinations will also be performed during the study (Section 2, Schedule of Activities).

Fundoscopy may be completed as part of the physical examination, as necessary if, in the opinion of the investigator, it is needed to monitor safety in specific AGS patients.

9.4.3. Vital Signs

Vital signs (eg, blood pressure and pulse) will be measured at times indicated in the Schedule of Activities (Section 2). Any clinically significant findings that result in a diagnosis should be captured on the eCRF and reported as an AE. Additional measurements of vital signs may be performed at the discretion of the investigator.

9.4.4. Laboratory Tests

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 2).
- If laboratory values from non-protocol- specified laboratory assessments performed at the institution’s local laboratory require a change in patient management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then the results must be recorded in the eCRF.

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2). For pediatric patients, reference ranges should be based on the patients’ age groups as defined by the central laboratory.

Due to blood volume restrictions and patient conditions, some laboratory tests may not be collected. Use of local anesthetics (eg, eutectic mixture of local anesthetics [EMLA] cream) consistent with local prescribing information is permitted during the study visit to ease discomfort associated with venipunctures. Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Additional blood samples may be drawn if needed for safety purposes and/or if warranted and agreed upon between the investigator and Lilly or its designee.

Blood volume restrictions:

In cases where required blood samples cannot be collected due to blood volume limitations relative to patient size/age, the investigator must consult with the Lilly-designated medical personnel to determine which samples to prioritize. The investigator should also refer to the blood sample prioritization guidance tool which is a supplemental instruction provided by sponsor. When required samples are not collected due to restirctions, this will not be considered a protocol violation, but this will need to be documented in the medical record.

Fasting Laboratory Tests:

Fasting lipid profile: Patients should not eat or drink anything except water for 4 to 12 hours, depending on weight and age, as specified below. If a patient attends these visits in a nonfasting state, this will not be considered a protocol violation. Recommended fasting times by age and weight are as follows:

- Patients ≥12 years: fast for 12 hours prior to laboratory sampling;
- Patients 8 to <12 years and weighing >50 kg: fast for 12 hours prior to laboratory sampling;
- Patients 8 to <12 years and weighing ≤50 kg: fast for 8 hours prior to laboratory sampling;
- Children <8 years and weighing 25 to ≤50 kg: fast for 8 hours prior to laboratory sampling;
- Children <8 years and weighing 10 to <25 kg: fast for 6 hours prior to laboratory sampling; and
- Children <8 years and weighing <10 kg: fast for 4 hours prior to laboratory sampling.

Urine Sample Collection:

If a urine sample cannot be collected, in particular, from patients who have not been toilet trained or who have physical impairment caused by primary disease, this will not be considered a protocol violation, provided that the site maintains appropriate documentation of why the sample cannot be collected.

9.4.5. Other Tests

9.4.5.1. Pulmonary Function Monitoring for SAVI Patients

The progression of pulmonary disease will be monitored in an age-based manner in SAVI patients. Monitoring may include vital signs, pulse oximetry, imaging, laboratory tests (eg, KL6) and pulmonary function tests, including diffusing capacity of the lung for carbon monoxide. The contents of monitoring can be modified by the investigator. Pulmonary function monitoring will

be locally performed at any time during the study, including the follow-up period, if medically necessary in the opinion of the investigator.

9.4.5.2. Screening for BK Virus in Blood and Urine

Patients will be tested for the presence of BK virus in blood and urine at baseline (prior to the first dose of baricitinib) and periodically, thereafter, as specified in Section 2. BK virus test may be performed at any time during the study, including the follow-up period, if medically necessary in the opinion of the investigator.

9.4.6. Safety Monitoring

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

The Lilly clinical research physician will monitor safety data throughout the course of the study and will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

See Section 8.1 for discontinuation criteria related to specific AEs.

Vitals signs will be monitored as indicated in the Schedule of Activities (Section 2).

9.4.6.1. Hepatitis B Virus DNA Monitoring

Hepatitis B virus DNA testing will be performed in enrolled patients who tested positive for HBcAb or HBsAb at Visit 1 (screening).

Patients who are positive for HBcAb or HBsAb and negative for HBV DNA (undetectable based on central results) at screening will require HBV DNA monitoring at Week 12 (Visit 10), Week 24 (Visit 13), Week 36 (Visit 16), Week 48 (Visit 19), Week 52 (Visit 20), Week 64 (Visit 21), Week 76 (Visit 22), Week 88 (Visit 23), Week 100 (Visit 24), Week 112 (Visit 25), Week 124 (Visit 26), Week 136 (Visit 27), Week 148 (Visit 28), Week 160 (Visit 29), Week 172 (Visit 30), Week 184 (Visit 31), Week 196 (Visit 32), Week 208 (Visit 33), Week 220 (Visit 34), Week 232 (Visit 35), Week 244 (Visit 36), early termination visit (ETV), and the posttreatment follow-up period (V801). As an exception, patients who are HBcAb-negative, HBsAb-positive with a documented history of Hepatitis B vaccination will not be required to undergo HBV DNA testing at Visit 1 nor HBV DNA monitoring throughout the study.

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

- If a single result is obtained with a value that is below the limit of quantitation, the test should be repeated within approximately 2 weeks. If the repeat test does not detect the target, monitoring will resume according to the schedule of activities.
- If the patient has 2 or more HBV DNA test results with a value that is below the limit of quantitation, HBV DNA testing should be performed approximately once per month for the remainder of the study and referral to a hepatologist is recommended.

- If a result is obtained with a value that is above the limit of quantitation, at any time during the study, the patient will be permanently discontinued from investigational product (Section 8.1.1) and should be referred to a hepatology specialist.
    - In selected cases, investigators may temporarily continue investigational product in accordance with current immunomodulator management in the setting of HBV DNA positivity. This option may be considered in consultation with Lilly (or its designee) and evaluation of individual patient risks and benefits.

Note: Unscheduled visits may be used for monitoring of HBV DNA, when necessary.

Table JAJE.7. Interpretation of HBV Serology at Screening

HBsAg	HBcAb	HBsAb	HBV DNA	Interpretation
Positive	N/A	N/A	N/A	Patients with positive HBsAg are excluded
N/A	N/A	N/A	Detected	Patients with detectable HBV DNA are excluded
Negative	Negative	Negative	Not detected	Eligible for inclusion, provided the patient meets the inclusion criteria and does not meet other exclusion criteria
Negative	Positive	Negative	Not detected	May be eligible for inclusion, provided the patient meets the inclusion criteria and does not meet other exclusion criteria. Monitor HBV DNA periodically as described in the Schedule of Activities (Section 2) • Patients who are anti-HBc-, anti-HBs+ with a documented history of Hepatitis B vaccination will not be required to undergo HBV DNA testing/monitoring.
Negative	Negative	Positive	Not detected	
Negative	Positive	Positive	Not detected	

Abbreviations: anti-HBc = anti-hepatitis B core antibody; anti-HBs = anti-hepatitis B surface antibody; DNA = deoxyribonucleic acid; HBcAb = anti-hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; N/A = not applicable; in these cases, a positive or negative test result.

9.4.6.2. Hepatic Safety Monitoring

*9.4.6.2.1. Close hepatic monitoring**

Laboratory tests (Appendix 4), including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), GGT, and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a patient with baseline results of ...	**develops the following elevations:**
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

* All ULN values should be age adjusted (AAULN)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (eg, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the patient's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the patient's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels. Special care should be taken for pediatric patients to minimize the volume of blood taken during hepatic monitoring.

*9.4.6.2.2. Comprehensive hepatic evaluation**

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms**, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms**, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

* All ULN values should be age adjusted (AAULN)

** Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

For adult patients (≥18 years old)

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy .

For pediatric patients (<18 years old)

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR and D. Bil, if TBL was elevated.

Based on the participant's age, medical history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for viral hepatitis A, B, C, E; autoimmune hepatitis; or an abdominal imaging study (for example, ultrasound, MRI, or CT scan). Consider additional tests, based on the medical history and clinical picture, including tests for HDV, CMV, EBV, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Special care should be taken to prioritize more

pertinent blood tests and minimize the volume of blood taken during hepatic evaluation. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a pediatric hepatologist or gastroenterologist consultation, MRCP, ERCP, cardiac echocardiogram, or a liver biopsy as deemed appropriate for the clinical condition and participant's age.

If any of the above specific abnormalities in the section of close hepatic monitoring and comprehensive hepatic evaluation, are considered a feature of the disease (NNS/CANDLE, SAVI, or AGS), the investigator should discuss appropriate monitoring for the patient with Lilly or its designee.

9.4.6.2.3. Hepatic Safety Data Collection

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study patients who meet 1 or more of the following 5 conditions: *

- Elevation of serum ALT to ≥5 × ULN on 2 or more consecutive blood tests (if baseline ALT <1.5 × ULN);
    - In patients with baseline ALT ≥1.5 × ULN, the threshold is ALT ≥3 × baseline on 2 or more consecutive tests;
- Elevated TBL to ≥2 × ULN (if baseline TBL <1.5 × ULN) (except for cases of known Gilbert's syndrome);
    - In patients with baseline TBL ≥1.5 × ULN, the threshold should be TBL ≥2 × baseline;
- Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN);
    - In patients with baseline ALP ≥1.5× ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests;
- Hepatic event considered to be an SAE;
- Discontinuation of study drug due to a hepatic event.

Note: the interval between the two consecutive blood tests should be at least 2 days.

* All ULN values should be age adjusted (AAULN)

9.4.7. Growth Monitoring

Height, weight, and occipital frontal circumference measurement (children less than 3 years old) will be measured at pretreatment and posttreatment for the assessment of physical growth according to the Schedule of Activities (Section 2). Height and weight changes in pediatric patients at an individual level will be reviewed by the study medical monitor.

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected from all patients at the time points shown in Table JAJE.8. Pharmacokinetic samples will be used to determine the concentrations of baricitinib using a validated bioanalytical method.

Venous blood samples for the measurement of baricitinib concentrations will be collected from all patients enrolled in the study. At least 72 hours of dosing in a certain dosing regimen is needed before PK samples can be taken.

Table JAJE.8. Pharmacokinetic Sampling

PK sampling visits	PK sampling time points
Visit 7[a,b] and Visit 11[a,b]	Collect the following 4 PK samples in the morning [c]: • Pre-morning-dose • 1 hour post-morning-dose • 1.5 hours post-morning-dose • 4 hours post-morning-dose
Visit 12[a]	Collect the following 1 PK sample in the morning [c]: • Pre-morning-dose

Abbreviation: PK = pharmacokinetic.

[a] If PK samples cannot be processed within the specified time after collection, the PK samples may be collected on the next visit.

[b] In case where the blood volume required exceeds that of tolerable amount for 1 visit, the corresponding PK samples that could not be drawn on that visit can be taken on the next visit. It is also possible for them to be taken over a multiple of visits prior to the next PK-required visit.

[c] If PK samples are taken at the time points other than morning-dose, this will not be considered a protocol violation.

Additional unscheduled PK samples may be collected with Lilly or its designee approval to assess safety and dosing, and this can be considered especially in patients with eGFR <60 mL/min/1.73 m^2.

For both scheduled and unscheduled PK samples taken, the actual date and exact timing (24-hour clock) of PK sample collection should be recorded. The date and time of the last 2 doses prior to the PK sample taken should be recorded. In addition, doses taken by the patients during their stay in the clinic on the visits where PK samples were taken should also be recorded.

Pharmacokinetic samples will be kept in storage at a laboratory facility designated by Lilly. Bioanalytical samples collected to measure baricitinib concentration will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Refer to Section 9.1.2.6.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to baricitinib and to investigate genetic variants thought to play a role in NNS/CANDLE, SAVI, or AGS. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or IRBs impose shorter time limits.

Molecular technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

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

Blood samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2). Samples will be used for research on the drug target, disease process, variable response to baricitinib, pathways associated with NNS/CANDLE, SAVI, or AGS, mechanism of action of baricitinib, and/or research method, or to validate diagnostic tools or assay(s) related to these diseases.

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

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit, or for a shorter period, if local regulations require. The duration allows Lilly to respond to future regulatory requests related to the investigational product. Any samples remaining after 15 years will be destroyed.

10. Statistical Considerations

10.1. Sample Size Determination

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 patients for a specific disease if no eligible patients could be found.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign informed consent or assent (as applicable), and meet all eligibility criteria
Full analysis set	All enrolled subjects who take at least 1 dose of study treatment.

10.3. Statistical Analyses

10.3.1. General Statistical 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. Two-dimensional plots of various data may be utilized to explore the relationship between variables of interest. For example, plots of final dose level versus efficacy measures may be used to explore recommended dosing guidelines, and plots of efficacy measures versus laboratory measures may be used to explore risk/benefit relationships.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A list of all enrolled patients and their reason for discontinuation from the study will be created.

10.3.2.2. Patient Characteristics

A summary and list of demographic information and baseline characteristics of all enrolled patients will be created.

10.3.2.3. Concomitant Therapy

Concomitant therapy will be recorded at each visit and will be classified according to the World Health Organization Drug Dictionary. Concomitant therapy will be reported in patient listings.

10.3.2.4. Treatment Compliance

Treatment compliance with investigational product will be summarized for each treatment period. Patients will be considered compliant for each study period if they miss <20% of the expected doses. Dose reductions or temporary withdrawal because of safety reasons will not be considered a protocol violation. Proportions of patients compliant will be reported in patient listing. Patient compliance will be further defined in the statistical analysis plan.

10.3.3. Efficacy Analyses

The primary data presentation will be a summary or by-patient listings of the following items:

- change from baseline in the appropriate diary score by indication,
- baseline, final steroid doses and changes over time for those patients receiving steroids.

No formal statistical test of any hypothesis will be conducted.

Additional data displays such as descriptive summaries where applicable and listings of efficacy measures over time will be provided.

10.3.4. Safety Analyses

Safety measures will be summarized and/or listed. Standard listings will include TEAEs, SAEs, and results from laboratory tests. By definition, TEAEs are Aes that begin or increase in severity after the patient receives the first dose of baricitinib. Summaries of the incidence and event counts of TEAEs and SAEs, of abnormal shifts in laboratory values, or of per-visit distributions of laboratory results will be created. Other data, including body weight and height data will be reported in patient listing. Weight, height, occipital frontal circumference measurement (children less than 3 years old), and body mass index data will be merged to the Japanese children standard growth data issued by the Japanese Association for Human Auxology to compare subjects' growth with the standard (Isojima et al. 2016).

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Graphical/Visual analysis of the baricitinib concentration-time profile will be conducted to compare it with JAGA study result. Population PK approach (eg, PK parameters estimation using previously established population PK model) may be conducted to characterize PK in Japanese patients with NNS/CANDLE, SAVI, and AGS, if appropriate.
Pharmacokinetic/Pharmacodynamic analyses (eg, similarity with Study JAGA in relationship between baricitinib exposure [eg, area under the drug plasma versus time concentration from time zero top 24 hours at steady state ($AUC_{0\text{-}24,ss}$)] and IFN-related biomarkers, including, but not limited to, serum IP-10/CXCL10 level and IFN response gene score) may be explored.
Other analyses may also be conducted, if deemed appropriate.

10.3.6. Interim Analyses

A primary database lock is planned after the first 5 patients complete the Week 32 visit or the early termination visit. The analysis based on data from the primary database lock will be

conducted by Lilly or its designee for New Drug Application submission. No multiplicity adjustment will be implemented.

Other interim database lock may be performed, if needed (eg, regulatory agency requests to submit most recent safety data of the study).

The final database lock will occur after all patients complete the study, including posttreatment follow-up.

10.3.6.1. Adjudication Committee

An external Clinical Event Committee will adjudicate potential MACE (cardiovascular death, myocardial infarction, stroke), other cardiovascular events (such as hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, coronary revascularization such as coronary artery bypass graft or percutaneous coronary intervention), venous thrombotic events, arterial thromboembolic events, and noncardiovascular deaths. Details of membership, operations, recommendations from the Committee, and the communication plan will be documented in the charter. The Clinical Event Committee will adjudicate the events in a consistent and unbiased manner.

Potential events will be identified by the investigative site or by a medical review conducted by the Sponsor or designee. Additional data about each identified potential event should be provided to the sponsor via specific event adjudication forms.

11. References

Agarwal AK, Xing C, DeMartino GN, Mizrachi D, Hernandez MD, Sousa AB, Martínez de Villarreal L, dos Santos HG, Garg A. PSMB8 encoding the β5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. *Am J Hum Gen*. 2010;87(6):866872.

An J, Woodward JJ, Lai W, Minie M, Sun X, Tanaka L, Snyder JM, Sasaki T, Elkon KB. Inhibition of cyclic GMP-AMP synthase using a novel antimalarial drug derivative in Trex1-deficient mice. *Arthritis Rheumatol*. 2018;70(11):1807-1819.

Arima K, Kinoshita A, Mishima H, Kanazawa N, Kaneko T, Mizushima T, Ichinose K, Nakamura H, Tsujino A, Kawakami A, Matsunaka M, Kasagi S, Kawano S, Kumagai S, Ohmura K, Mimori T, Hirano M, Ueno S, Tanaka K, Tanaka M, Toyoshima I, Sugino H, Yamakawa A, Tanaka K, Niikawa N, Furukawa F, Murata S, Eguchi K, Ida H, Yoshiura K. Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. *Proc Natl Acad Sci USA*. 2011;108(36):1491414919.

Boy MG, Wang C, Wilkinson BE, Chow VF, Clucas AT, Krueger JG, Gaweco AS, Zwillich SH, Changelian PS, Chan G. Double-blind, placebo-controlled, dose-escalation study to evaluate the pharmacologic effect of CP690,550 in patients with psoriasis. *J Invest Dermatol*. 2009;129(9):22992302.

Brehm A, Liu Y, Sheikh A, Marrero B, Omoyinmi E, Zhou Q, Montealegre G, Biancotto A, Reinhardt A, Almeida de Jesus A, Pelletier M, Tsai WL, Remmers EF, Kardava L, Hill S, Kim H, Lachmann HJ, Megarbane A, Chae JJ, Brady J, Castillo RD, Brown D, Casano AV, Gao L, Chapelle D, Huang Y, Stone D, Chen Y, Sotzny F, Lee CC, Kastner DL, Torrelo A, Zlotogorski A, Moir S, Gadina M, McCoy P, Wesley R, Rother KI, Hildebrand PW, Brogan P, Krüger E, Aksentijevich I, Goldbach-Mansky R. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *J Clin Invest*. 2015;125(11):4196-4211.

Canna SW, Goldbach-Mansky R. New monogenic autoinflammatory diseases-a clinical overview. *Semin Immunopathol.* 2015;37(4):387-394.

Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. *Nat Rev Immunol*. 2015;15(7):429-440.

Crow YJ, Chase DS, Lowenstein Schmidt J, Szynkiewicz M, Forte GM, Gornall HL, Oojageer A, Anderson B, Pizzino A, Helman G, Abdel-Hamid MS, Abdel-Salam GM, Ackroyd S, Aeby A, Agosta G, Albin C, Allon-Shalev S, Arellano M, Ariaudo G, Aswani V, Babul-Hirji R, Baildam EM, Bahi-Buisson N, Bailey KM, Barnerias C, Barth M, Battini R, Beresford MW, Bernard G, Bianchi M, Billette de Villemeur T, Blair EM, Bloom M, Burlina AB, Carpanelli ML, Carvalho DR, Castro-Gago M, Cavallini A, Cereda C, Chandler KE, Chitayat DA, Collins AE, Sierra Corcoles C, Cordeiro NJ, Crichiutti G, Dabydeen L, Dale RC, D'Arrigo S, De Goede CG, De Laet C, De Waele LM, Denzler I, Desguerre I, Devriendt K, Di Rocco M, Fahey MC, Fazzi E, Ferrie CD, Figueiredo A, Gener B, Goizet C, Gowrinathan NR, Gowrishankar K, Hanrahan D, Isidor B, Kara B, Khan N, King MD, Kirk EP, Kumar R, Lagae L, Landrieu P, Lauffer H, Laugel V, La Piana R, Lim MJ, Lin JP, Linnankivi T, Mackay MT,

Marom DR, Marques Lourenço C, McKee SA, Moroni I, Morton JE, Moutard ML, Murray K, Nabbout R, Nampoothiri S, Nunez-Enamorado N, Oades PJ, Olivieri I, Ostergaard JR, Pérez-Dueñas B, Prendiville JS, Ramesh V, Rasmussen M, Régal L, Ricci F, Rio M, Rodriguez D, Roubertie A, Salvatici E, Segers KA, Sinha GP, Soler D, Spiegel R, Stödberg TI, Straussberg R, Swoboda KJ, Suri M, Tacke U, Tan TY, te Water Naude J, Wee Teik K, Thomas MM, Till M, Tonduti D, Valente EM, Van Coster RN, van der Knaap MS, Vassallo G, Vijzelaar R, Vogt J, Wallace GB, Wassmer E, Webb HJ, Whitehouse WP, Whitney RN, Zaki MS, Zuberi SM, Livingston JH, Rozenberg F, Lebon P, Vanderver A, Orcesi S, Rice GI. Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. *Am J Med Genet A*. 2015;167A(2):296–312.

Dalbeth N, So A. Hyperuricaemia and gout: state of the art and future perspectives. *Ann Rheum Dis*. 2010;69(10):1738-1743.

D'Arrigo S, Riva D, Bulgheroni S, Chiaparini L, Lebon P, Rice G, Crow YJ, Pantaleoni C. Aicardi-Goutières syndrome: description of a late onset case. *Dev Med Child Neurol*. 2008;50(8):631634.

de Jesus AA, Canna SW, Liu Y, Goldbach-Mansky R. Molecular mechanisms in genetically defined autoinflammatory diseases: disorders of amplified danger signaling. *Annu Rev Immunol.* 2015;33:823874-.

De Laet C, Goyens P, Christophe C, Ferster A, Mascart F, Dan B. Phenotypic overlap between infantile systemic lupus erythematosus and Aicardi-Goutières syndrome. *Neuropediatrics*. 2005;36(6):399402.

De Nardo D, Latz E. NLRP3 inflammasomes link inflammation and metabolic disease. *Trends Immunol*. 2011;32(8):373-379.

Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, Abela GS, Franchi L, Nuñez G, Schnurr M, Espevik T, Lien E, Fitzgerald KA, Rock KL, Moore KJ, Wright SD, Hornung V, Latz E. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature*. 2010;464(7293):1357-1361.

Eleftheriou D, Brogan PA. Genetic interferonopathies: An overview. *Best Pract Res Clin Rheumatol.* 2017;31(4):441-459.

Filocamo G, Davì S, Pistorio A, Bertamino M, Ruperto N, Lattanzi B, Consolaro A, Magni-Manzoni S, Galasso R, Camilla Varnier G, Martini A, and Ravelli A. Evaluation of 21numbered circle and 10-centimeter horizontal line visual analog scales for physician and parent subjective ratings in juvenile idiopathic arthritis. *J Rheumatol*. 2010;37(7):15341541.

Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, Covington MB, Thomas B, Collier P, Favata MF, Wen X, Shi J, McGee R, Haley PJ, Shepard S, Rodgers JD, Yeleswaram S, Hollis G, Newton RC, Metcalf B, Friedman SM, Vaddi K. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. *J Immunol.* 2010;184(9):5298-5307.

Garg A, Hernandez MD, Sousa AB, Subramanyam L, Martinez de Villarreal L, dos Santos HG, Barboza O. An autosomal recessive syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy-. *J Clin Endocrinol Metab.* 2010;95(9):E58-E63.

Goldbach-Mansky R. Current status of understanding the pathogenesis and management of patients with NOMIC/CINCA. *Curr Rheum Rep.* 2011;13(2):123-131.

Goldbach-Mansky R. Blocking interleukin-1 in rheumatic diseases. *Ann N Y Acad Sci*. 2009;1182:111123-.

Goldbach-Mansky R, Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI, Kim HJ, Brewer C, Zalewski C, Wiggs E, Hill S, Turner ML, Karp BI, Aksentijevich I, Pucino F, Penzak SR, Haverkamp MH, Stein L, Adams BS, Moore TL, Fuhlbrigge RC, Shaham B, Jarvis JN, O'Neill K, Vehe RK, Beitz LO, Gardner G, Hannan WP, Warren RW, Horn W, Cole JL, Paul SM, Hawkins PN, Pham TH, Snyder C, Wesley RA, Hoffmann SC, Holland SM, Butman JA, Kastner DL. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *N Engl J Med.* 2006;355(6):581-592.

Henderson C, Goldbach-Mansky R. Monogenic autoinflammatory diseases: new insights into clinical aspects and pathogenesis. *Curr Opin Rheumatol*. 2010;22(5):567-578.

Henrickson M, Wang H. Tocilizumab reverses cerebral vasculopathy in a patient with homozygous SAMHD1 mutation. *Clin Rheumatol*. 2017;36(6):1445-1451.

Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, Kavanaugh A, Weinstein SP, Belomestnov P, Yancopoulos GD, Stahl N, Mellis SJ. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum*. 2008;58(8):2443-2452.

Honda-Ozaki F, Terashima M, Niwa A, Saiki N, Kawasaki Y, Ito H, Hotta A, Nagahashi A, Igura K, Asaka I, Li HL, Yanagimachi M, Furukawa F, Kanazawa N, Nakahata T, Saito MK. Pluriopotent stem cell model of Nakajo-Nishimura syndrome untangles proinflammatory pathways mediated by oxidative stress. *Stem Cell Reports.* 2018;10(6):18351850.

Isojima T, Kato N, Ito Y, Kanzaki K, Murata M. Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. *Clin Pediatr Endocrinol*. 2016;25(2):71-76.

[JIDIC] Japanese Intractable Diseases Information Center. Shitei-Nanbyo 268. Available at: https://www.nanbyou.or.jp/entry/4583. June 2019. Accessed April 30, 2020.

Kamei A, Akasaka M, Soga N, Suzuki Y, Uchide M, Chida S. Aicardi-Goutières syndrome with systemic lupus erythematosus and hypothyroidism. *Brain Dev*. 2013;35(1):87-90.

Kim H, Sanchez GA, Goldbach-Mansky R. Insights from Mendelian interferonopathies: comparison of CANDLE, SAVI with AGS, monogenic lupus. *J Mol Med (Berl)*. 2016;94(10):1111-1127.

Kim H, Brooks KM, Tang CC, Wakim P, Blake M, Brooks SR, Montealegre Sanchez GA, de Jesus AA, Huang Y, Tsai WL, Gadina M, Prakash A, Janes JM, Zhang X, Macias WL, Kumar P, Goldbach-Mansky R. Pharmacokinetics, pharmacodynamics, and proposed dosing of the oral JAK1 and JAK2 inhibitor baricitinib in pediatric and young adult CANDLE and SAVI patients. *Clin Pharmacol Ther*. 2018;104(2):364-373.

Kitano Y, Matsunaga E, Morimoto T, Okada N, Sano S. A syndrome with nodular erythema, elongated and thickened fingers, and emaciation. *Arch Dermatol.* 1985;121(8):1053-1056.

Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, Krishnaswami S, Burgos-Vargas R, Wilkinson B, Zerbini CA, Zwillich SH. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase Iia trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum*. 2009;60(7):18951905.

Kuijpers TW. Aicardi-Goutières syndrome: immunophenotyping in relation to interfero-nalpha. *Eur J Paediatr Neurol*. 2002;6(Suppl A):A59A64.

Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, Wittkowski H, Bek S, Hartmann N, Bosset S, Hawkins PN, Jung T. In vivo regulation of interleukin 1beta in patients with cryoprin-associated periodic syndromes-. *J Exp Med.* 2009;206(5):1029-1036.

Lelouard H, Schmidt EK, Camosseto V, Clavarino G, Ceppi M, Hsu HT, Pierre P. Regulation of translation is required for dendritic cell function and survival during activation. *J Cell Biol.* 2007;179(7):1427-1439.

Liu Y, Ramot Y, Torrelo A, Paller AS, Si N, Babay S, Kim PW, Sheikh A, Lee CC, Chen Y, Vera A, Zhang X, Goldbach-Mansky R, Zlotogorski A. Mutations in proteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum.* 2012;64(3):895-907.

Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GAM, Tenbrock K, Wittkowski H, Jones OY, Kuehn HS, Lee CR, DiMattia MA, Cowen EW, Gonzalez B, Palmer I, DiGiovanna JJ, Biancotto A, Kim H, Tsai WL, Trier AM, Huang Y, Stone DL, Hill S, Kim HJ, St Hilaire C, Gurprasad S, Plass N, Chapelle D, Horkayne-Szakaly I, Foell D, Barysenka A, Candotti F, Holland SM, Hughes JD, Mehmet H, Issekutz AC, Raffeld M, McElwee J, Fontana JR, Minniti CP, Moir S, Kastner DL, Gadina M, Steven AC, Wingfield PT, Brooks SR, Rosenzweig SD, Fleisher TA, Deng Z, Boehm M, Paller AS, Goldbach-Mansky R. Activated STING in a vascular and pulmonary syndrome. *N Engl J Med*. 2014;371(6):507-518.

Mahoney FI BD. Functional Evaluation: The Barthel Index. *Maryland State Medical Journal.* 1965;14:61-65.

Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Annu Rev Immunol*. 2009;27:621-668.

McGonagle D, McDermott MF. A proposed classification of the immunological diseases. *PloS Med*. 2006;3(8):e297.

Medicherla B, Goldberg AL. Heat shock and oxygen radicals stimulate ubiquitin-dependent degradation mainly of newly synthesized proteins. *J Cell Biol.* 2008;182(4):663-673.

Moebius J, van den Broek M, Groettrup M, Basler M. Immunoproteasomes are essential for survival and expansion of T cells in virus-infected mice. *Eur J Immunol.* 2010;40(12):3439-3449.

Orcesi S, Pessagno A, Biancheri R, La Piana R, Mascaretti M, Rossi A, Rice GI, Crow YJ, Fazzi E, Veneselli E. Aicardi-Goutières syndrome presenting atypically as a sub-acute leukoencephalopathy. *Eur J Paediatr Neurol*. 2008;12(5):408411.

O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis*. 2013;72(suppl 2):ii111-ii115.

O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Ann Rev Med*. 2015;66:311-328.

Oyanagi K, Sasaki K, Ohama E, Ikuta F, Kawakami A, Miyatani N, Miyatake T, Yamada S. An autopsy case of a syndrome with muscular atrophy, decreased subcutaneous fat, skin eruption and hyper gamma-globulinemia: peculiar vascular changes and muscle fiber degeneration. *Acta Neuropathol.* 1987;73(4):313-319.

Ramot Y, Czarnowicki T, Maly A, Navon-Elkan P, Zlotogorski A. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome: a case report. *Pediatr Dermatol.* 2011;28(5):538-541.

Reits EA, Hodge JW, Herberts CA, Groothuis TA, Chakraborty M, Wansley EK, Camphausen K, Luiten RM, de Ru AH, Neijssen J, Griekspoor A, Mesman E, Verreck FA, Spits H, Schlom J, van Veelen P, Neefjes JJ. Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy. *J Exp Med*. 2006;203(5):1259-1271.

Rice GI, Meyzer C, Bouazza N, Hully M, Boddaert N, Semeraro M, Zeef LAH, Rozenberg F, Bondet V, Duffy D, Llibre A, Baek J, Sambe MN, Henry E, Jolaine V, Barnerias C, Barth M, Belot A, Cances C, Debray FG, Doummar D, Frémond ML, Kitabayashi N, Lepelley A, Levrat V, Melki I, Meyer P, Nougues MC, Renaldo F, Rodero MP, Rodriguez D, Roubertie A, Seabra L, Uggenti C, Abdoul H, Treluyer JM, Desguerre I, Blanche S, Crow YJ. Reverse-transcriptase inhibitors in the Aicardi–Goutières syndrome. *N Engl J Med*. 2018;379(23):22752277.

Sanchez GA, De Jesus AA, Goldbach-Mansky R. Monogenic autoinflammatory diseases: disorders of amplified danger sensing and cytokine dysregulation. *Rheum Dis Clin North Am*. 2013;39(4):701-734.

Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, Schalm S, Murias S, Dare JA, Brown D, Stone DL, Gao L, Klausmeier T, Foell D, de Jesus AA, Chapelle DC, Kim H, Dill S, Colbert RA, Failla L, Kost B, O'Brien M, Reynolds JC, Folio LR, Calvo KR, Paul SM, Weir N, Brofferio A, Soldatos A, Biancotto A, Cowen EW, Digiovanna JJ, Gadina M, Lipton AJ, Hadigan C, Holland SM, Fontana J, Alawad AS, Brown RJ, Rother KI, Heller T, Brooks KM, Kumar P, Brooks SR, Waldman M, Singh HK, Nickeleit V, Silk M, Prakash A, Janes JM, Ozen S, Wakim PG, Brogan PA, Macias WL, Goldbach-Mansky R. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J Clin Invest*. 2018;128(7):3041-3052.

Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629-637.

Seifert U, Bialy LP, Ebstein F, BechOtschir D, Voigt A, Schröter- F, Prozorovski T, Lange N, Steffen J, Rieger M, Kuckelkorn U, Aktas O, Kloetzel PM, Krüger E. Immunoproteasomes preserve protein homeostasis upon interferon-induced oxidative stress. *Cell.* 2010;142(4):613-624.

Strehl B, Textoris-Taube K, Jäkel S, Voigt A, Henklein P, Steinhoff U, Kloetzel PM, Kuckelkorn U. Antitopes define preferential proteasomal cleavage site usage. *J Biol Chem*. 2008;283(26):17891-17897.

Torrelo A, Patel S, Colmenero I, Gurbindo D, Lendínez F, Hernández A, López-Robledillo JC, Dadban A, Requena L, Paller AS. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. *J Am Acad Dermatol.* 2010;62(3):489-495.

Torrelo A, Colmenero I, Requena L, Paller AS, Ramot Y, Richard Lee CC, Vera A, Zlotogorski A, Goldbach-Mansky R, Kutzner H. Histologic and immunohistochemical features of the skin lesions in CANDLE syndrome. *Am J Dermatopathol.* 2015;37(7):517-522.

Valentino L, Pierre J. JAK/STAT signal transduction: regulators and implication in hematological malignancies. *Biochem Pharmacol.* 2006;71(6):713-721.

Voigt A, Jäkel S, Textoris-Taube K, Keller C, Drung I, Szalay- G, Klingel K, Henklein P, Stangl K, Kloetzel PM, Kuckelkorn U. Generation of in silico predicted coxsackievirus B3-derived MHC class I epitopes by proteasomes. *Amino Acids*. 2010;39(1):243-255.

Wang H, Das L, Tan Hung Tiong J, Vasanwala RF, Arkachaisri T. CANDLE syndrome: an extended clinical spectrum. *Rheumatology (Oxford).* 2014;53(11):2119-2120.

Yao Y, Higgs BW, Morehouse C, de Los Reyes M, Trigona W, Brohawn P, White W, Zhang J, White B, Coyle AJ, Kiener PA, Jallal B. Development of potential pharmacodynamic and diagnostic markers for anti-IFN-alpha monoclonal antibody trials in systemic lupus erythematosus. *Hum Genomics Proteomics*. 2009:pii374312.

Yewdell JW. The seven dirty little secrets of major histocompatibility complex class I antigen processing. *Immunol Rev.* 2005;207:8-18.

12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
ADAR	Adenosine deaminase, RNA-specific
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AGS	Aicardi-Goutières Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some ethical review boards [ERBs]).
AST	aspartate aminotransferase
$AUC_{0\text{-}24,ss}$	area under the drug plasma versus time concentration from time zero top 24 hours at steady state
BID	twice daily (divided dose 2 times per 24 hours)
NNS/CANDLE	Nakajo-Nishimura Syndrome/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	cryopyrin-associated periodic syndromes
cGAMP	cyclic guanosine monophosphate- adenosine monophosphate
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.

Term	Definition
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CRP	C-reactive protein
D. Bil	direct bilirubin
DEG	differentially expressed gene
DMARD	disease modifying anti-rheumatic drugs
DNA	deoxyribonucleic acid
dsRNA	double-stranded ribonucleic acid
DVT	deep vein thrombosis
ECG	electrocardiogram
EDC	electronic data capture
eCRF	Sometimes referred to as clinical report form. A printed or electronic form for recording study patients' data during a clinical study, as required by the protocol.
eGFR	estimated glomerular filtration rate
ERB	ethical review board
FCL	familial chilblain lupus
GOF	gain-of-function
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HbcAb	anti-hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HbsAb	hepatitis B surface antibody
HBV	hepatitis B virus
HCV	hepatitis C virus

Term	Definition
HIV	human immunodeficiency virus
HZ	herpes zoster
i-proteasome	immunoproteasome complex
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IFN	interferon
IL	interleukin
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IP-10/CXCL10	interferon inducible protein 10/C-X-C motif chemokine 10
IRB	investigational review board
IRG-S	IFN response gene score
JAGA	I4V-MC-JAGA
JAJE	I4V-JE-JAJE
JAK	Janus kinase
JID	Japanese Intractable Diseases
JMP	joint contractures, muscle atrophy, and panniculitis
LOF	loss-of-function
MACE	major adverse cardiovascular events
MCP-1	monocyte chemoattractant protein 1

Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
OAT3	organic anion transporter 3
PE	pulmonary embolism
PK	pharmacokinetics
PPD	purified protein derivative
PRAAS	proteasome associated autoinflammatory syndromes
PSMB8	proteasome subunit beta type-8
QD	once daily
qPCR	quantitative polymerase chain reaction
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAVI	STING-associated vasculopathy with onset during infancy
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SOC	MedDRA System Organ Class
STAT	signal transducers and activators of transcription
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TNF	tumor necrosis factor
TYK2	tyrosine kinase 2
ULN	upper limit of normal

Term	Definition
V/F	apparent volume of distribution
VTE	venous thromboembolic event
VZV	varicella-zoster virus
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology[b]	**Serum Chemistry[b]**	**Other Tests[b]**
Hemoglobin	Sodium	Hepatitis B Surface antigen (HbsAg)[f]
Hematocrit	Potassium	Anti-Hepatitis B Core antibody (HbcAb)[f]
Erythrocyte count (RBC)	Total bilirubin	Hepatitis B Surface antibody (HbsAb)[f]
Mean cell volume (MCV)	Direct bilirubin	Hepatitis B Virus DNA
Mean cell hemoglobin concentration (MCHC)	Alkaline phosphatase	Human immunodeficiency virus (HIV)[f]
Leukocytes (WBC)	Alanine aminotransferase/Serum glutamic pyruvic transaminase (ALT/SGPT)	Hepatitis C antibody[f,g]
Reticulocyte	Aspartate aminotransferase/Serum glutamic oxaloacetic transaminase (AST/SGOT)	Thyroid-stimulating hormone (TSH)[f]
Absolute counts of:	Blood urea nitrogen (BUN)	Thyroxine (T4)[f]
Neutrophils, segmented	Creatinine	Pregnancy Test (serum, urine)[h]
Neutrophils, juvenile (bands)	Calcium	Follicle-stimulating hormone[f,i]
Lymphocytes	Glucose	PPD or QuantiFERON®-TB Gold test or T-SPOT®.TB test[j]
Monocytes	Albumin	Baricitinib plasma concentration
Eosinophils	Total protein	BK virus quantitative PCR, plasma BK virus quantitative PCR, urine
Basophils	Creatine phosphokinase (CPK)	Urine cytology[e]
Platelets	Uric acid	Iron studies (iron, TIBC and ferritin)
	Gamma glutamyl transferase (GGT)	Pharmacogenetic Sample (DNA)
Urinalysis[b,e]	Aldolase[c]	
Specific gravity	Estimated glomerular filtration rate (eGFR)[k]	**Biomarkers**
pH		IFN response gene score[l]
Protein	**Lipid[b,d]**	Cytokine panel (serum IP-10/CXCL10, etc)
Glucose	Total cholesterol (TC)	
Ketones	Low-density lipoprotein (LDL)	**Inflammatory marker**
Bilirubin	High-density lipoprotein (HDL)	High sensitivity C-reactive protein (hsCRP)
Urobilinogen	Triglycerides	
Blood		
Leukocyte esterase		
Nitrite		

Abbreviations: DNA = deoxyribonucleic acid; eGFR = electronic glomerular filtration rate; HCV = hepatitis C virus; IFN = interferon; PPD = purified protein derivative; RBC = red blood cells; RNA = ribonucleic acid; TIBC = total iron-binding capacity; TB = tuberculosis; WBC = white blood cells.

[a] In case where required blood samples cannot be collected due to blood volume limitation relative to patient size/age, the investigator must consult with Lilly or its designee to determine which samples to collect. This will not be considered a protocol violation but will need to be documented in the medical record.

[b] Unscheduled blood chemistry, hematology, urinalysis, and other tests may be performed at the discretion of the investigator.

[c] Perform if inflammatory myositis is present.

[d] Fasting lipid profile. Patients should not eat or drink anything except water according to Section 2 (Schedule of Activities).

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

[f] Test required at Visit 1 only to determine eligibility of patient for the study.

[g] A positive hepatitis C antibody result will be confirmed with a positive hepatitis C virus result (HCV RNA).

[h] Serum pregnancy test will be performed centrally at the screening visit (Visit 1) on all female patients who are of appropriate age for childbearing potential. After the screening visit, urine pregnancy tests will be performed locally on female patients of childbearing potential. Female patient of childbearing potential will be defined as ≥10 years old and has reached menarche, or if the there is a reason to believe that the patient is sexually active. At the discretion of the investigator, female patients who are <10 years old may also be tested as needed.

[i] To confirm postmenopausal status for women >40 and ≤55 years of age who have had a cessation of menses, a follicle-stimulatin hormone test will be performed. Nonchildbearing potential is defined as a follicle-stimulating hormone ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea.

[j] An interferon-γ release assay (QuantiFERON®-TB Gold or T-SPOT®) test is the preferred alternative to the PPD test for the evaluation of TB infection, and it may be used instead of the PPD test and may be read locally. One retest is allowed for patients with an "indeterminate" QuantiFERON-TB Gold assay or "borderline" T-SPOT.TB assay. Patients with 2 indeterminate QuantiFERON-TB Gold assays or 2 borderline T-SPOT.TB assays will be excluded.

[k] eGFR calculated using the Japanese Society for Pediatric Nephrology formula (for patients ≥2 years and ≤18 years of age), the Bedside Schwartz 2009 formula (for patients <2 years of age), and CKD-EPI Creatinine 2009 equation (for patients >18 years of age).

[l] Samples for IFN response gene score will be collected in RNA PAXgene tube.

Appendix 3. Study Governance Considerations

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

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

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

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

Recognizing that study sites and ethical review boards (ERBs) may have different requirements for obtaining assent, Lilly recommends the following guidelines for obtaining assent of children who will be participating in the study: the investigator should explain the study on the child's developmental level and determine whether the child has the capability to read and understand a written assent form. If so, the investigator should have the child sign and date the assent form that is most appropriate to the child's developmental level. If the child does not sign any assent form, the investigator is to document why no such form was signed for this patient. If the patient reaches the legal age of maturity during the course of the study, it is the responsibility of the investigator to obtain consent from the patient before the patient continues in the study.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

Appendix 3.1.2. Recruitment

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

Appendix 3.1.3. Ethical Review

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

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

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

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

- the protocol and related amendments and addenda, current Investigator's Brochure and updates during the course of the study,
- ICF and Assent Form (as applicable),
- other relevant documents (eg, curricula vitae, advertisements).

The investigator will be responsible for reporting significant issues related to participant safety, participant rights, or data integrity.

Appendix 3.1.4. Regulatory Considerations

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

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

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

All or some of the obligations of Lilly may be assigned to a third party.

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

Appendix 3.1.5. Investigator Information

Physicians with a specialty in autoinflammatory type 1 interferonopathies with appropriate experience with diagnosis and treatment of patients with NNS/CANDLE, SAVI, or AGS will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

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

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

Appendix 3.1.7. Final Report Signature

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

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

Appendix 3.2. Data Quality Assurance

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly or its

representatives, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system (EDC) will be used in this study for the collection of CRF data. The site maintains a separate source for the data entered by the site into Lilly or its representatives' provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported- outcome measures (eg, a rating scale), a daily dosing schedule, or an event diary. Certified copy of paper patient diary will be provided to the Sponsor after masking personal information. Diary data will be encoded and stored electronically in a third party's database. Validated data will subsequently be transferred from a third party to Lilly's data warehouse, using standard Lilly file transfer process.

Data collected via the sponsor-provided data capture system(s) will be stored at third party(ies). The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor (eg, laboratory test data) will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I4V-JE-JAJE is described in the Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Hepatic Evaluation Testing

See protocol Section 9.4.6.2 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs – red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs – white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (Peth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HbsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [d]	Anti-actin antibody b
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA d
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA d
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.

[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

Appendix 5. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

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

Considerations for making a change

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

Informed Consent

Additional consent/assent from the participant will be obtained, as applicable, and/or as required by ERB's and local regulations. Assent will also be obtained to the same parameters, with consent for participants reaching the legal age for consent during the trial for continued participation, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and

- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional circumstances

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

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

1. **Remote visits**

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

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to,

- AE and SAE reports
- concomitant medications (including immunization record), and
- compliance with the patient diary, and
- product complaints, and
- physician's Global Assessment of Disease Activity, and
- classification of disease severity, and
- Barthel Index.

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

2. **Study intervention and ancillary supplies (including participant diaries)**

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

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

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the

shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Appendix 6. Protocol Amendment History

Amendment d: 07 April 2022

The overall changes and rationale for the changes made to this protocol are described in the following table:

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis	Added wording to explain that the study will be considered a postmarketing clinical trial after marketing authorization under summary of design	To clarify the development phase of the study at marketing authorization of baricitinib for the indications in Japan according to Japan local regulations
	Updated visit and week numbers for maintenance treatment period from Visit 24 (Week 100) to Visit 30 (Week 172)	To update week and visit numbers accordingly
Section 2. Schedule of Activities	Added "X" for IP dispensed for visit 24	To allow IP dispense at visit 24
	Added maintenance treatment period visits 25 through 30	To extend maintenance treatment period
	Revised visit numbers to relevant footnotes to reflect changes on the added maintenance period visits (footnote k and w)	For retaining consistency of visit additions
Section 5. Study Design	Added wording to explain that the study will be considered a postmarketing clinical trial after marketing authorization under summary of design	To clarify the development phase of the study at marketing authorization of baricitinib for the indications in Japan according to Japan local regulations
	Updated Figure JAJE. 1.	To reflect changes made to the schedule of activities
Section 8.1.1. Permanent Discontinuation from study treatment	Updated wording for permanent discontinuation from study treatment	To reflect template common text
Section 9.1.2.5. Barthel Index	Wording for score scale was corrected	To correct for error
Section 9.4.6.1. Hepatitis B Virus DNA Monitoring	Added relevant visits	To reflect changes made to the schedule of activities
Section 10.3.2.4. Treatment Compliance	Deleted "patient compliance with the investigational product will be assessed at each visit"	To align with SAP

Section # and Name	Description of Change	Brief Rationale
Appendix 3.1.3. Ethical Review	Added "The investigator will be responsible for reporting significant issues related to participant safety, participant rights, or data integrity."	To align with protocol requirement update
Appendix 3.1.7. Final Report Signature	Revised to "The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study."	For clarity on final report signature

Amendment c: 09 December 2020

The overall changes and rationale for the changes made to this protocol are described in the following table:

Section # and Name	Description of Change	Brief Rationale
Section 2. Schedule of Activities	Removed X from "IP dispensed" at Visit 24 Added "FSH testing" information to footnote "l". Added footnote "y" for urine sampling.	To correct an error. To align with other sections To add new exception
Section 3.3. Benefit/Risk Assessment	"NSS" was added	To use correct wording
Section 5.5. Justification for Dose	AUC results were updated.	To correct errors
Section 6.1. Inclusion Criteria	Inclution criteria 1: removed bullets	Redundancy. Same information is in other section.
Section 6.2. Exclusion Criteria	Exclution criteria 14: modified	To make the sentence clear
Section 9.2.2. Adverse Events of Special Interest	Modified for the descrition of data collection	To align with an instruction of data collection
Section 9.4.4. Laboratory Tests	Added information for "blood volume restrictions", "fasting laboratory tests", and "urine sample collection"	To align with other sections
Section 9.4.6.1. Hepatitis B Virus DNA Monitoring	Modified for HBV DNA testing at Visit 1	To make the sentence clear
Section 9.4.6.2.1. Close hepatic monitoring	Changed TBL elevation value Added footnote and sentence for blood volume	To correct To follow latest lilly guidance for hepatic monitoring
Section 9.4.6.2.2. Comprehensive hepatic evaluation	Added footnote and paragraphs for pediatric patients	To follow latest lilly guidance for hepatic monitoring
Section 9.4.6.2.3. Hepatic Safety Data Collection	Added footnote	To follow latest lilly guidance for hepatic monitoring
Appendix 5. Provisions for Changes in Study Conduct During Exceptional Circumstances	Added new procedure during exceptional circumstances	To maintain this study during COVID-19 restrictions

Amendment b: 28 July 2020

The overall changes and rationale for the changes made to this protocol are described in the following table:

Section # and Name	Description of Change	Brief Rationale
Section 3.2.4.1. Preclinical findings in induced pluripotent stem (iPS) cells Section 3.2. Background, Summary Section 3.3. Benefit/Risk Assessment	CANDLE was changed to NNS or NNS/CANDLE.	To align the wording with other sections and related document
Section 5.1.1.1. Treatment Dose During Dose Adjustment Period Table JAJE.5. Dose Escalation Schedule by Weight and Renal Function	Inequality symbols were corrected from > to ≥ for 40 kg weight class.	To correct error
Section 7.1. Treatments Administered	Inequality symbols were corrected to appropriately describe patient weight class above and below 40kg.	To correct error
Section 9.4.6.2.2. Comprehensive hepatic evaluation	New section was included	To reflect the changes as required on the latest protocol template
Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality	The table was replaced with the latest version of the required template.	To reflect the changes as required on the latest protocol template

Amendment a: 18 Jun 2020

The overall changes and rationale for the changes made to this protocol are described in the following table:

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis		
Objectives and endpoints table	Modified endpoints for secondary objective on patient's daily diary scores	Change from baseline in patient's mean daily diary scores was separated from other endpoints to make it clear that mean daily diary score at primary endpoint is captured in the primary objective.
	Re-wording for growth monitoring objective.	Align with other sentences
	Removed footnote d and e	Not related to the table
Dose Adjustment Period	Swapped the sentences and removed one sentence.	Make the paragraph clear
Primary Treatment Period	Modified the paragraph	To align with the changes in Section 5.1
Maintenance Treatment Period	Added explanation	Make the visit schedule clear
Post-Treatment Follow-Up Period	Modified the sentence on the case of commercial baricitinib	Make the visit schedule clear
Statistical Analysis	Removed sentences	Redundancy. Same information is in Section 10.3.1.
Section 2. Schedule of Activities		
Table JAJE.1. Schedule of Activities (Screening Period and Pretreatment Period) Table JAJE.2. Schedule of Activities (Dose-Adjustment Period, Primary Treatment Period, Maintenance Treatment Period) Table JAJE.3. Schedule of Activities (Early Termination, Post-follow-up Period)	Modified the age criteria for occipital frontal circumference measurement	Not include 3 years old
Table JAJE.3. Schedule of Activities (Early Termination, Post-follow-up Period)	Added "Classification of disease severity (for NNS/CANDLE)" and "Barthel Index (for SAVI, AGS)" in ETV	
Table JAJE.1, 2, and 3. Schedule of Activities footnotes	Modified the sentences Added information	Correct errors Clear explanation Allow flexible visit window
Section 3.2. Background		
Autoinflammatory Diseases	Modified a word	Correct grammatical error
Summary	Removed paragraph	Redundancy.

Section # and Name	Description of Change	Brief Rationale
Section 4. Objectives and Endpoints		
Table JAJE.4. Objectives and Endpoints	Modified endpoints for secondary objective	Change from baseline in patient's mean daily diary scores was separated from other endpoints to make it clear that mean daily diary score at primary endpoint is captured in the primary objective.
Section 5.1. Overall Design		
Screening Period	Modified sentence on vaccination record	Change tuberculosis and herpes zoster as corresponding vaccine name Include varicella-zoster virus (VZV) vaccine
	Removed sentences on live vaccine	Redundancy. Same information is in Section 6.2.
Pre-treatment Period (NNS/CANDLE only)	Modified a word	Correct grammatical error
Dose Adjustment Period	Swapped the sentences and removed one sentence	Make the paragraph clear
Primary Treatment Period Maintenance Treatment Period	Added information and rewrote paragraphs	Made the paragraphs clear and consistent with schedule of activities and other paragraphs
Post Treatment Follow-Up Period	Modified the sentence on the case of commercial baricitinib Added information	Make the visit schedule clear Allow flexible visit window
Figure JAJE.1.Illustration of study design for Clinical Protocol I4V-JE-JAJE. footnote	Corrected wording	Correct errors
	Added a sentence on patients' transition when baricitinib becomes commercially available	Make the procedure clear
Section 5.1.1. Dose adjustment	Separated "Section 5.1.1. Dose adjustment" into two sections 5.1.1. Treatment Dose 5.1.2. Patient Diary and Diary Score	Make the contents flow easier
Section 5.1.1. Treatment Dose	Added sub sections in Section 5.1.1 5.1.1.1.Treatment dose during dose adjustment period 5.1.1.2.Treatment dose during primary treatment period and maintenance period 5.1.1.3.Dose modification during treatment period 5.1.1.4.Pharmacokinetic Sampling	Make the contents flow easier

Section # and Name	Description of Change	Brief Rationale
	Rearranged and Re-wrote the entire section	
Table JAJE.5. Dose Escalation Schedule by Weight and Renal Function	Changed dose escalation scheme	eGFR threshold to determine baricitinib dose was changed from eGFR 120 to eGFR 60 mL/min/1.73 m2. Weight category of '<20 kg' was further divided to '5-<10 kg' and '10-<20 kg'. Hence, the corresponding doses and dose frequency were updated.
Section 5.1.2. Patient Diary and Diary Score	Added sub-titles Modified sentences Added explanation on how to calculate dairy diary score	Make the contents flow easier
Section 5.5. Justification for Dose	Modified section for explanation for new dose escalation schedule	Clarification for new dose escalation schedule
Section 6.1. Inclusion Criteria		
Inclusion criterion#4	Modified the definition of "Women not of child-bearing potential or non-breastfeeding"	Alignment with the "Protocol Template Requirements (TL-01579)"
Inclusion criterion#6	Changed body weight criteria	Alignment with the weight category of dose escalation scheme
Section 6.2. Exclusion Criteria		
Exclusion criterion#28	Made bullet points Remove sentence	Make the contents flow easier Redundancy
Section 7.2. Method of Treatment Assignment	Modified sentence	Make the contents flow easier
Section 7.8. Treatment after the End of the Study	Changed the content	Fit to the section
Section 8.1.1. Permanent Discontinuation from Study Treatment	Modified sentence in the case of discontinuation	Become stricter
Section 8.1.2. Temporary Discontinuation from Study Treatment		
Table JAJE.6. Guidance on Interruption of Investigational Product	Modified eGFR criteria on interruption and restart of baricitinib	Align with eGFR category for dosing
	Modified virus infection	Add varicella-zoster virus
Section 9.1.2.6. Collection of patient's relative retrospective medical records	Modified the applicable age for Occipital frontal circumference measurement	Not include 3 years old
Section 9.2.1. Serious Adverse Events	Modified sentences on pregnancy cases	Add detailed information
Section 9.2.2. Adverse Events of Special Interest	Modified sentences on virus infection and thrombocytosis	To add the definition of thrombocytosis

Section # and Name	Description of Change	Brief Rationale
Section 9.4.7. Growth Monitoring	Modified the applicable age for Occipital frontal circumference measurement	Not include 3 years old
Section 9.5. Pharmacokinetics	Modified sentences on eGFR category	Align with dose escalation table
Section 10.3.1. General Statistical Considerations	Modified	Align with the sentences in Section 1 synopsis
Section 10.3.4. Safety Analyses	Modified the applicable age for Occipital frontal circumference measurement	Not include 3 years old
Appendix 1. Abbreviations and Definitions	Added abbreviations	
Appendix 2. Clinical Laboratory Tests	Modified footnote	Align with exclusion criterion#23
Throughout Protocol	Minor editorial and formatting adjustments	Did not change meaning, therefore did not note with hard tracked changes

Signature Page for VV-CLIN-124073 v1.0

Approval	PPD 04-Sep-2023 01:54:26 GMT+0000

Approval	PPD 04-Sep-2023 02:27:42 GMT+0000

Signature Page for VV-CLIN-124073 v1.0